VOLUME 42 FEBRUARY 4, 1977 NUMBER 3 JOCEAH

THE JOURNAL OF Organic Chemistry

PUBLISHED BIWEEKLY BY THE AMERICAN CHEMICAL SOCIETY

THE JOURNAL OF Organic Chemistry

Published by the
AMERICAN CHEMICAL SOCIETY

BOOKS AND JOURNALS DIVISION

D. H. Michael Bowen, *Director;* Marjorie Laflin, *Assistant to the Director*

Editorial Department: Charles R. Bertsch, Head; Marianne C. Brogan, Associate Head; Eileen B. Segal, Production Editor; Fern S. Jackson, Assistant Editor; Andrew J. D'Amelio, Editorial Assistant

Magazine and Production Department: Bacil Guiley, Head

Research and Development Department: Seldon W. Terrant, Head

Advertising Office: Centcom, Ltd., 50 W. State St., Westport, Conn. 06880.

Published biweekly by the American Chemical Society at 20th and Northampton Sts., Easton, Pa. 18042. Second class postage paid at Washington, D.C., and at additional mailing offices.

Editorial Information

Instructions for authors are printed in the first issue of each volume. Please conform to these instructions when submitting manuscripts.

Manuscripts for publication should be submitted to the Editor, Frederick D. Greene, at his Cambridge, Mass., address.

Correspondence regarding **accepted papers and proofs** should be directed to the Editorial Department at the ACS Easton address.

Page charges of $70.00 per page are assessed for papers published in this journal. Ability to pay does not affect acceptance or scheduling of papers.

Bulk reprints or photocopies of individual articles are available. For information write to Business Operations, Books and Journals Division, at the ACS Washington address. Requests for **permission to reprint** should be directed to Permissions, Books and Journals Division, at the ACS Washington address.

The American Chemical Society and its Editors assume no responsibility for the statements and opinions advanced by contributors.

Subscription and Business Information

1977 subscription rates—including surface postage:

	Domestic	PUAS	Canada, Foreign
Member	$26.00	$35.00	$36.00
Nonmember	104.00	113.00	114.00
Supplementary material	15.00	19.00	20.00

Air mail and Air freight rates are available from Membership & Subscription Services, at the ACS Columbus address.

New and renewal subscriptions should be sent with payment to the Office of the Controller at the ACS Washington address. **Changes of address** must include both old and new addresses with ZIP code and a recent mailing label. Send all address changes to the ACS Columbus address. Please allow 6 weeks for change to become effective. **Claims for missing numbers** will not be allowed if loss was due to failure of notice of change of address to be received in the time specified; if claim is dated, (a) North America, more than 90 days beyond issue date, (b) all other foreign, more than one year beyond issue date; or if the reason given is "missing from files". Hard copy claims are handled at the ACS Columbus address.

Microfiche subscriptions are available at the same rates but are mailed first class to U.S. subscribers, air mail to the rest of the world. Direct all inquiries to Special Issue Sales at the ACS Washington address or call (202) 872-4554.

Single issues in hard copy and/or microfiche are available from Special Issues Sales at the ACS Washington address. Current year $5.00. Back issue rates available from Special Issues Sales. **Back volumes** are available in hard copy and/or microform. Write to Special Issues Sales at the ACS Washington address for further information. **Microfilm** editions of ACS periodical publications are available from volume 1 to the present. For further information, contact Special Issues Sales at the ACS Washington address.

Supplementary material mentioned in the journal appears in the microfilm edition. Single copies may be ordered directly from Business Operations, Books and Journals Division, at the ACS Washington address.

	U.S.	PUAS, Canada	Other Foreign
Microfiche	$2.50	$3.00	$3.50
Photocopy			
1–7 pages	4.00	5.50	7.00
8–20 pages	5.00	6.50	8.00

Orders over 20 pages are available only on microfiche, 4 × 6 in., 24× negative, silver halide. Orders must state photocopy or microfiche if both are available. Full bibliographic citation including names of all authors and prepayment are required. Prices are subject to change.

American Chemical Society
1155 16th St., N.W.
Washington, D.C. 20036
(202) 872-4600

Membership & Subscription Services
American Chemical Society
P.O. Box 3337
Columbus, Ohio 43210
(614) 421-7230

Editorial Department
American Chemical Society
20th and Northampton Sts.
Easton, Pa. 18042
(215) 258-9111

Notice to Authors last printed in the issue of January 7, 1977

JOCEAH 42(3) 401–584 (1977)
ISSN 0022-3263

THE JOURNAL OF Organic Chemistry®

VOLUME 42, NUMBER 3 FEBRUARY 4, 1977

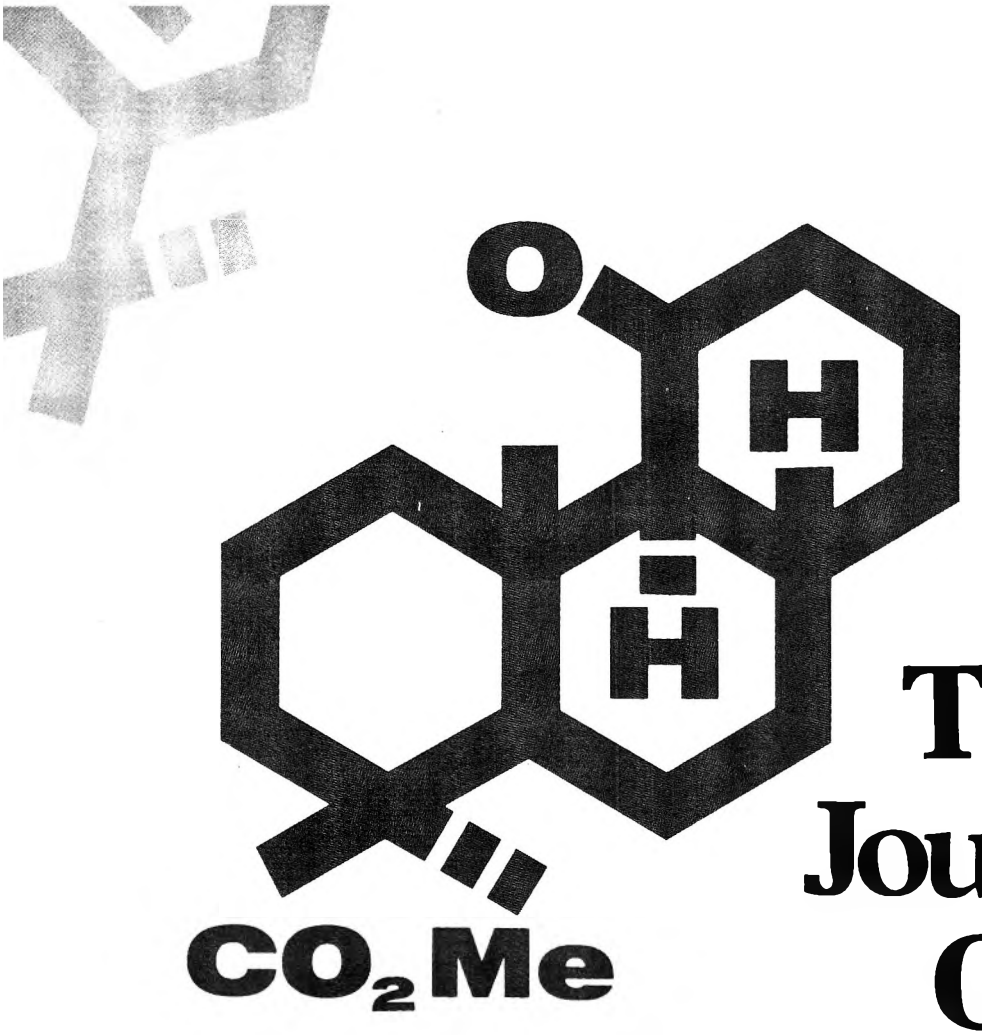
NOTES

COMMUNICATIONS

■ Supplementary material for this paper is available separately (consult the masthead page for ordering information); it will also appear following the paper in the microfilm edition of this journal.

* In papers with more than one author, the asterisk indicates the name of the author to whom inquiries about the paper should be addressed.

AUTHOR INDEX



Reactions, natural products, mechanisms, theory and spectroscopy covered comprehensively in

The Journal of Organic Chemistry

Recognized by many organic chemists as the leading American journal in the field, this biweekly publication brings subscribers over 1,000 articles, notes and communications each year—over 4,000 pages including original contributions on fundamental researches in all branches of the theory and practice of organic chemistry. Improved procedures, accounts of novel observations or compounds of special interest are also noted. Complete and mail the coupon NOW to join the thousands of organic chemists who find this journal vital in keeping current in the field.

AVAILABLE IN HARD COPY OR MICROFICHE.

The Journal of Organic Chemistry
American Chemical Society **1977**
1155 Sixteenth Street, N.W.
Washington, D.C. 20036

Yes, I would like to receive THE JOURNAL OF ORGANIC CHEMISTRY at the one-year rate checked below:

	U.S.	Foreign and Canada	Latin America
ACS Member*	☐ $26.00	☐ $36.00	☐ $35.00
Nonmember	☐ $104.00	☐ $114.00	☐ $113.00

Bill me ☐ Bill company ☐ Payment enclosed ☐

Air freight rates available on request.

Name _____

Street _____ Home ☐ Business ☐

City _____ State _____ Zip _____

Journal subscriptions start in January '77.
Allow 60 days for your first copy to be mailed.
*NOTE: Subscriptions at ACS member rates are for personal use only.

THE JOURNAL OF Organic Chemistry®

VOLUME 42, NUMBER 3

FEBRUARY 4, 1977

An Abortive $(CH)_{12}$ Synthesis. Cis-Fused Divinyl Cyclopropanes Which Cannot Cope

E. Vedejs,* W. R. Wilber, and (in part) R. Twieg

Chemistry Department, University of Wisconsin, Madison, Wisconsin 53706

Received October 27, 1975

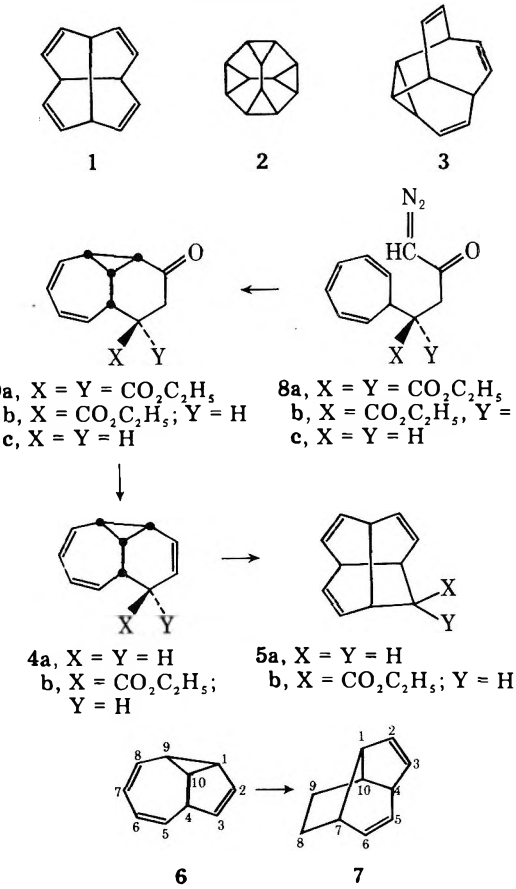
A synthetic approach to tricyclo[5.5.0.0^{4,10}]dodeca-2,5,8,11-tetraene (**1**) by Cope rearrangement of *cis*-divinylcyclopropane precursors failed. Several derivatives of tricyclo[5.4.0.0^{2,11}]undeca-3,5,9-triene (**4b, 21, 27, 28** and **29**) were prepared as potential substrates for Cope rearrangement. All of these compounds rearranged by thermal 1,3 shift; no evidence for the desired Cope products was found. The related substances **4b, 27,** and **29** rearrange to derivatives of tricyclo[6.3.0.0^{3,9}]undeca-4,6,10-triene. The related compounds **21** and **28,** having an additional sp^2 carbon in the six-membered ring, undergo a different 1,3 shift to give derivatives of tricyclo[6.3.0.0^{4,8}]undeca-2,6,10-triene. Synthesis of **4b** and **29** involves the cyclization of diazo ketone precursors as a key step. Cyclization of diazo ketone **8b** apparently gives both syn and anti fused products **9b** and **11b,c.** The geometry of **11b,c** allows facile 1,5-hydride shift to **10b,c.** Increased steric bulk in the diazo ketone side chain (as in **8a**) favors the pathway via **10a.** Conversion of **9b** to **4b** requires zinc–acetic acid induced reductive elimination of an intermediate bromohydrin **15.** This reaction gives 33% of **4b** and 64% of **16,** the product of transannular cyclization. The free radical derived from one-electron reduction of bromohydrin **15** appears to be the species responsible for transannular cyclization.

The chemistry of $(CH)_n$ hydrocarbons has been studied intensively over the past decade. As a result, many of the possible $(CH)_6$, $(CH)_8$, and $(CH)_{10}$ structures have been synthesized and much is known about the diverse and surprising rearrangements which occur thermally and photochemically.[1] Some of the possible $(CH)_{12}$ isomers have also been reported,[2] but numerous fascinating geometries await synthesis and study.

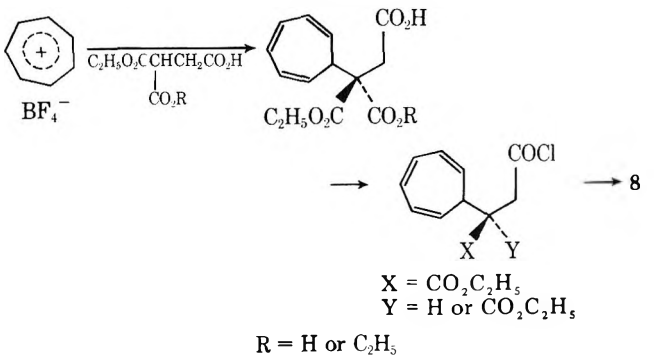
The tetraene **1** is among the more alluring target molecules in the $(CH)_{12}$ family. This substance has been proposed as a potential substrate for photochemical [2a + 2a + 2a + 2a] cycloaddition to the truncated tetrahedron **2.**[3] Whether this cyclization will compete with the more mundane (and far more precedented) di-π-methane rearrangement to **3** remains to be established.

We planned to synthesize **1** by an approach based on the Cope rearrangement of a *cis*-divinylcyclopropane such as **4.** Numerous related rearrangements are known,[4] including the closely analogous conversion of **6** to **7** at room temperature.[5] Molecular models indicate that overlap between C_4 and C_9 as required for the Cope rearrangement distorts the six-membered ring. Consequently we anticipated that **4** might be less reactive than **6.** On the other hand, the hypothetical product **5** appears less strained than **7,** a factor which would tend to lower the activation barrier.

After the Cope rearrangement, the functional groups X, Y must allow facile ring expansion. Also, these groups should be compatible with a sequence starting from the readily available tropylium fluoroborate. Suitable diazo ketones **8** are easily prepared according to Scheme I. Our plan was to convert these intermediates into **5a** (X = $CO_2C_2H_5$; Y = H), hydroxylate the



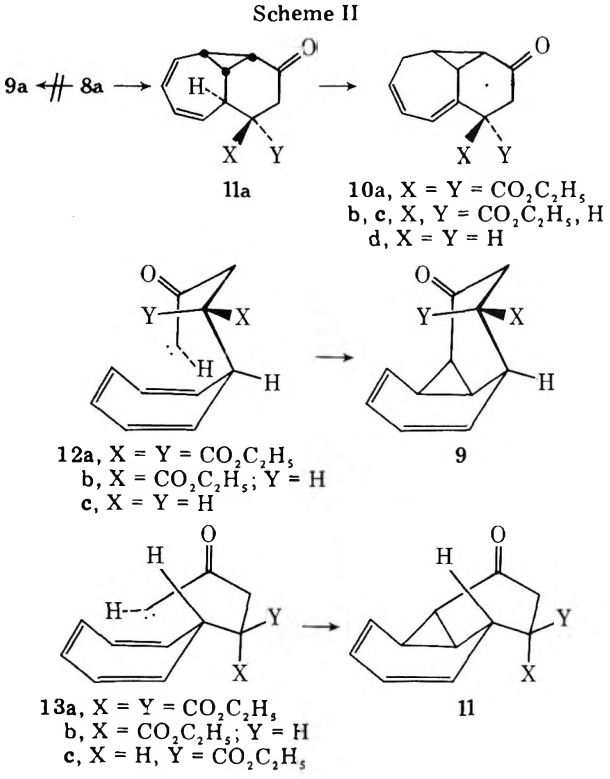
Scheme I



ester enolate (to **5**, X = $CO_2C_2H_5$; Y = OH), reduce and tosylate (to **5**, X = CH_2OTs; Y = OH), and perform a pinacol-type ring expansion. Simple enough in principle, these plans encountered unforseen difficulties at every turn.

The first major problem arose in the diazo ketone cyclization to **9**. Decomposition of **8a** in refluxing benzene/$CuSO_4$ gave a single major product in 44% yield. This material was obviously a cyclopropyl ketone (carbonyl at 1695 cm^{-1}), but only three vinyl protons could be found in the NMR spectrum. The absence of a signal for an allylic C_7 bridgehead proton indicated structure **10a** (Scheme II). No other product con-

Scheme II



taining a cyclopropyl ketone could be found, even when the diazoalkane decomposition was performed at room temperature using soluble copper catalysts.

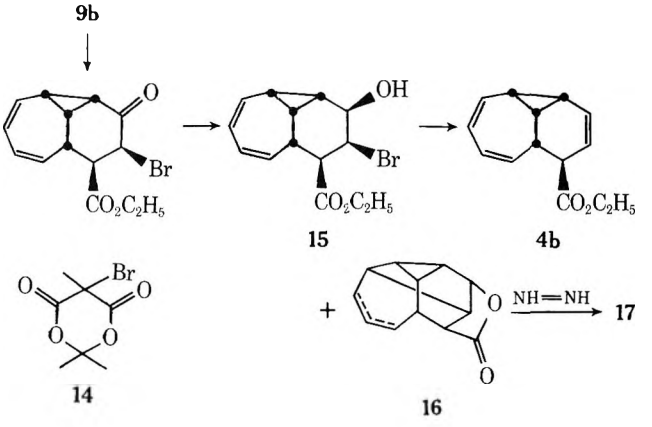
In contrast to the behavior of **8a**, decomposition of the unsubstituted model compound **8c**[6] gave the unrearranged cyclopropyl ketone **9c** (15%). In the case of **8b**, a complex mixture containing unrearranged product **9b** and the rearranged isomers **10b,c** was obtained. Reexposure of **9b** to the reaction conditinons (80°C, benzene + $CuSO_4$) did not cause any discernible rearrangement to **10b,c**. Since **9b** is not the precursor of **10b,c**, we conclude that the latter products must be formed from an anti-fused cyclopropyl ketone **11** (X or Y = $CO_2C_2H_5$ or H).

Molecular models indicate that **11** has ideal geometry for a 1,5 H shift to **10b,c**. Furthermore, the syn transition state **12b** leading to syn-fused **9b** suffers significant transannular interactions within the endo cavity of the developing tricyclic skeleton, while the anti geometry **13b,c** is relatively unstrained. Apparently, the transition state geometries similar to **12** are feasible only if Y = H. This hypothesis would explain the apparent failure of **8a** to cyclize to **9a**.

The optimum yield of **9b** (23%, ratio of **9b:10b,c** ca. 1:1) was obtained by diazo ketone decomposition in refluxing toluene (110 °C, $CuSO_4$). Relatively more **10b,c** was formed at 80 °C (**9b:10b,c** 0.75), while photosensitized diazo ketone decomposition[8] at 25 °C gave **10b,c** (22%) but no **9b**. Qualitatively, these results suggest that higher reaction temperatures allow a higher population of the pseudoaxial conformer **12b** required for cyclization to cis-fused **9b**.

With **9b** in hand, we turned to the problem of converting the sensitive cyclopropyl ketone into a vinyl cyclopropane **4b**. Treatment of **9b** with lithium bis(trimethylsilyl)amide at −70 °C followed by the selective brominating agent **14**[9] gave an α-bromo ketone in yields as high as 89% (Scheme III). Re-

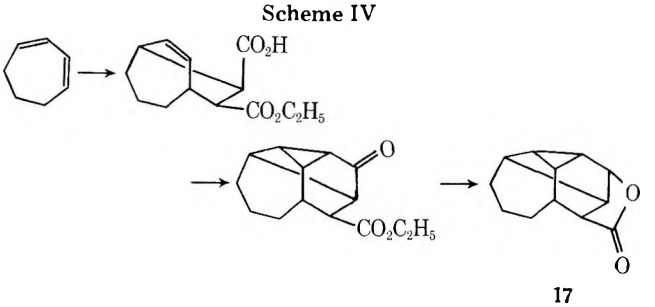
Scheme III



duction with sodium borohydride converted the bromo ketone into *all-cis*-bromohydrin **15**. The exo,cis stereochemistry of ester and bromine substituents in **15** follows from $J_{7,8}$ = 10.5 Hz, and $J_{8,9}$ = 2.0 Hz and is consistent with bromination from the less hindered exo face. Inspection of molecular models does not allow unambiguous assignment of hydroxyl stereochemistry from $J_{9,10}$ = 2.0 Hz and $J_{10,11}$ = 10.0 Hz, but the all-cis relationship is strongly indicated by subsequent reactions of **15**.

Reductive elimination of **15** to **4b** with a variety of electron donors was examined in detail. Under the best conditions (Zn/HOAc) the desired vinyl cyclopropane **4b** was obtained in 33% yield, but the major product of the reaction proved to be a crystalline mixture of two inseparable isomers **16**. Reduction of the isomer mixture **16** with diimide gave a single saturated lactone **17** which is identical with material synthesized by an independent route (Scheme IV). It is perhaps

Scheme IV

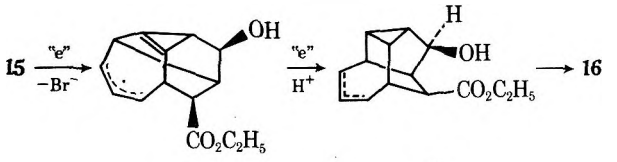


reassuring at this point that synthesis of **17** confirms the structure of **15** and its precursors as well as the structure of

16. In particular, only an all-cis fused tricyclo[5.4.0.0^{2,11}]-undecane can possibly be related to 17, and facile lactonization seems reasonable only if hydroxyl and ester stereochemistry in 15 is cis.

The undesired cyclization of 15 to 16 becomes the sole reaction when one-electron reducing agents such as Cr(II) are used. In all probability, the transannular cyclization occurs by a free-radical mechanism[10] as shown in Scheme V.

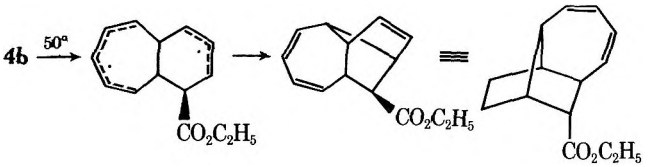
Scheme V



18

The accumulation of disastrous side reactions and isomer separation problems reduces the optimum overall yield of 4b from tropylyium ion to 3%. Nevertheless, sufficient material was available to investigate the crucial Cope rearrangement of 4b and related structures. The thermal stability of 4b proved surprisingly high, and temperatures above 50 °C were required to induce rearrangement. After 40 h at 55 °C, 4b was converted cleanly into a new isomer. Although the NMR spectrum of this substance can be reconciled with the desired Cope product 5a, the thermolysis product retains a conjugated 1,3-diene chromophore (λ_{max} 258 nm, ϵ 3600 in ethanol) and therefore cannot be a derivative of 5. On the basis of extensive decoupling studies in the presence of Eu(fod)$_3$ and the striking similarities in chemical shift data and coupling constants between analogous protons of *endo*-2-carbomethoxynorborn-5-ene[11] and the thermolysis product, the latter must be assigned structure 19 as shown in Scheme VI. This isomer is

Scheme VI



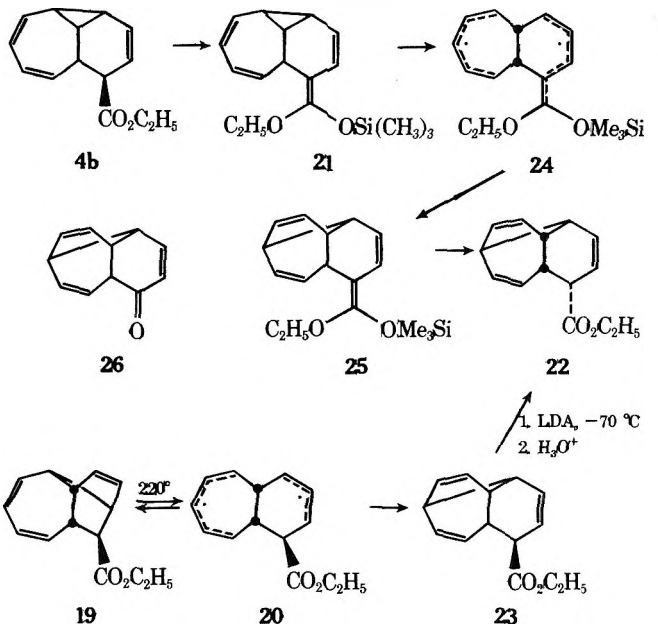
20 19

formally the result of a *vinylcyclopropane → cyclopentene* rearrangement, presumably via diradical 20.

Several attempts were made to convert the strained norbornene derivative 19 into the relatively unstrained isomer 5a by thermolysis. Indeed, rearrangement of 19 occurred in the injection port of a gas chromatograph (220 °C) resulting in partial conversion into an isomer. Complete separation of the new product from starting 19 could not be achieved but the incomplete spectral evidence was very encouraging. The thermolysis product of 19 did not have a conjugated chromophore, and retained the proper ratio of vinyl and aliphatic protons required for structure 5b. However, the high-temperature rearrangement was too inefficient to qualify as a potential step in the synthetic sequence.

If rearrangement of 19 involves thermodynamically controlled cyclization of diradical 20, then it should be possible to lower the reaction temperature by providing additional diradical stabilization. Accordingly, we examined the thermal behavior of ketene acetals derived from the ester function of 4b. Treatment of 4b with lithium diisopropylamide (LDA) at −70 °C followed by trimethylchlorosilane gave 21 without complications (Scheme VII). Surprisingly, thermolysis of 21 at the lower temperature used to convert 4b into 19 did not give an analogous product having a conjugated 1,3-diene chromophore after hydrolytic cleavage of the trimethylsilyl

Scheme VII



4b 21 24 26 25 22 19 20 23

group. Instead, a single isomer 22 was formed which at first appeared to be the same as the product obtained from 19 at 220 °C. The NMR spectra of 22 and the thermolysis product from 19 were identical in the olefinic region, but the carboxylate α-methine protons of the two isomeric esters did not coincide. Since other physical and spectral characteristics of the isomers are indistinguishable, we suspected that high-temperature pyrolysis of 19 must give a diastereomer of 22. Treatment of the pyrolysate from 19 with LDA at −70 °C followed by quenching with aqueous acid (−70 °C) results in formation of 22. Thus 22 and the pyrolysis product of 19 differ only in the stereochemistry of the ester group (barring some remarkable anionic rearrangement), a finding which shatters any realistic hope that *either* isomer might be 5b. The latter can only exist as one diastereomer because the parent hydrocarbon 5a has a C_2 axis of symmetry.

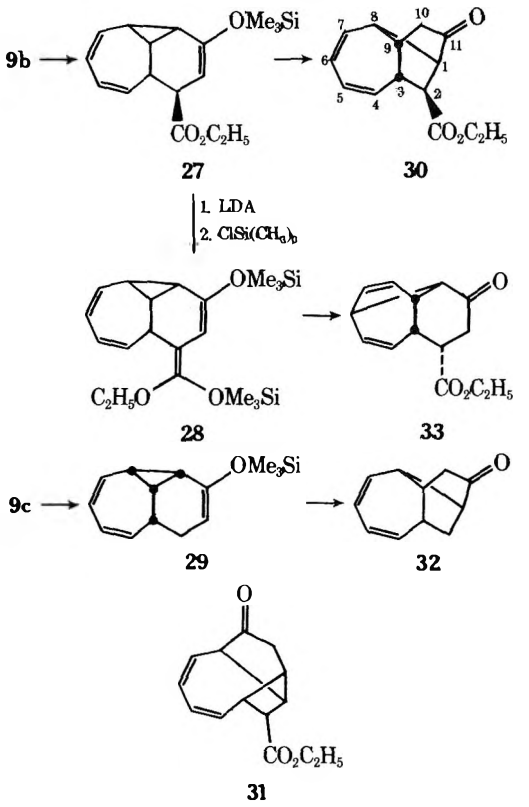
The only reasonable alternative structure which might result from reclosure of diradical 20 is the ester 23. Deprotonation of 23 with LDA followed by enolate protonation from the least hindered side would give diastereomer 22. Apparently, *the thermolysis of 21 at 55 °C involves a diradical 24 which for* some conformational reason prefers to close directly to 25. Hydrolysis of 25 by protonation from the least hindered face of the ketene acetal leads to 22.[12]

The structures assigned to 22 and 23 are consistent with extensive spectral data, but the methine region in the NMR spectra is not sufficiently resolved for conclusive structure assignment. On the other hand, the NMR features of 25 compare favorably with those of the model compound 26[14] which has the same carbon skeleton and a closely analogous substitution pattern.

In desperation, we examined thermolysis of enol ether derivatives 27, 28, and 29. Treatment of 9b with lithium bis-*(trimethylsily)amide followed by trimethylchlorosilane* afforded 27, and repetition of the process gave 28. Similarly, 9c was converted into 29 via the enolate.

A single keto ester 30 was obtained from rearrangement of 27 at 55 °C with subsequent hydrolysis. The product 30 has the same chromophore as 18, an appropriately similar NMR spectrum, and a norbornanone carbonyl absorption at 1750 cm^{-1}. A conclusive assignment of structure follows from NMR decoupling studies which establish a continuous chain including C_2–C_9, and also demonstrate the connection between C_9, C_{10}, and C_{11}. The only alternative structure 31 which meets the connectivity requirements is ruled out by chemical shift

Scheme VIII



and Eu(fod)$_3$ evidence. The analogous rearrangement of **29** gave **32** after hydrolysis. Comparisons of UV and NMR data leave no doubt that **19**, **30**, and **32** have the same carbon skeleton and differ only in the substitution pattern of the norbornane subunit.

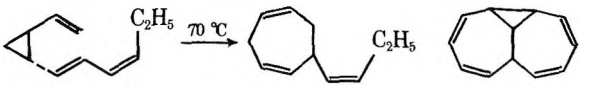
Finally, pyrolysis of **28** was examined. The only significant product other than recovered **9b** obtained after hydrolysis was the keto ester **33**. A combination of Eu(dpm)$_3$ and NMR decoupling techniques allows unequivocal assignment of all protons and all vicinal and geminal coupling constants in the molecule. The connectivity requirements are uniquely satisfied, and no alternative structures are possible. This evidence taken together with data presented earlier provides strong support for the view that **22**, **23**, and **33** have the same carbon skeleton.

Conclusions

The thermal behavior of **4b**, **21**, **27**, **28**, and **29** shows convincingly that the tricyclo[5.4.0.0^{2,11}]undeca-3,5,9-triene derivatives are among the very rare cis-fused divinylcyclopropane systems which fail to undergo Cope rearrangement.[4m,15] The related structures **4b**, **27**, and **29**, all having a double bond and an sp^3-hybridized carbon in the six-membered ring, rearrange by homolytic cleavage at C_2–C_{11} with rebonding at C_2–C_9. The structures **21** and **28**, having a double bond and an sp^2-hybridized carbon in the six-membered ring, form a bond between C_4 and C_{11} at the expense of the C_2–C_{11} bond. Differing kinetic preferences for rebonding in the diradical intermediates are probably determined by conformational changes depending on the hybridization at C_8. Conversion of **19** into **23** at 220 °C is due to strain energy associated with the norbornene moiety of **19**, and presumably reflects a kinetic preference for C_4–C_{11} bonding rather than C_4–C_9 bonding which would convert diradical **20** into **5**.

The failure of any of the cis-fused divinylcyclopropanes **4b**, **21**, **27**, **28**, and **29** to undergo Cope rearrangement may be due to geometric factors. The preferred conformation of **4b** and derivatives juxtaposes C_3 and C_9 rather than C_4 and C_9 as required for the six-center Cope transition state. A reasonable bonding distance between C_4 and C_9 can be achieved in a molecular model by flattening the six-membered ring. Apparently, this distortion introduces sufficient strain to raise the activation barrier for Cope rearrangement relative to model compounds such as **6**. Diradical cleavage of the C_2–C_{11} bond becomes the lowest energy pathway and formation of products by 1,3 shift is the result.

Given a sufficiently high barrier for Cope rearrangement, it is not surprising that a diradical process would compete. Diradical rearrangement of a *trans*-1-vinyl-2-dienyl cyclopropane **34** has been observed previously with E_a = 28.5



34 **35** **36**

kcal/mol at 70–90 °C.[16] The activation parameters for rearrangement of **4b** to **19** at 55–65 °C are in reasonable agreement (E_a = 31.7 ± 1.3 kcal/mol, $\Delta H^{\ddagger}$ = 31 ± 1.2 kcal/mol, $\Delta S^{\ddagger}$ = 13 ± 5 eu). We can only envy the smooth formation of Cope product **35** from **34** in spite of the intervention of a diradical. In our system, diradical intermediates rearrange exclusively by 1,3 shift with catastrophic consequences for the synthetic approach to **1**. Along more speculative lines, we suspect that potential thermal routes to **1** (such as by rearrangement of the hypothetical hydrocarbon **36**) will encounter disaster for similar reasons.

Experimental Section

General. Spectra were recorded using the following: NMR, Jeolco MH 100 or Varian XL-100 instruments; IR, Beckman IR-8; UV, Cary 15. Melting points were determined on a hot stage microscope apparatus and are uncorrected. Tetrahydrofuran was dried by distillation from lithium aluminum hydride.

Preparation of Intermediates in Scheme I. 3,3-Dicarboethoxy-3-(7-cyclohepta-1,3,5-trienyl)propionic Acid. To diethyl malonate (120 g, 0.75 mol) in 2 l. of dry tetrahydrofuran is added sodium hydride (24.0 g of a 50% dispersion in mineral oil, 0.50 m) at such a rate as to maintain gentle reflux. To the resulting clear solution is added over 0.5 h *tert*-butyl chloroacetate (82.9 g, 0.44 mol), and the reaction is stirred at reflux for 18 h. Commercial hexane (2 l.) is added, the reaction mixture is filtered, the solvent is evaporated, and the residual oil is distilled. After a forerun of starting materials, the monoalkylation product (116.2 g, 0.425 mol, 85%) distills at 112–118 °C (1.4 mm): n^{24}D 1.4298; NMR (CCl_4) δ 4.15 (2 H, q, J = 7.2 Hz), 3.65 (1 H, dd, J = 7.0, 8.0 Hz), 2.70 (2 H, d, J = 7.5 Hz), 1.40 (9 H, s), 1.25 (3 H, t, J = 7.2 Hz), IR (neat) 1725, 1420 cm^{-1}.

The distillate from above (31 g) is added dropwise to concentrated H_2SO_4 (70 g) at a rate such that the temperature is maintained at 0–5 °C (salt–ice bath). Three minutes after addition (total reaction time ca. 15 min) the solution is poured over ice (ca. 200 g), the aqueous layer is saturated with Na_2SO_4, and the product extracted with ether (4 × 100 ml). The organic phase is extracted with saturated Na_2CO_3 (4 × 50 ml), each carbonate extract is immediately added to a rapidly stirred mixture of 20% HCl–saturated NaCl–ether, and the ether layers are separated and dried over anhydrous $MgSO_4$. After evaporation, monoethyl(2-carboethoxy)succinate (27 g) is obtained as a pale yellow oil which solidifies in the freezer.

The crude monoethyl(2-carboethoxy) succinate (22 g) from above is added to a solution of cycloheptatrienyl fluoroborate[17] (19.8 g) in pyridine (50 ml). After 18 h at 25 °C, the solution is adjusted to pH 1 with 20% HCl and extracted with ether (3 × 100 ml). After drying over $MgSO_4$ and evaporation of ether, 3,3-dicarboethoxy-3-(7-cyclohepta-1,3,5-trienyl)propionic acid crystallizes from hexane (27 g, two crops): NMR ($CDCl_3$) δ 1.24 (6 H, t, J = 7 Hz), 2.03 (1 H, t, J = 6 Hz), 3.08 (2 H, s), 4.25 (4 H, q, J = 7 Hz), 5.38 (2 H, dd, J = 9, 6 Hz), 6.25 (2 H, m), 6.70 (2 H, m), 11.42 (1 H, s).

3-Carboethoxy-3-(7-cyclohepta-1,3,5-trienyl)propionic Acid. The distillate obtained from alkylation of diethyl malonate and *tert*-butyl chloroacetate as described above (164 g, 0.6 mol) is dissolved in absolute ethanol (300 ml) and combined with a solution of potassium hydroxide (39.6 g of 85% commercial grade, 0.6 mol) in 300 ml of absolute ethanol. The reaction mixture is swirled in a 1-l. flask over a steam bath, and swirling is continued while the reaction is kept at reflux for 10 min by intermittent heating. After cooling and reaction

at room temperature (12 h) the solvent is removed by rotary evaporation (aspirator) and the residual oil is dried overnight under oil pump vacuum. The crude intermediate is partitioned between 1500 ml of ether and 30% aqueous hydrochloric acid. The ether is removed on a rotary evaporator (aspirator vacuum), and the residual oil is diluted with 200 ml of ether and cooled to 0 °C. Concentrated sulfuric acid (30 ml) is dripped into the solution with vigorous swirling in a 0 °C bath. After addition is complete, the reaction mixture is stirred for 1 h at 0°. Ice (200 g) is added, and the reaction is partitioned between 1 l. of ether and 250 ml of saturated brine. The aqueous phase is extracted with two 500-ml portions of ether. The ether layers are combined, dried over anhydrous magnesium sulfate, and concentrated. The residual oil is freed of ether under high vacuum, and slowly solidifies. The waxy solid is purified by trituration with carbon tetrachloride to give 2-carboethoxysuccinic acid (90.0 g, 0.474 mol, 79%) as a white solid, mp 76–70 °C, sufficiently pure for further reactions.

3-Carboethoxy-3-(7-cyclohepta-1,3,5-trienyl)propionic Acid. 2-Carboethoxysuccinic acid (90 g) dissolved in 400 ml of commercial pyridine and coolled to 0 °C is added to a cold solution of tropylium fluoroborate[17] (90 g) in 400 ml of commercial pyridine, and the reaction mixture is stirred for 13 h at room temperature. The clear tan solution is warmed to 85–90 °C, and stirred at that temperature for 7 h, after which time carbon dioxide evolution has ceased. After cooling, the reaction mixture is washed into a separatory funnel with 1 l. of ether; 2 l. of 30% sulfuric acid is poured through the ether layer, recovered, and poured through several times more. This must be done carefully to avoid local overheating and consequent loss of product out the top of the funnel. Ether is added from time to time, replacing that lost by the heat of the neutralization reaction, keeping the volume at approximately 1.5 l. After back-extraction of the acidic wash with two 500-ml portions of ether, the ether phases are combined and washed with two 500-ml portions of 10% HCl, then with acidic saturated brine, dried over sodium sulfate, and evaporated to give crude 3-carboethoxy-3-(7-cycloheptatrienyl)propionic acid as a dark oil after removal of residual solvent by oil pump vacuum (10 g): IR (neat) 3570–2380, 1710 cm^{-1}; NMR ($DCCl_3$) δ 11.2 (1 H, s) 6.6 (2 H, t, J = 3 Hz), 6.2 (2 H, dt, J = 10, 3, 3 Hz), 5.3 (2 H, dd, J = 10, 7 Hz), 4.2 (2 H, q, J = 7.0 Hz), 3.2–2.6 (3 H, m), 1.98 (1 H, q, J = 7 Hz), 1.25 (3 H, t, J = 7.0 Hz). This product is sufficiently pure for subsequent steps.

Diazo Ketone 8a. Piperidine (distilled from BaO) is added to a saturated solution of 3,3-dicarboethoxy-3-(7-cyclohepta-1,3,5-trienyl)propionic acid (2 g) in ether until the odor of excess piperidine is apparent. Additional ether is added to a total volume of 25 ml and the piperidinium salt is allowed to crystallize in the freezer (2.3 g, two crops).

A solution of the salt (2 g) in dry chloroform (2 ml, distilled from P_2O_5) is added dropwise to thionyl chloride (2 g) in anhydrous ether (20 ml) over 20 min at 0 °C. The mixture is allowed to warm to 20° and is stirred for 1 h (SO_2 evolution!). Dry hexane (50 ml) is added, and the solution is decolorized with Norit, filtered, and evaporated to yield the crude acid chloride as a pale yellow oil.

The acid chloride is dissolved in ether (20 ml) and added dropwise to a solution of diazomethane (ca. 0.8 g) in ether (35 ml) at 0 °C over 20 min. After 1 h at 0 °C and 2 h at 20 °C, the solvents are evaporated under a nitrogen stream. Rapid filtration chromatography of the residue over silica gel using chloroform–hexane gives a small forerun of colorless side products followed by a yellow diazo ketone fraction. Evaporation of the solvent (aspirator) gives **8a** as a yellow oil (1.5 g): NMR (CCl_4) δ 1.25 (6 H, t, J = 7 Hz), 1.93 (1 H, t, J = 6 Hz), 2.96 (2 H, s), 4.16 (4 H, q, J = 7 Hz), 5.29 (2 H, dd, J = 9, 6 Hz), 5.33 (1 H, s), 6.1 (2 H, m), 6.6 (2 H, m); IR (neat) 2100, 1725, 1640 cm^{-1}.

Diazo Ketone 8b. A solution of 3-carboethoxy-3-(7-cyclohepta-1,3,5-trienyl)propionic acid (130 g, 0.55 mol) in anhydrous ether (400 ml) is treated dropwise with dry (distilled from barium oxide) dicyclohexylamine (100 g, 0.552 mol) while cooling and swirling in an ice bath. Commercial hexane (600 ml) is then added, and the solution cooled to 4 °C overnight. After filtration, the solid is washed with hexane, and the mother liquors are concentrated for a second crop of the dicyclohexylammonium salt (186 g, 0.445 mol, 81%) as pale tan needles in pellets and clumps (mp 105–107 °C). The mother liquors of the second crop are evaporated to give a dark brown oil (45 g) which can be used in subsequent steps, although the products are more difficult to purify.

The crystalline salt (33.8 g, 0.081 mol) is dissolved in dry benzene (125 ml, distilled from CaH_2) and the solution is added dropwise to thionyl chloride (16.6 g, 0.14 mol) at room temperature. After 2 h of stirring, hexane (250 ml) is added, the slurry is filtered, and the cake of dicyclohexylamine hydrochloride washed with 200 ml of 30% benzene/hexane. Evaporation of the solvent, followed by several evaporative distillations of benzene–thionyl chloride azeotrope, yields crude acid chloride as a dark oil.

A solution of diazomethane generated from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (107 g, 0.5 mol)[18] is cooled to 0 °C. The crude acid chloride from above (ca. 21 g) in ether (50 ml) is added over 20 min. The solution is stirred at 0 °C for 1 h and stored overnight (10 h) at 4 °C. The solvent is blown off with dry nitrogen in a good hood. The crude yellow oil remaining is taken up in ether and deposited on an approximately equal weight of silica gel by drying in a rotary evaporator. This is deposited on top of a 6 by 2 in. column of silica gel under hexane. The column is eluted with hexane until the yellow band of diazo ketone is ready to elute, at which time the eluent is changed to 10% ether in hexane. The column is further eluted until there is no diazo absorption in the IR spectrum of the eluent. The diazo ketone containing fractions (ca. 2 l.) are cooled to −15 °C overnight, while pale yellow crystals separate from the solution. After filtration, diazo ketone **8b** (6.0–8.4 g, 0.023–0.032 mol, 46–64%) is isolated as yellow crystals, mp 56.0–57.0 °C. The mother liquors can be evaporated to give another 4–6 g of yellow oil, essentially pure **8b** by IR, NMR, and TLC; this can be used for further reactions, although yields are lower than for the crystalline material. IR (neat) 2120, 1730, 1640 cm^{-1}; NMR ($CDCl_3$) δ 6.8 (2 H, m), 6.4 (2 H, dt, J = 10, 3 Hz), 5.4 (3 H, m), 4.3 (2 H, q, J = 7 Hz), 2.6–3.5 (3 H, m), 1.9 (1 H, m), 1.3 (3 H, t, J = 7 Hz).

Diazo Ketone Decomposition. Decomposition of 8a. Preparation of 10a. A solution of **8a** (0.2 g) in dry benzene (5 ml, distilled from CaH_2) is added over 30 min to a vigorously stirred suspension of anhydrous $CuSO_4$ in refluxing benzene (10 ml). The mixture is refluxed for 30 min after addition is complete, filtered, and evaporated to give a dark oil. Preparative layer chromatography over silica gel (Brinkman PF 254) with 20% hexane in chloroform gives a single major zone, R_f 0.3. After extraction with ether and evaporation, crude **10a** is obtained as a crystalline solid (0.08 g, 44%). Colorless crystals of **10a** (mp 102–103 °C) are obtained from ether [Anal. ($C_{17}H_{20}O_5$) C, H]: UV (ethanol) λ_{max} 252 nm (ϵ 8520); IR ($CHCl_3$) 1725, 1695 cm^{-1}; NMR ($CDCl_3$) δ 1.27 (3 H, t, J = 7 Hz), 1.29 (3 H, t, J = 7 Hz), 1.32 (1 H, m), 1.8–2.2 (4 H, m), 2.63 (1 H, d, J = 18 Hz), 3.32 (1 H, d, J = 18 Hz), 4.22 (4 H, q, J = 7 Hz), 5.9–6.3 (3 H, m).

Minor chromatography zones at R_f 0.4–0.6 and R_f 0.1–0.2 do not give characterizable products. None of these zones has significant carbonyl absorption at 1695 cm^{-1} characteristic of cyclopropyl ketones.

Thermal ($CuSO_4$) Decomposition of 8b. Isolation of 10b,c and 9b. A solution of **8b** (0.2 g) in dry toluene (5 ml, distilled from CaH_2) is added to a vigorously stirred suspension of anhydrous $CuSO_4$ (0.5 g, dried under vacuum at 300 °C) over 1 h. The mixture is refluxed for 1 h after addition is complete, cooled, filtered, and evaporated (aspirator) to give a dark brown residue.

Preparative layer chromatography over silica gel (Brinkman PF 254) using 15% ether/hexane, five developments, allows separation of three main zones: R_f >0.5, unidentified mixture of cycloheptatrienyl-containing products, no cyclopropyl ketone carbonyl absorption; R_f 0.4, 0.039 g (21%) of **10b,c**; and R_f 0.3, 0.041 g (23%).

Crystallization of the R_f 0.3 zone from CCl_4 gives colorless prisms of **9b** (mp 56–57.5 °C): UV (hexane) λ_{max} 253 nm (ϵ 4900); IR ($CHCl_3$) 1725, 1695 cm^{-1}; NMR (CCl_4) δ 5.65–6.05 (4 H, m), 4.1 (2 H, q, J = 7 Hz), 3.4 (1 H, m), 2.8 (1 H, m), 1.9–2.3 (4 H, m), 1.66 (1 H, dd, J = 8, 11 Hz), 1.2 (3 H, t, J = 7 Hz); exact mass 232.10769 found for $C_{14}H_{16}O_3$ (calcd, 232.10993).

Repeated preparative layer chromatography of the R_f 0.4 zone (four developments) results in partial separation of the **10b,c** mixture. The leading edge of the major zone gives the exo ester as a viscous oil: UV (ethanol) λ_{max} 251 nm (ϵ 4500); IR (neat) 1730, 1690 cm^{-1}; NMR (CCl_4) δ 6.3 (1 H, m), 6.0 (1 H, m), 5.7 (1 H, br d, J = 3 Hz), 4.15 (2 H, q, J = 7 Hz), 3.73 (1 H, dd, J = 12, 5 Hz), 2.8 (1 H, dd, J = 18, 5 Hz), 2.45 (1 H, dd, J = 18, 12 Hz), 1.8–2.4 (4 H, m), 1.2–1.35 (3 H, t, overlapping 1 H, m).

Crystallization of the trailing zone from CCl_4–hexane gives colorless needles of the endo ester (mp 89.5–93.5 °C); UV (ethanol) λ_{max} 252 nm (ϵ 7000); IR ($CHCl_3$) 1725, 1685 cm^{-1}; NMR (CCl_4) δ 6.3 (1 H, m), 5.95 (2 H, m), 4.1 (2 H, q, J = 7 Hz), 3.50 (1 H, d, J = 6 Hz), 3.05 (1 H, d, J = 18 Hz), 1.5–2.4 (5 H, m), 1.2–1.4 (3 H triplet overlapping 1 H multiplet); exact mass 232.11292 found for $C_{14}H_{16}O_3$. The exo and endo ester isomers are present in comparable amounts in the initial R_f 0.4 chromatography fraction.

Photosensitized Decomposition of 8b. A solution of **8b** (1.877 g, 0.00723 mol) and Michler's ketone (404 mg) in 2 l. of benzene deoxygenated by a dry nitrogen stream is exposed to a Hanovia lamp in a Pyrex well for 15 h, after which time the diazo IR absorption disap-

pears. The solvent is evaporated and the residue subjected to preparative layer chromatography on silica gel PF-254 (five developments by 15% ether/hexane) as before.

The area at R_f 0.3 contains no discernible **9b**. The R_f 0.4 zone gives **10b,c** (0.386 g, 22.4%) as a 1:9 mixture of endo:exo carboethoxy isomers.

Preparation of 8c. Cycloheptatrienylacetic acid[7,19] is converted into the acid chloride and the derived diazo ketone as described in the literature.[4g] To achieve Arndt–Eistert homologation, a solution of the diazo ketone (3.85 g) in THF (50 ml) is added dropwise over 30 min to a vigorously stirred solution of $AgNO_3$ (4 g), $Na_2S_2O_3$ (4.2 g), and water (170 ml) at 65 °C. After 1 h the mixture is cooled, acidified to pH 2 with 5% nitric acid, and extracted with ether (2 × 100 ml). The organic phase is extracted with 5% NaOH (3 × 50 ml), the base extract neutralized with 20% HCl, and extracted with ether (2 × 100 ml). The ether layer is dried ($MgSO_4$) and evaporated (aspirator) to give 3-(7-cyclohepta-1,3,5-trienyl)propionic acid as a pale yellow oil (3.3 g). Without further purification, the crude product is dissolved in ether (15 ml) and treated with dicyclohexylamine (3.9 ml). The colorless crystals of dicyclohexylammonium 3-(7-cyclohepta-1,3,5-trienyl)propionate are collected in two crops from ether (5.6 g). Conversion of the salt to 3-(7-cycloheptatrienyl)propionyl chloride and the derived diazo ketone is accomplished by the same method used to prepare **8b**. Starting with 8.56 g of dicyclohexylammonium salt and 8.25 g of $SOCl_2$, 4.47 g of crude acid chloride is obtained. Reaction with diazomethane generated in the usual way from 40 g of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide followed by filtration chromatography on silica gel (10 × 3 cm column) with hexane gives diazo ketone **8c** (3.4 g) as a yellow oil: IR (neat) 2120, 1630 cm^{-1}; NMR (CCl_4) δ 6.62 (2 H, m), 6.0–6.3 (2 H, m), 5.36 (1 H, s), 5.13 (2 H, dd, J = 9, 6 Hz), 1.5–2.6 (5 H, m).

Decomposition of 8c. Isolation of 9c. A solution of **8c** (2 g) is added to a vigorously stirred solution of anhydrous $CuSO_4$ (2 g) in refluxing benzene as described for preparation of **9b**. Separation of the crude product by preparative layer chromatography over silica gel with 15% acetone/hexane (three developments) gives two major zones (R_f 0.3 and 0.4) and four minor zones (R_f 0.15, 0.45, 0.55, and 0.7). No characterizable products can be isolated from the minor zones. The zone at R_f 0.4 (0.64 g) cannot be separated into individual components by TLC. Separation by GLC on 10 ft × 0.375 in. 10% Carbowax/Chromosorb P (170 °C) results in extensive thermal degradation, but the shortest retention time component corresponds by NMR to a component of the R_f 0.4 preparative TLC fraction. This noncrystalline product is spiro[6.4]undeca-6,8,10-trien-2-one based on spectral data: IR (neat) 1740 cm^{-1}; NMR (CCl_4) δ 6.5–6.7 (2 H, m), 6.0–6.3 (2 H, m), 5.28 (2 H, d, J = 10 Hz), 1.98 (2 H, s), 1.9–2.5 (4 H, m).

The NMR spectrum of the R_f 0.4 zones contains a doublet of doublets at δ 4.93, characteristic of a monosubstituted cycloheptatrienyl ring, other complex olefinic signals between δ 5.8 and 6.7, and a complex aliphatic region, δ 1.9–3. The combined integral ratio of olefinic:aliphatic protons is 7:9 (structure **10d** requires a ratio of 3:9).

The R_f 0.3 zone (0.27 g, 15%) gives a colorless oil consisting of **9c** (ca. 90% pure) and traces of side products: IR (neat) 1690 cm^{-1}; NMR (CCl_4) δ 5.7–6.3 (3 H, m), 3.15 (1 H, m), 1.7–2.3 (7 H); *m/e* 160 for $C_{11}H_{12}O$.

Conversion of 9b to 4b. Bromination of 9b. To the base from hexamethyldisilazane (4.00 g, 0.025 mol) and buthylithium (18.1 ml of a 2.19 M solution in hexane, 0.020 mol), prepared at −78 °C in dry tetrahydrofuran (20 ml) in a 100-ml oven-dried flask, is added keto ester **9b** (3.78 g, 0.0163 mol) dissolved in dry tetrahydrofuran (10 ml), and the reaction mixture stirred for 2 h at −78 °C. A solution of norbornene (3.8 g, 0.040 mol) and 5-bromo-2,2,5-trimethyl-1,3-dioxane-4,6-dione **14**[13] (4.74 g, 0.020 mol) in dry tetrahydrofuran (15 ml) is added, the cooling bath is removed, and the reaction mixture is allowed to warm to room temperature while stirring. (Omission of the norbornene lowers the yield by 15–30%; we assume that norbornene acts as a positive bromine trap.) After 20 min, the reaction is quenched with a mixture of 10% HCl (10 ml) and saturated brine (10 ml). The aqueous phase is separated and extracted with ether (20 ml), which is combined with the organic phase; the solvents are then removed (aspirator). The residue is deposited on silica gel (5 g) and placed on top of a 6 by 2 in. diameter column of silica gel under hexane. Elution with hexane (500 ml) removes the silyl compounds. Elution with 25% ether/hexane (500 ml) affords the bromo ketone (4.52 g, 0.0145 mol, 89%) as a pale yellow oil which slowly solidifies (mp 74.5–78 °C). This material is used without recrystallization: IR (neat) 1727, 1700 cm^{-1}; NMR (CCl_4) δ 5.7–6.4 (4 H, m), 4.46 (1 H, d, J = 3 Hz), 4.0–4.3 (2 H, m), 3.2–3.4 (2 H, m), 1.6–2.2 (3 H, m), 1.25 (3 H, t, J = 7 Hz). NMR shift decoupling studies, see Table I; exact mass observed 310.02168 for $C_{14}H_{15}O_3Br$ (calcd, 310.02050).

Table I. NMR Data for Ethyl 9β-Bromotricyclo[5.4.0.0^{2,11}]-undeca-3,5-dien-10-one-8β-carboxylate

Proton	Multiplicity	Shift europium added (arbitrary increments) 0	1st	2d	3d
1	q	2.18	2.42	2.56	2.80
2	t	1.96	2.10	2.22	2.40
3	dd	6.10	6.23	6.38	6.58
4	dd	5.84	5.84	5.86	5.86
5	dd	5.84	5.84	5.90	6.00
6	dd	6.40	6.54	6.64	6.84
7	m	3.34	4.26	4.56	5.20
8	dd	3.20	4.26	4.64	5.34
9	d	4.45	5.86	6.30	7.14
11	dd	1.66	2.68	3.00	3.60

Coupling constants (Hz): $J_{1,2}$ = 7.5; $J_{1,7}$ = 7.5; $J_{1,11}$ = 7.5; $J_{2,3}$ = 3; $J_{3,4}$ = 10; $J_{4,5}$ = 5; $J_{5,6}$ = 10; $J_{6,7}$ = 7.0; $J_{7,8}$ = 10; $J_{8,9}$ = 3 Hz.

Ethyl 9β-Bromo-1β,7β-tricyclo[5.4.0.0^{2,11}]undeca-3,5-dien-10β-ol-8β-carboxylate (15). In a 500-ml round-bottom flask the bromo ketone from above (4.52 g, 0.0145 mol) is dissolved in dry tetrahydrofuran (100 ml); commercial absolute ethanol (60 ml) is added, and the solution cooled with stirring to −78 °C. Sodium borohydride (1.52 g, 0.040 mol) is added, the cooling bath is removed, and the reaction mixture is stirred vigorously while slowly warming to room temperature. After 1 h, the reaction is quenched with Rochelle salts (10 g) dissolved in distilled water (40 ml). Sodium chloride (20 g) and 10% HCl (30 ml) are added, the phases separated, and the aqueous phase washed with ether (50 ml). The combined organic phases are evaporated; the residue is taken up in ether (400 ml), which is then washed with 10% HCl (150 ml) and saturated brine (150 ml), dried over magnesium sulfate, and evaporated, leaving **15** (4.32 g, 0.0138 mol, 95%) as a colorless oil which solidifies. Recrystallization from ether/chloroform/hexane yields pure **15**: mp 92.0–93.0 °C; IR (neat) 3450, 1730 cm^{-1}; NMR (CCl_4) δ 6.44 (1 H, dd, J = 11, 8 Hz), 6.15 (1 H, br d, J = 10 Hz), 5.93 (1 H, dd, J = 10, 5 Hz), 5.72 (1 H, dd, J = 11, 5 Hz), 4.75 (1 H, t, J = 2 Hz), 4.15 (2 H, m), 3.5 (1 H, br d, J = 10 Hz), 3.20 (1 H, dt, J = 8, 7 Hz), 2.5 (1 H, br d, J = 10 Hz), 2.45 (1 H, dd, J = 10, 2 Hz), 1.75 (1 H, q, J = 8 Hz), 1.6 (1 H, m), 1.3 (3 H, t, J = 7 Hz), 0.8 (1 H, ddd, J = 9, 8, 2 Hz); exact mass observed 312.03803 for $C_{14}H_{17}O_3Br$ (calcd, 312.03615).

Zinc Reduction of 15. Preparation of 4b. A solution of **15** (4.32 g, 0.0138 mol) in glacial acetic acid (180 ml) is cooled to 15 °C with a cold water bath while zinc dust (200 g) is added with vigorous mechanical stirring at such a rate that the internal temperature remains below 25 °C. The suspension is vigorously stirred for 13 h at room temperature; ether (150 ml) is added, and the stirring continued for 10 min more. The reaction mixture is filtered, and the cake of zinc and zinc salts is well washed with ether (300 ml). The filtrate is washed with 10% KOH (3 × 350 ml), which washings are back extracted with ether (100 ml). The ether phases are combined and evaporated; the residual oil is placed on a column of silica gel (50 g) in hexane. Elution with 3% ether/hexane (700 ml) yields ethyl 1β,7β-tricyclo[5.4.0.0^{2,11}]-undeca-3,5,9-triene-8β-carboxylate (**4b**) as a colorless, pleasant-smelling oil (0.998 g, 0.00462 mol, 33.5%): UV (ethanol) λ_{max} 257 nm (ϵ 2800); IR (neat) 1725 cm^{-1}; NMR (CCl_4) δ 6.4 (1 H, ddd, J = 9, 8, 2 Hz), 5.5–6.0 (5 H, complex), 4.03 (2 H, q, J = 7 Hz), 3.1 (1 H, q, J = 7 Hz), 2.8 (1 H, pentet, J = 3 Hz), 1.9 (1 H, q, J = 8 Hz), 1.6 (1 H, br t, J = 8 Hz), 1.2 (4 H, 7 Hz triplet, 3 H, overlapping 1 H multiplet); exact mass observed for $C_{14}H_{16}O_2$ 216.11589 (calcd, 216.11502).

Elution of the column with ether (700 ml) yields a mixture of the lactones 4-oxapentacyclo[6.5.0.0^{2,13}.0^{3,7}.0^{6,12}]tridec-9-en-5-one and -10-en-5-one (**16**) as a colorless oil which slowly solidifies (1.655 g, 0.00880 mol, 63.7%). Recrystallization from ether/hexane gives colorless needles of the mixture, mp 60.5–62.0 °C. Repeated recrystallizations do not change the isomer ratio: IR (neat) 1765 cm^{-1}; NMR (CCl_4) δ 5.4–6.2 (2 H, complex), 5.0 (1 H, m), 1.2–2.9 (9 H, complex); exact mass observed 188.08525 for $C_{12}H_{12}O_2$ (calcd, 188.08372).

Structure Proof of 16. Synthesis of 17 (Scheme IV). 8-Carboethoxybicyclo[3.2.2]non-6-ene-9-carboxylate Dicyclohexylammonium Salts. To a solution of sodium (1.960 g, 0.085 mol) in

absolute ethanol (50 ml) is added bicyclo[3.2.2]non-6-ene-8-*syn*,9-*syn*-dicarboxylic anhydride[20] (11.60 g, 0.0605 mol), and the solution warmed to 67 °C for 2 h. The solvent is removed on a rotary evaporator (aspirator) and the product partitioned between ether (200 ml) and 10% HCl (200 ml). The ether is separated, dried over magnesium sulfate, and evaporated. The product is extracted from the residual oil into hot hexane which is evaporated to yield the half ester carboxylic acid as a viscous oil. The oil is dissolved in ether (30 ml) and treated with dicyclohexylamine. Crystallization at −4 °C overnight gives colorless crystals (19.2 g, two crops), mp 93.5–99.5 °C.

Ethyl Tetracyclo[5.4.0.0^{2,11}.0^{3,9}]undecan-10-one-8-carboxylate. The crystalline salt from above (12.6 g, 0.03 mol) is dissolved in chloroform (40 ml) and treated with thionyl chloride (5 ml) at 20 °C for 2.5 h. Hexane (60 ml) is added, the suspension is filtered, and the cake of dicyclohexylammonium chloride is washed with hexane (100 ml). After solvent removal (aspirator), any residual thionyl chloride is removed by azeotropic distillation (aspirator) with dry (distilled from calcium hydride) benzene (50 ml). The resulting acid chloride is dissolved in ether (50 ml) and added to diazomethane prepared from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (30 g)[20] in ether solution at 0 °C as described for preparation of **8b**. Filtration chromatography over silica gel (2 × 10 cm column) with hexane gives a yellow fraction which yields diazo ketone upon evaporation (7.34 g). A solution of the diazo ketone (4.37 g 0.0167 mol) in dry benzene (30 ml, distilled from CaH_2) is dripped over 1 h into a refluxing suspension of copper sulfate (4.0 g, predried at 350 °C and stored in a desiccator) in dry benzene (40 ml). After stirring for an additional 1 h, the suspension is filtered and the solvent removed (aspirator). The residual oil is taken into warm pentane (leaving a small amount of a brown, tarry substance) and the pentane evaporated to yield a colorless oil (3.7 g). The NMR spectrum lacks distinctive features other than to show the presence of ester and the absence of vinyl hydrogens; exact mass, observed 234.12498 for $C_{14}H_{18}O_3$ (calcd 243.12558).

Ethyl Tetracyclo[5.4.0.0^{2,11}.0^{3,9}]undecan-10-ol-8-carboxylate. The crude tetracyclic keto ester from above (12.9 g, 0.0055 mol) in ethanol (20 ml) is stirred at −20 °C with sodium borohydride (0.25 g, 0.0066 mol) for 1 h and then allowed to warm to 20 °C. The reaction is quenched with Rochell salts (3 g) in water (15 ml) and partitioned between ether (100 ml) and 10% HCl (30 ml). The ethereal phase is washed with 10% HCl (20 ml) and saturated brine (20 ml), dried over magnesium sulfate, and evaporated (aspirator). The residual colorless oil crystallizes from ether/hexane, giving the tetracyclic hydroxy ester (0.275 g, 0.00115 mol, 21%) as colorless crystals (mp 74.5–77.0 °C). The mother liquors can be evaporated to yield more product as an oil (overall 1.27 g, 0.00536 mol, 97%) which is suitable for use in the next reaction: IR ($HCCl_3$) 3510, 1720 cm^{-1}; NMR ($CDCl_3$) δ 4.4 (1 H, dd, J = 5, 2 Hz), 4.13 (2 H, q, J = 7 Hz), 3.4 (1 H, d, J = 9 Hz), 2.95 (1 H, s), 2.6 (1 H, br), 2.22 (2 H, m), 1.2–2.0 (8 H, m), 1.25 (3 H, t, J = 7 Hz), 0.95 (1 H, q, J = 6 Hz); exact mass observed 236.14099 for $C_{14}H_{20}O_3$ (calcd, 236.14123).

Lactonization to 17. The crude (not crystallized) hydroxy ester from above (1 g, 0.004 mol) is refluxed with sodium ethoxide from sodium (2.3 g) and ethanol (100 ml) overnight. The solution is cooled and treated with 20% HCl (20 ml) and the solvents are evaporated (aspirator). The residue is partitioned between ether (50 ml) and water (20 ml), and the ether layer is separated and washed with saturated brine (20 ml), dried over magnesium sulfate, and evaporated to give a brown oil (0.661 g). Preparative layer chromatography over silica gel using 20% ether/hexane affords **17** (0.38 g, 48%) as a colorless oil which slowly solidifies. Recrystallization from ether gives colorless prisms of **17** (mp 84.5–86.5 °C): IR ($CHCl_3$) 1765 cm^{-1}; NMR ($CDCl_3$) δ 5.0 (1 H, dd, J = 6, 4 Hz), 1.6–2.7 (12 H, complex), 1.25 (1 H, q, J = 7 Hz); exact mass observed 190.09882 for $C_{12}H_{14}O_2$ (calcd, 190.09937).

Attempted lactonization of the hydroxy ester under milder conditions gives recovered starting material. This may be due to unfavorable ester stereochemistry caused by epimerization during cleavage of the starting maleic anhydride adduct with sodium ethoxide.

Diimide Reduction of the Lactones 16. To a solution of lactones **16** (0.104 g, 0.000553 mol) in commercial pyridine (50 ml) is added potassium azodicarboxylate (10.4 g, 0.0553 mol), and the suspension mechanically stirred at room temperature while glacial acetic acid is dripped in over a 2-h period. After stirring for an additional 1 h, ether (200 ml) is added, and the reaction mixture is washed with 10% KOH (100 ml), 10% HCl (3 × 100 ml), and saturated brine (100 ml), dried over magnesium sulfate, and evaporated. The NMR spectrum indicates incomplete reduction, and the product is resubjected to the reaction. After three treatments, ca. 30% starting **16** still remains. To allow separation of product from starting material, the crude product is treated with bromine (0.05 g, 0.0003 mol) in CCl_4 (1 ml) at 0 °C, the solvent evaporated, and the crude product separated by preparative layer chromatography over silica gel. The zone corresponding to **17** is collected (0.06 g, 60%) which solidifies. Recrystallization from ether affords colorless prisms (mp 84.5–86.5 °C) identical by mixture melting point, NMR, IR, and TLC with **17** prepared independently.

Table II. NMR Europium Shift Decoupling Experiments on Ethyl Tricyclo[6.3.0.0^{3,9}]undeca-4,6,10-triene-2-*endo*-carboxylate

Chemical shifts, δ (CCl_4)		Eu(dpm)$_3$ added (arbitrary increments)		
Proton	Mult	0	1	2
9	s	2.37	2.62	2.90
8	br d	2.23	2.50	2.78
7	*a*	*a*	*a*	*a*
6	*a*	*a*	*a*	*a*
5	*a*	*a*	*a*	*a*
4	dd	6.22	6.38	6.52
3	cx m	2.50	3.58	4.66
2	t	2.90	3.94	5.06
1	br s	3.46	4.10	4.80
11	dd	6.10	6.68	7.28
10	dd	6.50	6.75	7.02

[a] Broad complex multiplet at δ 5.5–6.0, unseparated by europium. $J_{8,9}$ = ?, $J_{9,10}$ = 3, $J_{7,8}$ = 5.5, $J_{3,8}$ = 2, $J_{1,8}$ = 1.5, $J_{4,5}$ = 10, $J_{3,4}$ = 8, $J_{2,3}$ = 4, $J_{1,2}$ = 4, $J_{1,11}$ = 3, $J_{10,11}$ = 6 Hz.

Thermolysis of Divinylcyclopropane Derivatives. Ethyl Tricyclo[6.3.0.0^{3,9}]undeca-4,6,10-triene-2-*endo*-carboxylate (19). Triene ester **4b** (0.108 g, 0.00050 mol) dissolved in carbon tetrachloride (0.3 ml) in an NMR tube is placed in a 55.00 °C thermostated bath, and the NMR spectrum is monitored from time to time. Ester **4b** disappears with first-order kinetics (k_1 = 1.56 × 10^{-5} s^{-1}, ρ = 0.995 for six points). After 8 half-lives (88 h), there is only one product visible in the NMR. Rinsing the reaction into a tared flask with ether and evaporation yields ester **19** (0.108 g, 0.00050 mol, 100%) as a pale yellow oil: IR (neat) 1725 cm^{-1}; NMR (CCl_4) δ 6.50 (1 H, dd, J = 6, 3 Hz), 5.6–6.2 (5 H, m), 4.0 (2 H, q, J = 7 Hz), 3.46 (1 H, br s), 2.90 (1 H, t, J = 4 Hz), 2.2–2.5 (3 H, m), 1.1 (3 H, t, J = 7 Hz); exact mass observed 216.11370 for $C_{14}H_{16}O_2$ (calcd, 216.11502); UV (EtOH) λ_{max} 258 nm (ε 3650). GLC: retention time 52.5 min on 20% SE-30 on 60/80 Chromosorb P 20 ft × 0.125 in. at 150 °C, He flow 60 ml/min. NMR shift/decoupling studies: see Table II. Rearrangement at 65.00 °C proceeds with k_1 = 6.53 × 10^{-5} s^{-1} (ρ = 0.985, six points). This gives an Arrhenius ΔE_{act} = 31.7 (± 1.2) kcal mol^{-1} and log A = 16.19. An Eyring treatment gives $\Delta H^{\ddagger}$ = 31.0 (± 1.2) kcal/mol, $\Delta S^{\ddagger}$ = +13 (± 5) cal deg^{-1} mol^{-1}.

Pyrolysis of 19 under GLC Conditions. A solution of **4b** (50% in acetone) is injected (injection block temperature 220 °C) onto a 20 ft × 0.125 in. 20% SE-30 on Chromosorb P column at 150 °C with helium flow of 60 ml/min. The peak corresponding in retention time to **19** (52.5 min) is collected; it accounts for over 95% of the volatile materials, and contains (by NMR) approximately 30% **23** and 70% **19**. Preparative scale pyrolysis of **4b** (0.03 g) at 170 °C in a solution consisting of biphenyl (0.1 g), *o*-terphenyl (0.1 g), and naphthalene (0.05 g) in an NMR tube gives a mixture of **19** and **23**. After 15 h, the NMR signals due to **19** are no longer visible. Preparative layer chromatography of the mixture (six developments, hexane) over silica gel affords a zone corresponding to **19** in R_f. Extraction of the product with ether gives an oil (0.01 g, 34%) consisting of **23** contaminated with ca. 15% of **19**: NMR ($CDCl_3$) δ 6.5 (1 H, dd, J = 6, 3 Hz), 5.7–6.1 (4 H, complex), 5.1 (1 H, dd, J = 10, 4 Hz), 4.15 (2 H, q, J = 7 Hz), 2.94 (1 H, br s), 2.3–2.6 (4 H, complex), 1.25 (3 H, t, J = 7 Hz).

Preparation of 21 and Rearrangement to 25. Isolation of 22. Triene ester **4b** (0.0291 g, 0.000134 mol) is added to the base from diisopropylamine (0.200 g, 0.00198 mol) and butyllithium (0.80 ml of 1.01 M solution, 0.000808 mol) in dry tetrahydrofuran (10 ml) stirring under nitrogen at −78 °C, and the resultant orange solution is stirred for 45 min at −78 °C. Chlorotrimethylsilane (0.500 g, 0.0046 mol) is added, and the colorless solution is brought to room temperature with stirring. After 20 min, the solvent is removed on a rotary evaporator (aspirator); carbon tetrachloride (5 ml) is added to the residual slurry, and again the solvents are evaporated. Carbon tetrachloride (2 ml) is added, and the slurry is filtered through a tight

Table III. Europium Shift/Decoupling NMR Experiments on Ethyl Tricyclo[6.3.0.0^{4,9}]undeca-2,6,10-triene-5-*exo*-carboxylate (22)

Proton	Mult	Chemical shift, δ	Normalized $\Delta\delta$ (Eu)
4	br s	2.64	12.1
3	dddd	5.10	13.4
2	dd	6.10	3.5
1	br s	2.50	2.5
11	dd	6.50	1.4
10	dd	5.77	1.0
9	br s	2.50	3.7
8	br s	2.50	3.0
7	ddd	5.85	3.6
6	dd	6.05	12.3
5	br s	3.34	17.5

$J_{3,4} = 4, J_{4,9} = ?, J_{4,5} = 4, J_{2,3} = 9, J_{1,2} = 6, J_{1,11} = 3, J_{1,8} = 4, J_{10,11} = 5.5, J_{9,10} = 2, J_{8,9} = ?, J_{7,8} = 4, J_{6,7} = 10, J_{5,7} = 2, J_{5,6} = 1$ Hz.

Table IV. Europium Shift/Decoupling NMR Experiments on Ethyl Tricyclo[6.3.0.0^{4,9}]undeca-2,10-dien-7-one-5-*exo*-carboxylate (33)

Proton	Mult	Shift, δ	Normalized $\Delta\delta$ [Eu(dpm)$_3$]
4	ddd	2.8	4.6
3	dddd	5.14	4.3
2	dd	6.16	2.6
1	ddd	2.8	4.1
11	dd	6.49	1.2
10	dd	5.74	1.00
9	ddd	2.8	3.7
8	dd	2.6	10.3
6α	dd	2.5	14.1
6β	dd	2.6	12.2
5	ddd	2.9	5.6

$J_{3,4} = 6, J_{4,9} = 3, J_{4,5} = 3, J_{2,3} = 10, J_{1,2} = 5.5, J_{1,11} = 3, J_{1,8} = 5.5, J_{11,10} = 6, J_{10,9} = 3, J_{9,8} = 5.5, J_{6\alpha,6\beta} = 18, J_{6\alpha,5} = 10, J_{6\beta,5} = 7$ Hz.

plug of fiberglass in a disposable pipet (this having been assembled and dried at 100 °C for 2 h) with the aid of a carbon tetrachloride rinse (1 ml). This filtrate contains almost pure enol silane **21**: NMR (CCl_4) δ 6.5 (1 H, dd, J = 8, 11 Hz), 6.0 (1 H, d, J = 12 Hz), 5.5–5.7 (3 H, m), 5.34 (1 H, dd, J = 4, 10 Hz), 3.8 (2 H, q, J = 7 Hz), 3.4 (1 H, m), 1.8 (2 H, m), 1.2 (4 H, m), 0.2 (9 H, s).

Heating **21** to 70 °C for 15 h results in clean rearrangement to enol silane **25**: NMR (CCl_4) δ 6.5 (1 H, dd, J = 6, 3 Hz), 6.15 (1 H, d, J = 10 Hz), 5.7 (2 H, m), 5.5 (1 H, dd, J = 10, 5 Hz), 4.90 (1 H, dddd, J = 10, 4, 0.8, 0.8 Hz), 3.8 (2 H, q, J = 7 Hz), 3.0 (1 H, m), 2.2–2.6 (3 H, m), 1.2 (3 H, t, J = 7 Hz), 0.2 (9 H, s).

Aqueous hydrolysis (2:1 THF–H_2O, 2 h, 20 °C) yields almost pure ethyl tricyclo[6.3.0.0^{4,9}]undeca-2,6,10-triene-5-*exo*-carboxylate (**22**), which is purified by preparative gas chromatography. Retention time on a 20 ft × 0.125 in. 20% SE-30 on Chromosorb P column at 150 °C with a helium flow of 60 ml/min: 58.0 min. IR (neat) 1720 cm^{-1}; NMR ($CDCl_3$) δ 6.50 (1 H, dd, J = 6, 3 Hz), 5.7–6.1 (4 H, m), 5.1 (1 H, dddd, J = 9, 4, 0.8, 0.8 Hz), 4.15 (2 H, q, J = 7 Hz), 3.3 (1 H, br s), 2.4–2.6 (4 H, m), 1.25 (3 H, t, J = 7 Hz). NMR europium-shift/decoupling experiments: see Table III.

Epimerization of 23 to 22. A mixture of **19** and **23** (0.216 g, 0.001 mol) obtained by pyrolysis (ratio of **19**:**23** ca. 10:1) is dissolved in dry THF at −78 °C and treated with lithium diisopropylamide (1.5 ml of 0.7 M solution in hexane–THF) under nitrogen flow. After 45 min at −78 °C, water (2 ml) is added to the stirred mixture. Partition between ether–water followed by drying ($MgSO_4$) and evaporation gives an oil (0.16 g). Preparative GLC (20 ft × 0.125 in. 20% SE-30/Chromosorb P, 150 °C) gives two peaks in the ratio 9:1. The major (lower retention time) peak is pure **19** while the minor peak is identical with **22** in all respects.

Preparation of Ethyl Tricyclo[6.3.0.0^{3,9}]undeca-4,6-dien-11-one-2-carboxylate (30). Keto ester **9b** (0.085 g, 0.000366 mol) in dry tetrahydrofuran (1 ml) is added to the base from hexamethyldisilazane (0.400 g, 0.00330 mol) and butyllithium (0.80 ml of 1.05 M solution, 0.00084 mol) stirring under nitrogen at −78 °C in dry tetrahydrofuran (10 ml). After stirring for 15 min at −78 °C, the reaction is quenched with chlorotrimethylsilane (0.80 g, 0.0073 mol) and stirred for 5 min while being warmed to room temperature. After the solvent is removed on a rotary evaporator (aspirator), carbon tetrachloride (2 ml) is added to the residual slurry, and the solvents are once again evaporated. The residual brown oily solid is suspended in carbon tetrachloride and filtered through an oven-dried plug of tightly packed glass wool in a disposable pipet. Evaporation yields enol silane **27**: NMR (CCl_4) δ 5.6–6.2 (4 H, m), 4.6 (1 H, d, J = 5 Hz), 4.1 (2 H, q, J = 7 Hz), 3.5 (1 H, m), 2.9 (1 H, m), 1.9 (1 H, q, J = 8 Hz), 1.4 (1 H, m), 1.25 (3, H, t, J = 7 Hz), 0.9 (1 H, m), 0.1 (9 H, s).

Heating **27** in CCl_4 for 18 h results in rearrangement. Hydrolysis in 2:1 THF–H_2O for 2 h at 25 °C followed by preparative layer chromatography over silica gel (20% ether/hexane, three developments) gives recovered **9b** in the slower zone (0.016 g, 23%), and **30** (0.034 g, 40%) in a faster zone: UV (ethanol) λ_{max} 259 nm (ϵ 4010), 268 (3640); IR 1755, 1725 cm^{-1}; NMR (CCl_4) δ 5.6–6.1 (4 H, m), 4.1 (2 H, m), 3.24 (1 H, t, J = 4 Hz), 3.0 (1 H, br d, J = 4 Hz), 2.85 (1 H, m), 2.6 (1 H, m) 2.45 (1 H, br s), 2.1 (2 H, ABX, J_{AB} = 19, J_{AX} = 4, J_{BX} ~0 Hz), 1.2 (3 H, t, J = 7 Hz). Decoupling studies in the presence of Eu(fod)$_3$ allow assignment of the folowing coupling constants (Hz): $J_{9,10} = 4, J_{7,8} = 6, J_{6,7} = 10, J_{5,6} = 6, J_{4,5} = 10, J_{3,4} = 8, J_{2,3} = 4, J_{1,2} = 4$.

Preparation of Ethyl Tricyclo[6.3.0.0^{4,9}]undeca-2,10-dien-7-one-5-carboxylate (33). In an oven-dried three-neck flask, one of whose necks is equipped with a short-path distillation setup, hexamethyldisilazane (1.21 g, 0.0075 mol) is added to dry tetrahydrofuran (20 ml), and butyllithium (2.0 ml of a 2.18 M solution in hexane, 0.00434 mol) is added under nitrogen flow. The solution is cooled with stirring to −78 °C, and keto ester **9b** (0.612 g, 0.00244 mol) dissolved in dry THF (30 ml) is added, and the solution stirred 90 min at −78 °C, at which time chlorotrimethylsilane (1.3 ml) is added. The solution is now heated to distill off the excess chlorotrimethylsilane. Dry THF (20 ml) is added, and the reaction cooled once again to −78 °C, at which time the base from hexamethyldisilazane (1.21 g, 0.0075 mol) and butyllithium (2.0 ml of a 2.18 M solution in hexane, 0.00434 mol) in dry THF (20 ml) is added by syringe. After 90 min, chlorotrimethylsilane (1.3 ml) is added, the dry ice bath is removed, and the reaction mixture is stirred for 20 h at room temperature. After quenching with 10% HCl (5 ml) 30 min, the volatiles are removed on a rotary evaporator (ASPIRATOR(/ Partition of the crude product between ether and water, followed by drying and solvent removal, yields the crude product as a brown oil (0.534 g). Preparative layer chromatography on silica gel PF-254 (four developments with 20% ether/pentane) affords pure **33** (0.102 g, 0.00044 mol, 16%) as a pale yellow oil, from the UV-inactive band behind **30** but ahead of starting material (both of which are UV active): IR (neat) 1730 cm^{-1}; NMR (CCl_4) δ 6.49 (1 H, dd, J = 6, 3 Hz), 6.16 (1 H, dd, J = 10, 6 Hz), 5.74 (1 H, dd, J = 6, 3 Hz), 5.14 (1 H, m), 4.1 (2 H, q, J = 7 Hz), 2.4–3.0 (7 H, m), 1.2 (3 H, t, J = 7 Hz); europium shift/decoupling NMR experiments, see Table IV. Exact mass observed 232.10894 for $C_{14}H_{16}O_3$ (calcd, 232.10993).

Rearrangement of 29. Isolation of Tricyclo[6.3.0.0^{3,9}]undeca-4,6-dien-11-one (32). A solution of **9c** (0.28 g, 0.00175 mol) in dry THF (10 ml) is added over 5 min to the base from hexamethyldisilazane (0.515 g, distilled) and *n*-butyllithium (1.2 ml of 2.33 M hexane solution, 0.0029 mol) in dry THF (15 ml) at −78 °C under nitrogen flow. After 90 min at −78 °C, chlorotrimethylsilane (0.6 ml) is added and the solution is stirred for 1 h at −78 °C and then allowed to reach room temperature. The THF solution of **29** is then warmed for 2 h each to 43 and 54 °C. Aliquots are withdrawn and hydrolyzed with methanol (2 h, room temperature). Analysis by TLC (15% acetone/hexane) on silica gel shows only recovered **9c**. The THF solution is then refluxed for 18 h, cooled to 45 °C, and treated with methanol (40 ml). After 2 h at 45 °C, the product is partitioned between ether and water, the ether layer is dried ($MgSO_4$) and evaporated, and the residual oil is separated by preparative TLC (15% acetone/hexane, silica gel PF 254). The main zone (R_f 0.3–0.4) is collected to yield **32** as a colorless oil (0.16 g, 58%), contaminated by ca. 10% of an unknown side product. Preparative GLC on 10 ft × 0.25 in. 10% Carbowax/Chromosorb P at 180 °C gives two minor peaks (retention times 9 and 14 min) and a peak at 16.5 min, identical by NMR with the major component in the major TLC fraction. Collection of the main GLC peak gives **32** as a colorless oil: UV (methanol) λ_{max} 269 nm (ϵ 4440), 259 (4905); IR (neat) 1740 cm^{-1}; NMR (CCl_4) δ 5.5–6.1 (4 H, complex), 2.8 (1 H, d, J = 4 Hz), 2.0–2.6 (6 H, complex), 1.86 (1 H, d, J = 18 Hz),

1.66 (1 H, dd, J = 13, 9 Hz). Decoupling experiments in the presence of Eu(fod)$_3$ indicate the following coupling constant assignments: $J_{1,2\text{-exo}} = 4$, $J_{9,10\text{-exo}} = 4$, $J_{9,10\text{-endo}} < 1$, $J_{10\text{-exo},10\text{-endo}} = 19$ Hz.

Registry No.—**4b,** 61063-63-6; **8a,** 61063-55-6; **8b,** 61063-56-7; **8c,** 61063-57-8; **9b,** 61063-58-9; **9c,** 61063-59-0; **10a,** 61063-60-3; **10b,** 61063-61-4; **10c,** 61116-91-4; **14,** 34817-42-0; **15,** 61063-62-5; **15** ketone derivative, 57261-23-1; **16** 9-ene, 61063-64-7; **16** 10-ene, 61092-33-9; **17,** 61092-34-0; **19,** 61063-65-8; **21,** 61063-66-9; **22,** 61063-67-0; **23,** 61116-92-5; **25,** 61063-68-1; **27,** 61063-69-2; **29,** 61063-70-5; **30,** 61063-71-6; **32,** 61063-72-7; **33,** 61063-73-8; *tert*-butyl chloroacetate, 107-59-5; diethyl malonate, 105-53-3; *tert*-butyl ethyl 2-carboethoxysuccinate, 61063-74-7; monoethyl(2-carboethoxy) succinate, 61063-75-0; cycloheptatrienyl fluoroborate, 61063-76-1; 3,3-dicarboethoxy-3-(7-cyclohepta-1,3,5-trienyl)propionic acid, 61063-77-2; 2-carboethoxysuccinic acid, 61063-78-3; 3-carboethoxy-3-(7-cycloheptatrienyl)propionic acid, 61063-79-4; piperidine, 110-89-4; 3,3-dicarboethoxy-3-(7-cyclohepta-1,3,5-trienyl)propionic acid piperidine, 61063-80-7; 3,3-dicarboethoxy-3-(7-cyclohepta-1,3,5-trienyl)propionyl chloride, 61063-81-8; dicyclohexylamine, 101-83-7; 3-carboethoxy-3-(7-cyclohepta-1,3,5-trienyl)propionic acid dicyclohexylamine salt, 61063-82-9; diazomethane, 334-88-3; 3-carboethoxy-3-(7-cyclohepta-1,3,5-trienyl)propionyl chloride, 61063-83-0; cycloheptatrienylacetic acid diazo ketone, 61063-84-1; 3-(7-cyclohepta-1,3,5-trienyl)propionic acid, 61063-85-2; dicyclohexylammonium 3-(7-cyclohepta-1,3,5-trienyl)propionate, 61063-86-3; 3-(7-cycloheptatrienyl)propionyl chloride, 61063-87-4; spiro[6,4]undeca-6,8,10-trien-2-one, 61063-88-5; bicyclo[3.2.2]non-6-ene-8-*syn*,9-*syn*-dicarboxylic anhydride, 29577-71-7; ethyl bicyclo[3.2.2]non-6-ene-8-*syn*,9-*syn*-dicarboxylic acid, 61063-89-6; dicyclohexylammonium ethyl bicyclo[3.2.2]non-6-ene-8-*syn*,9-*syn*-dicarboxylic acid, 61116-93-6; bicyclo[3.2.2]non-6-ene-8-*syn*-carboxylic acid 9-*syn*-carbonyl chloride, 61063-91-0; ethyl tetracyclo[5.4.0.0^{2,11}.0^{3,9}]undecan-10-one-8-carboxylate, 61063-90-9; ethyl tetracyclo[5.4.0.0^{2,11}.0^{3,9}]undecan-10-ol-8-carboxylate, 61092-35-1.

References and Notes

(1) L. T. Scott and M. Jones, Jr., *Chem. Rev.*, **72,** 181 (1972); S. Masamune and N. Darby, *Acc. Chem. Res.*, **5,** 272 (1972), and references cited therein.

(2) W. v. E. Doering and P. S. Rouse, unpublished results; quoted by W. v. E. Doering and H. Krauch, *Angew. Chem.*, **68,** 661 (1956); M. E. Vol'pin, I. S. Akhrem, and D. N. Kursanov, *Zh. Obshch. Khim,* **28,** 330 (1958); H. Prinzbach and H. Knofel, *Angew. Chem.*, **81,** 900 (1969); G. Schröder and W. Martin, *ibid.*, **78,** 117 (1966); L. A. Paquette and J. C. Stowell, *J. Am. Chem. Soc.*, **93,** 5735 (1971); G. Schröder, *Chem. Ber.*, **97,** 3131 (1964); L. A. Paquette and M. J. Kukla, *J. Chem. Soc., Chem. Commun.*, 409 (1973); J. N. Labows, Jr., J. Meinwald, H. Rottele, and G. Schröder, *J. Am. Chem. Soc.*, **89,** 612 (1967); H. Rottele, W. Martin, S. F. M. Oth, and G. Schröder, *Chem. Ber.*, **102,** 3985 (1969); J. A. Berson and R. F. Davis, *J. Am. Chem. Soc.*, **94,** 3658 (1972); U. Erhardt and J. Daub, *J. Chem. Soc., Chem. Commun.*, 83 (1974); E. Vedejs and R. A. Shepherd, *J. Am. Chem. Soc.*, in press.

(3) R. B. Woodward and R. Hoffman, "The Conservation of Orbital Symmetry", Verlag Chemie, Weinheim/Bergstr., Germany, 1970, p 106.

(4) (a) W. v. E. Doering and W. R. Roth, *Angew. Chem.*, **75,** 27 (1963); (b) E. Vogel, K.-H. Ott, and K. Gajek, *Justus Liebigs Ann. Chem.*, **644,** 172 (1961); (c) W. v. E. Doering and W. R. Roth, *Tetrahedron,* **19,** 715 (1963); (d) G. Schröder, *Angew. Chem.*, **75,** 722 (1963); (e) G. Schröder, *Chem. Ber.*, **97,** 3140 (1964); (f) R. Merenyi, J. F. M. Oth, and G. Schröder, *ibid.*, **97,** 3150 (1964); (g) W. v. E. Doering, B. M. Ferrier, E. T. Fossel, J. M. Hartenstein, M. Jones, Jr., G. Klumpp, R. M. Rubin, and M. Saunders, *Tetrahedron* **23,** 3943 (1967); (h) H. E. Zimmerman and G. L. Grunewald, *J. Am. Chem. Soc.*, **88,** 183 (1966); (i) R. Criegee and R. Askani, *Angew. Chem.*, **80,** 531 (1968); (j) W. Grimme and K. Seel, *Angew. Chem., Int. Ed. Engl.*, **12,** 507 (1973); (k) L. Birladeanu, D. L. Harris, and S. Winstein, *J. Am. Chem. Soc.*, **92,** 6387 (1970); (l) J. M. Brown, B. T. Golding, and J. J. Stofko, Jr., *J. Chem. Soc., Chem. Commun.*, 319 (1973); (m) M. S. Baird and C. B. Reese, *Chem. Commun.*, 1519 (1970).

(5) (a) E. Vedejs, R. A. Shepherd, and R. P. Steiner, *J. Am. Chem. Soc.*, **92,** 2158 (1970); (b) K. Hojo, R. T. Seidner, and S. Masamune, *ibid.*, **92,** 6641 (1970); (c) T. J. Katz, J. J. Chung, and N. Acton, *ibid.*, **92,** 6643 (1970).

(6) The diazo ketone **8c** is available from cycloheptatrienylacetic acid[7] by Arndt–Eistert homologation, and treatment with thionyl chloride and then diazomethane.

(7) G. R. Jurch, Jr., and T. G. Traylor, *J. Am. Chem. Soc.*, **88,** 5228 (1966).

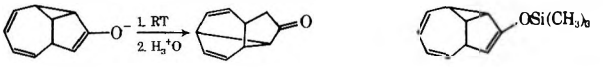
(8) M. Jones, Jr., W. Ando, M. E. Hendrick, A. Kluczycki, Jr., P. M. Howley, K. F. Hummel, and D. S. Malament, *J. Am. Chem. Soc.*, **94,** 7469 (1972).

(9) L. S. Melvin, Jr., and B. M. Trost, *J. Am. Chem. Soc.*, **94,** 1790 (1972).

(10) Intramolecular free radical–olefin cyclization has been observed previously in the chromous acetate reduction of steroidal bromohydrins: D. H. R. Barton, N. K. Basu, R. H. Hesse, F. S. Morehouse, and M. M. Pechet, *J. Am. Chem. Soc.*, **88,** 3016 (1966). Zinc reduction of the same bromohydrins gives reductive elimination to the olefin: J. Fried and E. F. Sabo., *ibid.*, **79,** 1130 (1957).

(11) H. Christol, J. Coste, and F. Plenat, *Ann. Chim. (Paris)*, **4,** 105 (1969); J. C. Davis, Jr., and T. V. van Auken, *J. Am. Chem. Soc.*, **87,** 3900 (1965).

(12) The best method for converting **4b** into **22** is to form the enolate of **4b** at −70 °C and allow it to come to 0 °C for a few minutes. Aqueous quenching then results in **22** as the sole product. Other examples of anionic counterparts to thermal rearrangements have been reported which are perhaps pertinent.[13] We have observed an apparent enolate Cope rearrangement



ii iii iv

of ii at room temperature. The same ketone iii is also obtained from the enol silane iv (20 h, room temperature). Attempted rearrangement of the enolate derived from **9b** at room temperature resulted in degradation.

(13) M. J. Goldstein and S. A. Kline, *Tetrahedron Lett.*, 1085 (1973).

(14) J. T. Groves and B. S. Packard, *J. Am. Chem. Soc.*, **94,** 3252 (1972); M. J. Goldstein and S.-H. Dai, *ibid.*, **95,** 933 (1973).

(15) (a) O. L. Chapman and R. A. Fugiel, *J. Am. Chem. Soc.*, **91,** 215 (1969). (b) **Note Added in Proof.** It has recently been shown that a ketone corresponding to **5** (X, Y, = O) undergoes a retro-Cope rearrangement.[15c] Thus, thermodynamic factors may be responsible for the failure of **4b, 21, 27, 28,** and **29** to rearrange to derivatives of **5**. (c) R. Aumann, *Angew, Chem.*, **88,** 375 (1976).

(16) J. A. Pettus, Jr., and R. E. Moore, *J. Am. Chem. Soc.*, **93,** 3087 (1971); W. Pickenhagen, F. Naef, G. Ohloff, P. Mueller, and J. C. Perlberger, *Helv. Chim. Acta,* **56,** 1868 (1973).

(17) K. Conrow, *Org. Synth.*, **43,** 101 (1963).

(18) T. J. DeBoer and H. J. Backer, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 943.

(19) K. Conrow, *J. Am. Chem. Soc.*, **81,** 5461 (1959).

(20) K. Alder and H. H. Molls, *Chem. Ber.*, **89,** 1960 (1956).

Protolytic and Pyrolytic Rearrangements of Polycyclic Methyl Cyclopropyl Ketones

Xavier Creary,* Frances Hudock,[1] Michael Keller, James F. Kerwin, Jr., and Joseph P. Dinnocenzo

Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556

Received July 27, 1976

Certain methyl cyclopropyl ketones containing methylated tricyclo[3.2.1.0^{2,4}] nuclei undergo rapid rearrangement in dilute trifluoroacetic acid to give α,β-unsaturated ketones and cyclic enol ethers. The mechanism is discussed in terms of the cyclopropyl carbinyl to homoallylic rearrangement. Release of strain and stability of the cationic intermediates are thought to contribute to the ease of the rearrangement. Methyl migration appears to be slower than hydride transfer to the initial cationic center. When migration cannot readily occur, internal enol capture results leading to enol ethers. The related thermal rearrangement of these ketones at temperatures greater than 200 °C provides a route to certain γ,δ-unsaturated ketones.

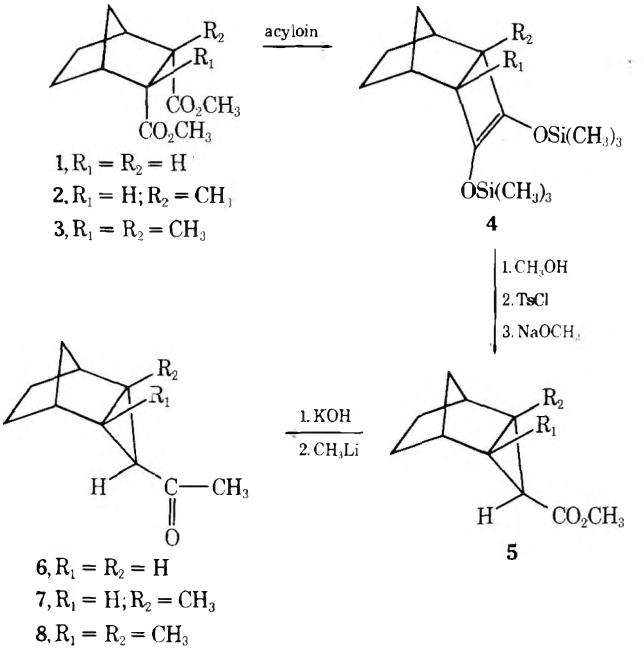
As part of a study of mechanistic pathways by which cyclopropyl systems undergo substitution reactions, we had use for a variety of cyclopropyl containing substrates. As precursors for the preparation of compounds that would undergo substitution reactions, we have developed methods for the formation of certain methyl substituted cyclopropyl ketones.

In our attempts to analyze and convert these ketones to suitable derivatives, we have found that in some cases, acid-catalyzed rearrangements occur with extreme ease. We report here the results of these protolytic rearrangements and also some related thermal rearrangements of some methyl cyclopropyl ketones.

Results and Discussion

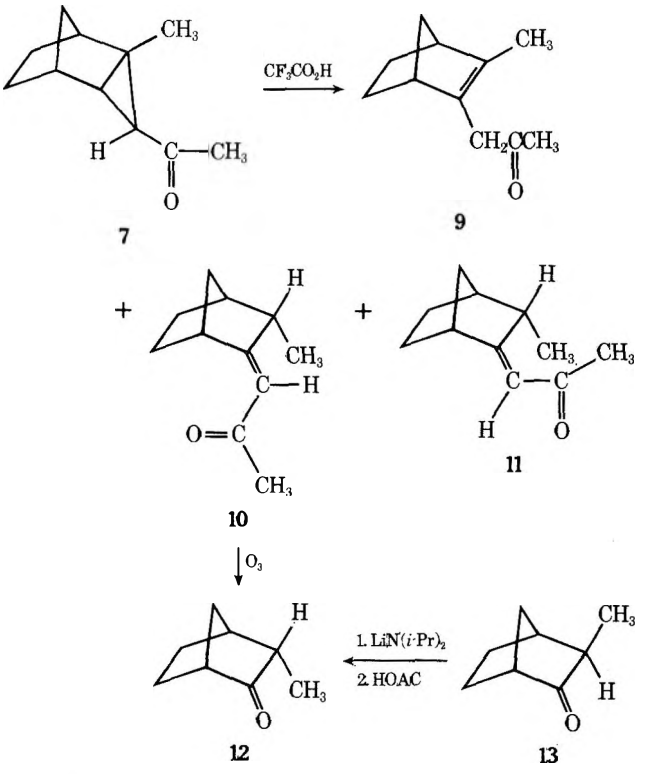
The general procedure outlined in Scheme I has been used to prepare cyclopropyl ketones **6, 7,** and **8.** Acyloin condensation of the appropriate diester followed by methanolysis, tosylate (or mesylate) formation, and Favorskii rearrangement gave the cyclopropyl derivatives **5.** Saponification followed by treatment of the corresponding acid with methyllithium gave methyl ketones **6, 7,** and **8.** We have previously reported on the Baeyer–Villiger oxidation of **6** with peroxytrifluoroacetic acid which gave a high yield of the corresponding acetate.[2] While the preparation of ketones **7** and **8** was straightforward, these ketones appeared to be unstable to gas chromatographic conditions. Additionally, attempted Baeyer–Villiger oxidation with peroxytrifluoroacetic acid gave extremely complex product mixtures. In order to determine the reasons for the unsuccessful peracid oxidation, ketone **7** was treated with dilute trifluoroacetic acid in methylene chloride at room temperature. A rapid exothermic reaction ensued. The products were an isomeric ketone mixture in 93% yield which consisted of trace amounts of ketone **9** and α,β-unsaturated ketones **10** and **11** in a ratio of 5.8:1. A control experiment showed these products to be stable under the reaction conditions.

Scheme I



The structure of the major ketone product **10** was assigned on spectral evidence as well as chemical degradation. Mass spectral data showed the rearrangement products to be isomeric. Infrared and ultraviolet spectral data showed that the two major products, **10** and **11,** were α,β-unsaturated ketones. Ketone **10** showed a single proton resonance at δ 3.92 in the NMR spectrum attributed to the allylic bridgehead proton. The larger than normal downfield shift of this bridgehead proton is attributed to the proximity of the acetyl group in this stereoisomer. The methyl group stereochemistry of **10** was assigned on the basis of ozonolysis, which gave, upon a reductive workup, *endo*-3-methylbicyclo[2.2.1]heptan-2-one (**12**). This ketone could be prepared independently by the formation of the enolate from *exo*-3-methylbicyclo[2.2.1]-heptan-2-one (**13**) with lithium diisopropylamide followed by quenching with acetic acid.[3] The product mixture after protonation consisted of a 3.5:1 mixture of ketones **12** and **13** with **12** predominating.

Scheme II

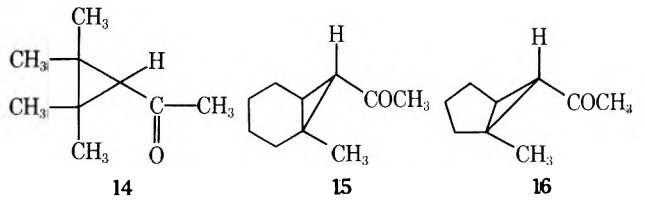


The stereochemistry of the minor α,β-unsaturated ketone **11** is based on mechanistic considerations to be discussed. The allylic bridgehead proton of **11** is not shifted downfield to any unusual extent and suggests an acetyl configuration anti to the bridgehead proton. Unfortunately, ozonolysis of **11** gave a complex product mixture and assignment of the methyl group stereochemistry could not be made in this manner.

The structure of ketone **9,** produced in minor amounts, was based on the fact that this isomeric ketone was not α,β-unsaturated. Catalytic hydrogenation gave the same product as hydrogenation of **10.** Spectral comparison and gas chromatographic retention time ruled out isomeric ketone **30** as being involved in the trifluoroacetic acid catalyzed rearrangement of **7.** Hence the most probable structure of the minor rearrangement product is given by **9.**[4]

These trifluoroacetic acid catalyzed rearrangement products offer an explanation for the unsuccessful attempt to oxidize **7** with peroxytrifluoroacetic acid. Apparently the trifluoroacetic acid produced in the formation of peracid from hydrogen peroxide and trifluoroacetic anhydride and as a by-product of oxidation processes catalyzes the rearrangement of **7.** These rearrangements are apparently faster than Baeyer–Villiger oxidation despite the presence of large amounts of potassium dihydrogen phosphate in the reaction medium.

Acids are known to catalyze rearrangement of cyclopropyl ketones.[5] However, the conditions required to promote these rearrangements are generally quite strenuous. We were therefore surprised at the ease with which rearrangement of **7** occurred. Under the same conditions, no rearrangement of **6, 14, 15,** or **16** occurred. Treatment of **6** with toluenesulfonic acid in refluxing chloroform does not even promote rearrangement. Yet **7** rearranges in 0.1 M trifluoroacetic acid at room temperature. The facile rearrangement of **7** is apparently a result of two factors: the stability of the cation initially

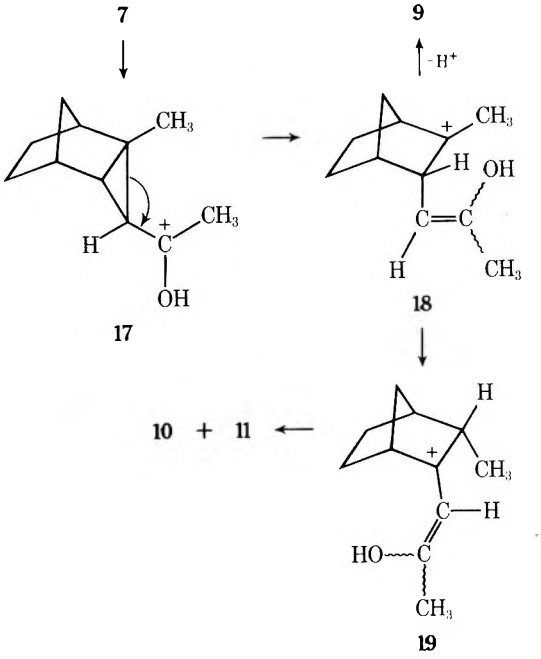


14 15 16

produced and the strain relieved in rearrangement of this system. Lack of rearrangement of **6** illustrates this first factor. Lack of rearrangement of the less strained cyclopropyl ketones **14, 15,** and **16** demonstrates the importance of the latter strain factor. The strain energies of **15** and **16** may be approximated by those of bicyclo[4.1.0]heptane and bicyclo[3.1.0]hexane, which are 30 and 34 kcal/mol, respectively.[5d] Although there are no theoretical estimates or experimental values for the strain energy associated with the *endo*-tricyclo[3.2.1.$0^{2,4}$]octyl system, the value is expected to be *greater* than that of the former two systems. The fusion of the norbornyl system (17 kcal/mol strain energy) to the cyclopropyl ring should result in a strain energy of **7** between that of **16** and a bicyclo[2.1.0]-pentyl system (57 kcal/mol).[5d] The extra ground state strain associated with the cyclopropyl ring of **7** provides a rationale for its more rapid acid-catalyzed rearrangement.

The mechanistic pathway shown in Scheme III illustrates some interesting features of the rearrangement. The cyclo-

Scheme III



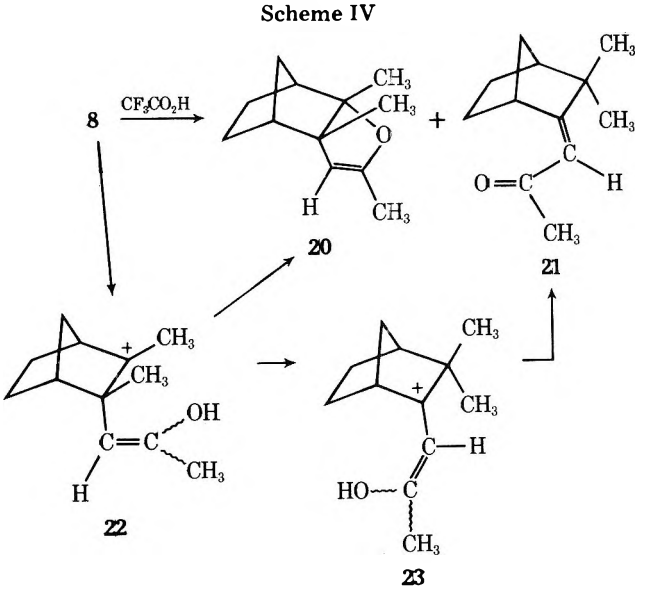
17 18 19

propyl carbinyl, homoallylic rearrangement of the protonated ketone **17** gives cation **18**. Exo hydride migration to give allylic cation **19** is apparently the major fate of **18**, and consistent with the expected facile exo 2,3-hydride shift in norbornyl cations.[6] This exo hydride shift accounts for the observed endo methyl stereochemistry in the major rearrangement product, **10**, and strongly suggests a similar methyl stereochemistry in **11**. Apparently methyl substitution at carbon 3 results in allylic cation **19** being produced in preference to the isomer with the larger group syn to the endo methyl group.[7] Deprotonation of **19** results in **10** while deprotonation of the isomeric allylic cation yields the minor isomeric α,β-unsaturated ketone **11**.[8]

Ketone **8** also rearranges rapidly in dilute trifluoroacetic acid solution. In this case the products obtained were enol ether **20** and α,β-unsaturated ketone **21** in a ratio of 1:2.6, respectively.

The structure of ketone **21** was based on its infrared and

Scheme IV



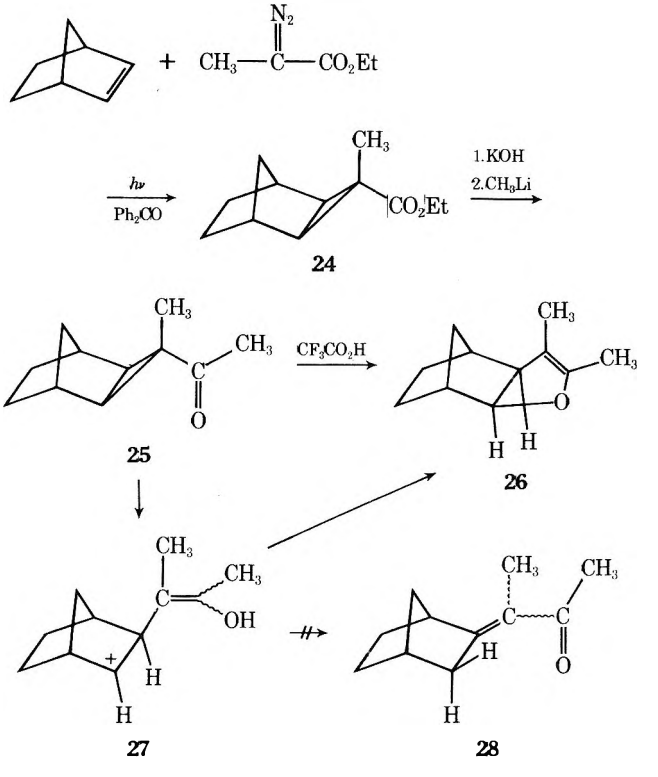
20 21 22 23

NMR spectral properties. The NMR spectrum showed an olefinic proton singlet at δ 5.78, a single proton multiplet at δ 3.95, attributed to the allylic bridgehead proton, and methyl singlets at δ 2.09 and δ 1.06. Apparently the geminal dimethyl substitution at carbon 3 results in formation of ketone **21** with the exclusion of the isomeric α,β-unsaturated ketone.

The structure of enol ether **20** was based on mass spectral, infrared, and NMR data. The mass spectrum showed that the product is isomeric with ketone **8** while the infrared spectrum showed the presence of a carbon–carbon double bond at 5.97 μ. The NMR spectrum showed an olefinic proton at δ 4.12, a methyl doublet at δ 1.70, and methyl singlets at δ 1.17 and 0.98. The unusual formation of enol ether **20** is in line with a lower propensity for exo methyl migration (relative to hydride) in this norbornyl system.[9] Competing with methyl migration in cation **22** is intramolecular cyclization to give **20**. This product is formally the result of a carbonyl analogue of the vinylcyclopropane to cyclopentene rearrangement.[10]

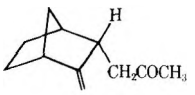
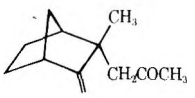
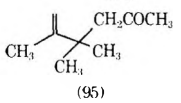
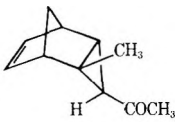
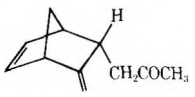
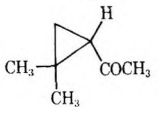
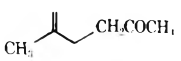
Ketone **25**[11] can be prepared, as shown in Scheme V, via

Scheme V



24 25 26 27 28

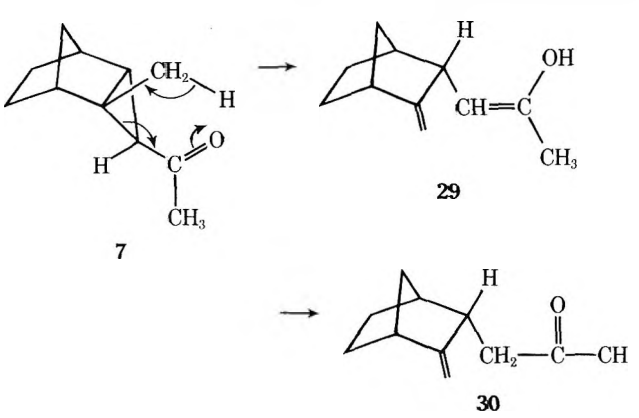
Table I. Rates of Rearrangement in *n*-Dodecane at 210 °C

Registry no.	Ketone	Half-life, h	Product (%)[c]
42856-13-3	7	1.5	 (83)
60802-85-9	8	0.13	 (94)
60802-86-0	14	1.2	 (95)
28465-15-8	 31	2.3[a]	 (84)
872-75-3	 32	0.11[b]	

[a] See ref 15. [b] Calculated from data of Roberts, ref 14. [c] Pyrolysis of neat ketone; isolated yield after distillation.

ester **24**, produced in the benzophenone sensitized addition of ethyl diazopropionate to norbornene.[12] In this system, we sought to determine the effect of increased steric strain due to an unfavorable interaction of the 3-methyl group with the methylene bridge. We also wanted to evaluate the effectiveness of potential endo hydride migration.[13] Slightly more strenuous conditions are required to promote rearrangement of **25**. Refluxing in 0.4 M trifluoroacetic acid in methylene chloride promoted rearrangement despite the necessity of involving a relatively unstable secondary cation, **27**. A low yield of enol ether **26** was produced as the sole isolable product. No α,β-unsaturated ketones, **28**, which would be a result of endo hydride migration, are observed. These observations reinforce the belief that endo hydride migration in norbornyl systems is a relatively slow process.[6,9]

In addition to undergoing facile acid-catalyzed rearrangements, ketones **7** and **8** are also thermally labile as is ketone **14**. At temperatures above 200 °C, we have observed rearrangements yielding γ,δ-unsaturated ketones. This process has been discussed by Roberts[14] and is considered to be a concerted thermal process giving products analogous to the Norrish type II photochemical process. Rearrangement of **7** gave ketone **30** via **29**. It is interesting to note that none of this ketone is produced in the acid-catalyzed rearrangement



process. Table I gives rates of this rearrangement and analogous processes in *n*-dodecane solvent as monitored by NMR spectroscopy. Rates of thermal rearrangement are all comparable, differing only by a factor of 20. Reasons for the slightly more facile rearrangements of **8** and **32** are not well understood. Statistical correction of the rate constants for **8** and **14** does not further simplify the data. However, the general rearrangement appears to be applicable for the preparation of the γ,δ class of unsaturated ketones.

Experimental Section

Acyloin Condensation of *endo*-2,3-Dicarbomethoxy-2-methylbicyclo[2.2.1]heptane. Sodium metal (23 g) was dispersed in 1 l. of dry, refluxing toluene in a Morton flask and 103.4 g of chlorotrimethylsilane was added. A solution of 45.1 g of *endo*-2,3-dicarbomethoxy-2-methylbicyclo[2.2.1]heptane (from hydrogenation, esterification of the methyl maleic anhydride, cyclopentadiene adduct) in 530 ml of toluene was added dropwise using a Hirsch dropping funnel over a 15-h period. Refluxing was continued for 1 h and the mixture was then filtered through Celite. Solvents were removed by distillation at reduced pressure. The crude product was distilled through a Vigreux column to give 53.7 g (73%) of the corresponding bis(trimethylsilyl) ether: bp 65–80 °C (0.15 mm); NMR (CCl_4) δ 2.15 (2 H, m), 1.9–1.4 (3 H, m), 1.3 (4 H, m), 1.12 (3 H, s), 0.10 (18 H, d).

Anal. Calcd for $C_{16}H_{30}O_2Si_2$: C, 61.87; H, 9.74. Found: C, 61.79; H, 9.75.

Preparation of *exo*-2-Methyl-3-carbomethoxytricyclo-[3.2.1.0^{2,4}]octane. A solution of 20.4 g of the bis(trimethylsilyl) ether prepared above in 100 ml of methanol was refluxed for 10 h. The methanol was removed at reduced pressure. The NMR spectrum of the crude α-hydroxy ketone showed a mixture of isomers. The major isomer (approximately 2 parts) showed a carbinyl proton doublet at δ 4.91, J = 9 Hz, and is presumed to be *endo*-3-hydroxy-5-methyltricyclo[4.2.1.0^{2,5}]nonan-4-one on the basis of this coupling constant. The minor isomer (approximately 1 part) shows a carbinyl proton doublet at δ 4.47, J = 4 Hz, and is presumably *endo*-3-hydroxy-2-methyltricyclo[4.2.1.0^{2,5}]nonan-4-one on the basis of the smaller coupling constant. The crude mixture of hydroxy ketones was converted directly to a tosylate mixture by treatment with 14.2 g of tosyl chloride in 90 ml of pyridine for 2 days at −5 °C. The pyridine solution was taken up into ether and water and the organic extract was washed with dilute hydrochloric acid to remove the pyridine. After drying, the solvent was removed by rotary evaporator. The NMR of the crude oil showed a mixture of tosylate (doublets at δ 5.36, J = 9 Hz, and 4.90, J = 3 Hz).

The crude tosylate mixture was dissolved in 40 ml of methanol and added to a solution of sodium methoxide prepared from 15.7 g of sodium in 240 ml of methanol at room temperature. The solution was slowly brought to reflux and reflux was continued for 2.5 h. The mixture was then cooled and taken up into ether and water containing 40 ml of acetic acid. The ether extract was washed with water and saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was removed by distillation through a Vigreux column and the residue was distilled to give 6.86 g [58% based on bis(trimethylsilyl) ether] of ring contracted ester: bp 65 °C (0.15 mm); NMR (CCl_4) δ 3.63 (3 H, s), 2.6–1.2 (9 H, m), 1.27 (3 H, s); mass spectroscopic molecular weight, 180.1156 (calcd for $C_{11}H_{16}O_2$, 180.1150).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.42; H, 9.02.

Preparation of *exo*-2-Methyltricyclo[3.2.1.0^{2,4}]octane-3-carboxylic Acid. A mixture of 4.85 g of 86% potassium hydroxide, 30 ml of water, 30 ml of methanol, and 6.86 g of *exo*-2-methyl-3-carbomethoxytricyclo[3.2.1.0^{2,4}]octane was refluxed for 2 h. Approximately 40 ml of the solvent was removed by distillation and the residue was added dropwise with stirring to a cold solution of 16 ml of concentrated hydrochloric acid in 150 ml of water. The precipitated acid was collected on a Buchner funnel and air dried to give 5.71 g (90%) of carboxylic acid: mp 139–144 °C; mass spectroscopic molecular weight 166.0990 (calcd for $C_{10}H_{14}O_2$, 166.0994).

Preparation of 7. Methyllithium (8 ml of a 1.7 M solution in ether) was diluted to 15 ml with ether and added dropwise to a solution of 1.00 g of *exo*-2-methyltricyclo[3.2.1.0^{2,4}]octane-3-carboxylic acid in 10 ml of ether at 0 °C. The mixture was brought to reflux for 1 h and cooled to room temperature and excess ethyl acetate was added dropwise to destroy excess methyllithium. Water was then added, the organic phase was separated and dried over anhydrous sodium sulfate, and the solvent was removed by distillation through a Vigreux column.

The residue was distilled to give 0.851 g (86%) of ketone **7**: bp 65–68 °C (0.8 mm); NMR (CCl_4) δ 2.6–1.0 (broad multiplets) with sharp singlets at 2.15 and 1.13; mass spectroscopic molecular weight, 164.1215 (calcd for $C_{11}H_{16}O$, 164.1201).

Preparation of *endo*-2,3-Dicarbomethoxy-2,3-dimethylbicyclo[2.2.1]heptane. Lithium diisopropylamide was prepared from 44.5 g of diisopropylamine and 184 ml of 2.4 M butyllithium in hexane. The solvent was removed under vacuum and the solid residue was dissolved in 250 ml of tetrahydrofuran under nitrogen. The mixture was cooled to −78 °C and a solution of 76 g of *endo*-2,3-dicarbomethoxy-2-methylbicyclo[2.2.1.]heptane in 150 ml of tetrahydrofuran was added dropwise. After stirring for 4 h at −78 °C, a solution of 124 g of methyl iodide in 420 ml of dimethyl sulfoxide was added while warming to room temperature. After stirring at room temperature for 4 h, the entire mixture was taken up into ether and water. The aqueous phase was extracted with an additional portion of ether and the combined ether extracts were washed with dilute hydrochloric acid to remove the amine. After washing with 2 portions of water and saturated sodium chloride solution, the organic phase was dried over anhydrous sodium sulfate and the solvent was removed by rotary evaporator. Gas chromatographic analysis indicated about 80% conversion to the alkylated diester. The mixture was recycled in portions to give samples of greater than 95% *endo*-2,3-dicarbomethoxy-2,3-dimethylbicyclo[2.2.1]heptane, bp 110–115 °C (0.6 mm), with traces of unalkylated diester as the only impurity: NMR (CCl_4) δ 3.53 (6 H, s), 2.2–1.0 (8 H, m), 1.23 (6 H, s).

Acyloin Condensation of *endo*-2,3-Dicarbomethoxy-2,3-dimethylbicyclo[2.2.1]heptane. Sodium metal (14 g) was dispersed in 600 ml of refluxing toluene and 62 g of chlorotrimethylsilane was added followed by a solution of 28.5 g of diester in 330 ml of toluene over a 9-h period. Reflux was continued for 13 h. The workup was identical with that previously described. After removal of the toluene by distillation at reduced pressure, the product was distilled to give 31.2 g (81%) of the corresponding bis(trimethylsilyl) ether: bp 78–90 °C (0.15 mm); NMR (CCl_4) δ 1.9–1.2 (8 H, m), 1.02 (6 H, s), 0.18 (18 H, s).

Anal. Calcd for $C_{17}H_{32}O_2Si_2$: C, 62.90; H, 9.94. Found: C, 63.14; H, 9.83.

Preparation of *exo*-2,4-Dimethyl-3-carbomethoxytricyclo[3.2.1.$0^{2,4}$]octane. A solution of 15.4 g of the bis(trimethylsilyl) ether prepared above and 75 ml of methanol was refluxed for 8 h and the solvent was removed under vacuum. The clear oil was converted directly to the tosylate by treatment with 11.73 g of *p*-toluenesulfonyl chloride in 70 ml of pyridine at 0 °C. After 3 days the entire mixture was taken up into ether and water. The ether extract was washed with hydrochloric acid to remove pyridine and dried in the usual manner. Solvent was removed by rotary evaporator. The crystalline product was washed with low-boiling petroleum ether and collected on a Buchner funnel. The yield of tosylate was 10.92 g (68%), mp 92–93 °C.

A solution of sodium methoxide was prepared from 9.2 g of sodium and 130 ml of methanol. The crude tosylate obtained above was added to the cold solution which was gradually brought to reflux. Reflux was continued for 2.5 h. The mixture was taken up into water and ether containing 24 ml of acetic acid. After a standard aqueous workup, the ether solvent was removed by distillation through a Vigreux column. The residue was distilled to give 3.78 g (59%) of ring contracted ester: bp 73 °C (0.15 mm); NMR (CCl_4) δ 3.53 (3 H, s), 2.09 (2 H, m), 1.9–1.1 (7 H, m), 1.20 (6 H, s). The mass spectrum showed a molecular ion at *m/e* 194.

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.57; H, 9.30.

Preparation of *exo*-2,4-Dimethyltricyclo[3.2.1.$0^{2,4}$]octane-3-carboxylic Acid. The procedure was analogous to that previously described for the monomethylated carboxylic acid. Saponification of 2.24 g of ester with 1.3 g of potassium hydroxide in 6 ml of methanol and 8 ml of water gave 2.06 g (99%) of *exo*-2,4-dimethyltricyclo[3.2.1.$0^{2,4}$]octane-3-carboxylic acid: mp 162–164 °C; mass spectroscopic molecular weight, 180.1153 (calcd for $C_{11}H_{16}O_2$, 180.1150).

Preparation of 8. A solution of 1.2 g of *exo*-2,4-dimethyl-3-carbomethoxytricyclo[3.2.1.$0^{2,4}$]octane in 15 ml of ether was cooled in ice as 9 ml of 1.8 M methyllithium, diluted with 10 ml of ether, was added dropwise. The mixture was refluxed for 1.5 h and ethyl acetate was added to destroy excess methyllithium. Water was added and a standard aqueous workup followed. Solvent was removed by distillation through a Vigreux column. The residue was distilled to give 1.06 g (89%) of ketone **8**: bp 55–56 °C (0.15 mm); NMR (CCl_4) δ 2.11 (3 H, s), 2.05–1.15 (8 H, m), 1.16 (6 H, s). The mass spectrum of **8** showed a molecular ion at *m/e* 178.

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.58; H, 10.47.

Acid-Catalyzed Rearrangement of 7. Ketone **7** (114 mg) was stirred at room temperature for 15 min with 6 ml of 0.4 M trifluoroacetic acid in methylene chloride. The mixture was then taken up into ether and water, washed with potassium carbonate solution and saturated sodium chloride solution, and dried over anhydrous sodium sulfate. Solvents were removed by distillation through a Vigreux column. The residue was distilled to give 106 mg (93%) of a mixture of ketones **9, 10,** and **11**. Samples of all three ketones were isolated by preparative gas chromatography using a 6-ft, 15% Carbowax 20M on Chromosorb P column at 145 °C. The major product of longest retention time, ketone **10**, had the following NMR spectrum (CCl_4): δ 5.81 (1 H, d, J = 2 Hz), 3.92 (1 H, m), 2.7–1.2 (11 H, m with sharp singlet at 2.07), 1.04 (3 H, d, J = 6.5 Hz). The UV spectrum showed λ_{max} at 248 nm (ε 13 400); IR $\nu_{C=O}$ and $\nu_{C=C}$ complex with absorptions at 5.91, 6.02, and 6.17 μ. The mass spectrum of **10** showed a molecular ion at *m/e* 164.

The product of intermediate retention time, ketone **11**, had the following NMR spectrum (CCl_4): δ 6.03 (1 H, d, J = 2.5 Hz), 2.9–1.2 (12 H, m with sharp singlet at 2.06), 1.08 (3 H, d, J = 7 Hz); IR $\nu_{C=O}$ and $\nu_{C=C}$ at 5.93 and 6.17 μ. The UV spectrum of an equimolar mixture of **11** and **i** showed λ_{max} at 247 nm (ε 10 400). The mass spectrum of **11** showed a molecular ion at *m/e* 164.

The product of shortest retention time, ketone **9**, showed a molecular ion at *m/e* 164 in the mass spectrum. The infrared showed $\nu_{C=O}$ at 5.82 μ. Ketone **9** was produced in only trace amounts. The ratio of **10** to **11** was 5.8:1 as determined by NMR of the product mixture. A control experiment showed that separate treatment of each of the products with 0.4 M trifluoroacetic acid in methylene chloride at room temperature for 15 min did not result in their interconversion. The rearrangement of **7** was also found to occur rapidly in 0.1 M trifluoroacetic acid in methylene chloride at room temperature.

Ozonolysis of 10. A 74-mg sample of ketone **10**, isolated by preparative gas chromatography, in 3 ml of methanol was cooled to −78 °C and ozonized exhaustively. A solution of sodium iodide and sodium thiosulfate was added and the mixture was taken up into ether and water. Gas chromatographic analysis of the mixture on a 6-ft, 10% XE 60 on Chromosorb P column showed three minor products of shorter retention time than the major product, ketone **12**. Ketone **12** was isolated by preparative gas chromatography and identified by infrared spectral comparison with an authentic sample prepared as described below. The major impurity is a methyl ester, with a molecular ion at *m/e* 156, which is formally a result of addition of methanol across the 2,3 bond of **12**.

Preparation of 12 from *exo*-3-Methylbicyclo[2.2.1]heptan-2-one (13). A solution of 0.5 g of *exo*-3-methylbicyclo[2.2.1]heptan-2-one (**13**) (prepared by methylation of the enolate anion derived from norcamphor with methyl iodide) in 3 ml of tetrahydrofuran was added dropwise to a solution at −78 °C of lithium diisopropylamide in tetrahydrofuran prepared from 0.69 g of diisopropylamine and 3.1 ml of 2.17 M butyllithium in hexane. The solution was allowed to warm to approximately −40 °C for 20 min and recooled to −78 °C. A solution of 0.6 g of acetic acid in ether was then added dropwise. The mixture was warmed to room temperature and taken up into ether and water and the ether extract was washed with dilute hydrochloric acid. The organic phase was then washed with saturated sodium chloride solution and dried over sodium sulfate. Gas chromatographic analysis showed the appearance of a new product, ketone **12**, along with some unchanged **13**. A sample of **12** was isolated by preparative gas chromatography and was identical with the ketone product produced in the ozonolysis of **10**. The ratio of **12** to **13** was 3.55:1 as determined by gas chromatography.

Acid-Catalyzed Rearrangement of 8. A mixture of 164 mg of ketone **8** and 8 ml of 0.2 M trifluoroacetic acid in methylene chloride was held at room temperature for 12 min and then taken up into ether and water. After washing with dilute potassium carbonate solution and drying, the solvents were removed by distillation through a Vigreux column. The residue was distilled to give 105 mg (65%) of a mixture of enol ether **20** and ketone **21**. Samples of each product were isolated by preparative gas chromatography on a 6-ft, 15% Carbowax on Chromosorb P column at 150 °C. The minor product of shorter retention time, **20**, had the following NMR spectrum (CCl_4): δ 4.10 (1 H, m), 2.05 (1 H, m), 1.83 (1 H, m), 1.71 (3 H, d, J = 1.3 Hz), 1.8–1.2 (6 H, m), 1.17 (3 H, s), 0.98 (3 H, s); IR $\nu_{C=C}$ 5.97 μ; mass spectroscopic molecular weight 178.

The major product of longest retention time, ketone **21**, had the following NMR spectrum (CCl_4): δ 5.78 (1 H, bs), 3.95 (1 H, m), 2.08 (3 H, s), 2.07–1.10 (7 H, m), 1.06 (6 H, s); IR $\nu_{C=O}$ and $\nu_{C=C}$ absorptions at 5.92, 6.02, and 6.61 μ. The ratio of ketone **21** to enol ether **20**

was 2.58:1 as determined by NMR.

Preparation of 24. A mixture of 0.54 g of ethyl diazopropionate, 0.87 g of benzophenone, 17.4 g of norbornene, and 2 ml of pentane was irradiated with a set of General Electric sun lamps for 6 h during which time the yellow color faded substantially. The norbornene was removed by distillation through a Vigreux column. The crude ester **24** was separated from benzophenone by distillation through a Vigreux column. The yield of ester **24** was 0.55 g (69%): bp 54–57 °C (0.08 mm); NMR (CCl_4) δ 4.01 (2 H, q, J = 7 Hz), 2.42 (2 H, m), 1.42 (3 H, s), 1.4–1.0 (7 H, m), 1.20 (3 H, t, J = Hz), 0.83–0.50 (1 H, m). The mass spectrum of **24** showed a molecular ion at m/e 194.

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.42; H, 9.29.

Saponification of 24. A mixture of 1.11 g of ester **24,** 0.78 g of potassium hydroxide, 6 ml of water, and 6 ml of methanol was refluxed for 3.5 h. The remainder of the procedure was analogous to that previously described. The yield of crude acid was 0.70 g (74%): mp 131–133 °C; NMR (CCl_4) δ 12.38 (1 H, bs), 2.44 (2 H, m), 1.7–1.2 (11 H, m with sharp singlet at 1.43), 0.9–0.5 (1 H, m); mass spectroscopic molecular weight, 166.0992 (calcd for $C_{10}H_{14}O_2$, 166.0994).

Preparation of 25. The same general procedure was followed as described for the preparation of **7** and **8** from the corresponding acids. Reaction of 0.72 g of carboxylic acid in 15 ml of ether with 5.6 ml of 1.8 M methyllithium in ether gave 0.64 g (91%) of ketone **25:** bp 66–68 °C (0.3 mm); NMR (CCl_4) δ 2.44 (2 H, m), 2.02 (3 H, s), 1.7–1.0 (11 H, m with a sharp singlet at 1.44), 0.90–0.55 (1 H, m); mass spectroscopic molecular weight, 164.1194 (calcd for $C_{11}H_{16}O$, 164.1201).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.20; H, 9.82.

Acid-Catalyzed Rearrangement of 25. A solution of 300 mg of ketone **25** in 8 ml of 0.4 M trifluoroacetic acid in methylene chloride was refluxed for 15 min and then worked up in the manner previously described. Gas chromatographic analysis revealed the presence of a single product and no starting ketone. The product, enol ether **26,** was isolated by preparative gas chromatography using a 6-ft, 15% Carbowax 20M on Chromosorb P column at 140 °C and had the following NMR spectrum (CCl_4): δ 4.17 (1 H, d, J = 8 Hz), 2.7–1.9 (3 H, m), 1.60 (3 H, m), 1.48 (3 H, m), 1.5–0.8 (6 H, m); IR $\nu_{C=C}$ at 5.87 μ. The mass spectrum showed a molecular ion at m/e 164.

Thermal Rearrangement of Methyl Cyclopropyl Ketones. In a typical procedure, 92 mg of ketone **7** and 21 mg of biphenyl (internal standard) were dissolved in n-dodecane and sealed in an NMR tube under nitrogen. The tube was immersed in an oil bath at 210 ± 1 °C. In all cases rates were monitored by following the appearance of the olefinic protons as a function of time. Thermal rearrangements in which products were isolated were carried out on the neat liquids in sealed tubes at 220 °C.

Registry No.—**2,** 60802-87-1; **3,** 60802-88-2; **4** (R_1 = H; R_2 = CH_3), 60802-89-3; **4** (R_1 = R_2 = CH_3), 60802-90-6; **5** (R_1 = H; R_2 = Me), 60802-91-7; **5** (R_1 = R_2 = CH_3), 60802-92-8; **9,** 60802-93-9; **10,** 60802-94-0; **11,** 60828-27-5; **20,** 17812-18-9; **21,** 60802-95-1; **24,** 60802-96-2; **24** free acid, 60802-97-3; **25,** 42856-10-0; **26,** 60802-98-4; i, 60828-28-6; *endo*-3-hydroxy-5-methyltricyclo[4.2.1.$0^{2,5}$]-nonan-4-one, 60802-99-5; *endo*-3-hydroxy-2-methyltricyclo-[4.2.1.$0^{2,5}$]nonan-4-one, 60803-00-1; *endo*-3-hydroxy-5-methyltricyclo[4.2.1.$0^{2,5}$]nonan-4-one tosylate, 60803-01-2; *endo*-3-hydroxy-2-methyltricyclo[4.2.1.$0^{2,5}$]nonan-4-one tosylate, 60803-02-3; *exo*-2-methyltricyclo[3.2.1.$0^{2,4}$]octane-3-carboxylic acid, 60803-03-4; *exo*-2,5-dimethyl-*endo*-3-hydroxytricyclo[4.2.1.$0^{2,5}$]nonan-4-one, 60803-04-5; *exo*-2,4-dimethyltricyclo[3.2.1.$0^{2,4}$]octane-3-carboxylic acid, 60803-05-6; ethyl diazopropionate, 6111-99-5; norbornene, 498-66-8; *exo*-2,5-dimethyl-*endo*-3-hydroxytricyclo[4.2.1.$0^{2,5}$]-nonan-4-one tosylate, 60803-06-7; chlorotrimethylsilane, 75-77-4; tosyl chloride, 98-59-9.

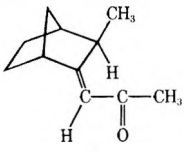
References and Notes

(1) NSF Undergraduate Research Participant, 1975–1976.

(2) X. Creary, *J. Org. Chem.*, **40,** 3326 (1975).

(3) For related examples of kinetic protonation from the less hindered side of enolate anions see (a) H. O. House, B. A. Tefertiller, and H. D. Olmstead, *J. Org. Chem.*, **33,** 935 (1968); (b) H. O. House and T. M. Bare, *ibid.*, **33,** 943 (1968); (c) F. Johnson and S. K. Malhotra, *J. Am. Chem. Soc.*, **87,** 5493, 5513 (1965).

(4) We have found that injection of **7** on a 15% Carbowax on Chromosorb P column at 150 °C also results in rearrangement of **7** to give **9, 10,** and **11** in different ratios than the trifluoroacetic acid catalyzed rearrangement. A fourth ketone, i, is also produced in approximately the same amount as **11.** The structure of i is assigned on the basis of the NMR spectrum of the



i

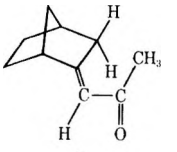
inseparable mixture of **11** and i, which shows a doublet (J = 7 Hz) at δ 1.00 and no unusual downfield shift of the allylic bridgehead proton. The origin of i is unclear as is the origin of the gas chromatographic rearrangement. A trace of "acid" on th column is a prime suspect.

(5) (a) H. M. Walborsky and L. Plonsker, *J. Am. Chem. Soc.*, **83,** 2138 (1961); (b) J. P. Freeman, *J. Org. Chem.*, **31,** 538 (1966); (c) G. Combaut and L. Giral, *Bull. Soc. Chim. Fr.*, 3258 (1969); (d) P. Schleyer, J. E. Williams, and K. R. Blanchard, *J. Am. Chem. Soc.*, **92,** 2377 (1970).

(6) G. D. Sargent in "Carbonium Ions", Vol. III, G. A. Olah and P. v. R. Schleyer, Ed., Wiley, New York, N.Y., 1972, p 1110.

(7) The rearrangements are suggested to proceed through enols **18** and **19.** Although we cannot eliminate the keto forms of these cations, we believe that one of the driving forces for hydride migration from the tertiary cationic center of **18** is the greater stability of allylic cation **19.**

(8) Ketone ii is produced from protonation of the corresponding enolate anion. Steric factors are probably responsible for the predominance of **10** and **21,** in which the acetyl stereochemistry is reversed, in the acid-catalyzed



ii

ketone rearrangement. See J. F. Bunnett, X. Creary, and J. E. Sundberg, *J. Org. Chem.*, **41,** 1707 (1976).

(9) For related rates of hydride and methyl migration under stable ion conditions, see (a) A. J. Jones, E. Huang, R. Haseltine, and T. S. Sorensen, *J. Am. Chem. Soc.*, **97,** 1133 (1975); (b) E. Huang, K. Ranganayakulu, and T. S. Sorensen, *ibid.*, **94,** 1780 (1972).

(10) For leading references see J. S. Swenton and A. Wexler, *J. Am. Chem. Soc.*, **93,** 3066 (1971).

(11) Ketone **25** has been prepared by a much more tedious route; see H. Monti and M. Bertrand, *Tetrahedron Lett.*, 2587 (1970).

(12) An analogous benzophenone sensitized addition to isobutylene has been reported. See M. B. Sohn and M. Jones, Jr., *J. Am. Chem. Soc.*, **94,** 8280 (1972).

(13) Such processes are generally quite unfavorable. See ref 6 and 9.

(14) R. M. Roberts, G. G. Landolt, R. N. Greene, and E. W. Heyer, *J. Am. Chem. Soc.*, **89,** 1404 (1967).

(15) Ketone **31** was prepared by a route analogous to the preparation of **7.** Monti and Bertrand[16] have previously reported the pyrolysis of **31** produced by an alternate method but give no kinetic data.

(16) H. Monti and M. Bertrand, *Tetrahedron Lett.*, 2591 (1970).

The Wolff Rearrangement Approach to the Tricyclo[3.2.0.0^{2,6}]heptane System

Leverett R. Smith[1] and Jerrold Meinwald*

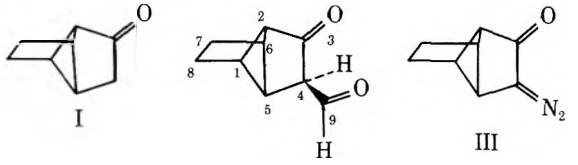
Spencer T. Olin Laboratory, Department of Chemistry, Cornell University, Ithaca, New York 14853

Received August 16, 1976

N,N-Dimethyltricyclo[3.2.0.0^{2,6}]heptane-7-carboxamide (IX) is obtained in low yield from the irradiation of 4-diazotricyclo[3.3.0.0^{2,6}]octan-3-one (III) in the presence of dimethylamine. Diazo ketone III was prepared using Rebek's polymeric tosyl azide from tricyclo[3.3.0.0^{2,6}]octan-3-one (I) via its previously unreported formyl derivative, II. Other products from the irradiation are described, and the ^{13}C NMR spectra of IX and its precursors are tabulated.

A long-standing interest in the chemistry of tricyclo[3.3.0.0^{2,6}]octane derivatives and other strained ring systems[2] led us to investigate the use of such precursors in a ring-contractive entry into the rather more strained tricyclo[3.2.0.0^{2,6}]heptane system, of which we are aware of only one previous example.[3] The earlier derivative was formed by photochemical ring closure of a bicyclic phenyl ketone, a method which appears amenable only to rather limited alteration of functionality; the extensive (if sometimes rather variable) success of the photochemical Wolff rearrangement of α-diazo ketones[4] encouraged us to try this approach. In the course of this project, the ^{13}C NMR spectra of a number of tricyclooctane derivatives were measured, and these we wish to report as well.

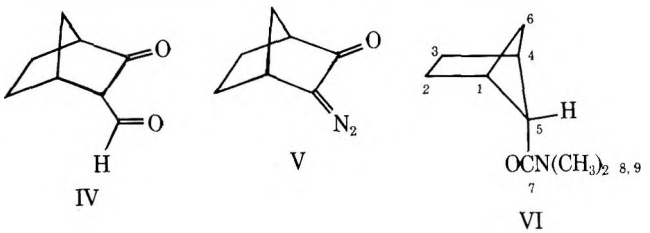
As our starting material, we chose the ketone I, which is readily if not rapidly preparable by a well-established route.[2a,e]



I II III

While conventional formylation procedures were unsuccessful, generation of the enolate anion of I with excess lithium tetramethylpiperidide in THF, followed by quenching in ethyl formate, all at −78 °C under nitrogen,[4c] led to a 32% yield of the pure formyl ketone (II). The NMR and IR spectra of II ($CDCl_3$) both show that II is exclusively in the unenolized dicarbonyl form; this is not unexpected in such a strained system.[4c]

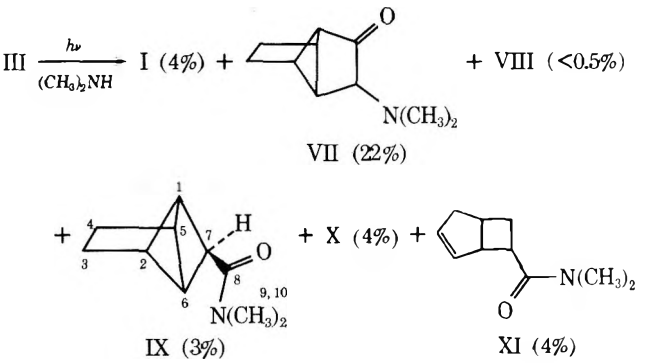
Reaction of II with tosyl azide in methylene chloride[5] gave a material whose IR and NMR spectra indicated the formation of the desired diazo ketone (III), but this product could not be purified without decomposition, either by distillation or other means. The desirability of obtaining III in a less crude state prompted us to prepare some of Rebek's "polymeric tosyl azide" reagent,[6] whose microanalytical and chemical properties (tested on acetylacetone and benzoylacetone in both ethanol and, more conveniently, in methylene chloride) equalled those reported. This reagent was also tested on 3-formylbicyclo[2.2.1]heptan-2-one[4a,7] (IV), and gave a 51% yield of the corresponding diazo ketone[4a,7] (V), whose IR and NMR spectra were satisfactory. Irradiation of the model diazo ketone V under the same sets of conditions as later used with III consistently gave 30–40% of the purified (TLC, silica gel, ether; or by GC) bicyclic amide[8] (VI). After gaining this experience with model compounds, we treated II with the polymeric azide to get up to 50% yield of crude, orange, oily III, which was characterized by its IR and NMR spectra, stored in solution at −20 °C, and used soon after its preparation. We are unable to explain the poor material balance in these latter diazo ketone preparations, except (trivially) to state that the lost material must have become irreversibly bound to the resin.



IV V VI

Irradiation of III was carried out using dimethylamine to trap the ketene intermediate, in the hope of suppressing the acid-catalyzed processes that can occur even in methanol.[4b] The reaction was first tried at low temperature (with dry ice cooling of acetone circulating through the immersion well, the outlet temperature was found to hover within a few degrees of −45 °C) in dimethylamine, then at 10 °C in ca. 4:1 ether/dimethylamine (use of methylene chloride as cosolvent gave appreciable amounts of dimethylamine hydrochloride). The product mixtures were very similar in both cases. After workup and preparative GC, several products were characterized, as summarized in Scheme I (in which the products are listed in order of GC retention times).

Scheme I



III → I (4%) + VII (22%) + VIII (<0.5%); + IX (3%) + X (4%) + XI (4%)

The separation is described in the Experimental Section, but it will be noted here that because compounds IX and X could not be separated from each other on a preparative scale on any of the GC columns used (SE-30, Carbowax 20M, or FFAP), X was selectively and efficiently destroyed by brief bromine treatment[9] to allow isolation of IX. However, X could be partially characterized by its mass spectrum and by comparing the NMR and IR spectra of the two in the mixture with those of IX alone, and seems likely to be structurally related to XI.

Tricyclooctanone I was identified by GC retention time, IR, and NMR spectra. Compound VII, at intermediate retention time, was readily separated from the others. Its IR spectrum showed the presence of a carbonyl group; its NMR spectrum

Table I. ^{13}C NMR Spectrum of IX[a]

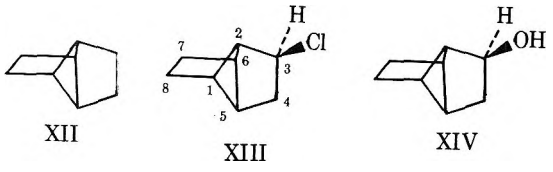
Position	Shift, ppm from Me_4Si	Multiplicity	J_{C-H}, Hz
C-1, C-6	41.3	d	163
C-2	52.0	dtr	142, 3.4
C-3	26.1	tr	130
C-4	27.6	tr	138
C-5	57.7	ddd	152, 12.8, 6.7
C-7	59.8	dtr	155, 13.4
C-8	172.4	s	
C-9, C-10	36.0	(broadened coalesced peak)	

[a] The sample was run in $CDCl_3$ using a JEOL PS-100 instrument, both with and without broad-band proton decoupling.

suggested that the tricyclooctane skeleton was intact and showed a six-proton singlet at δ 2.35, indicating amine *N*-methyl protons. Its mass spectrum confirmed the molecular formula and appeared otherwise consistent with the assigned structure. Products analogous to VII have been observed previously.[4c] Compounds VIII–XI appeared to be a series of dimethylamides. Product VIII was present in such small amount that it was not characterized beyond its mass spectrum.

Compound IX, the goal of our work, showed itself to be an amide on the basis of its IR spectrum (1640 cm^{-1}) and mass spectrum [base peak *m/e* 72, $(CH_3)_2NCO^+$], but its structure was most strikingly demonstrated by its NMR spectrum. This showed a slightly broadened singlet at δ 1.68 (4 H, assigned to the two methylene groups), "W-coupled" doublets at δ 2.63 and 3.22 (J = 6 Hz, H at C-2 and C-5), singlets at 2.50 (H at C-1 and C-6) and 2.92 (H at C-7), and six *N*-methyl protons at 2.96. This is in good qualitative agreement with the analogous spectrum described by Padwa and Eisenberg,[3] with the difference that the carboxamide substitution at C-7 in IX appears to "unbalance" the molecular environment rather less than the hydroxyl/phenyl substitution in their derivative. The ^{13}C NMR spectrum of IX, which also supports the given structure, is summarized in Table I.

Compound X appears to be an unsaturated amide, judging from the NMR spectrum of the IX/X mixture; its mass spectrum is also consistent with this view. The IR spectrum of the mixture is very similar to that of IX alone, except for the inclusion of bands at 3060 and 695 cm^{-1}. Compound XI was assigned the structure shown on the basis of its IR spectrum (amide), a mass spectrum indicating a very facile loss of C_6H_5 (very weak M^+, and a base peak at *m/e* 100 far stronger than any other in the spectrum), and finally on the basis of an NMR shift reagent experiment. Increments of "Resolve-Al EuFOD" (Aldrich) were added until the XI:reagent molar ratio reached ca. 1:1. A single proton (multiplet) moved most rapidly downfield; the olefinic "singlet" gradually became two multiplets, but moved very little; a nonidentical (presumed geminal) pair of protons also moved very little, and the other peaks moved at intermediate rates. Whether the carboxamide group is endo or exo is uncertain, but exo seems plausible because IX has the longest retention time on polar GC columns. The position of the double bond could not be assigned with complete certainty, but mechanistic speculation makes its $\Delta^{2,3}$ position appear likely. Precedents support the general plausibility of such a structure.[3,4c]



XII XIII XIV

The ^{13}C NMR spectra of I and II, and their precursors XII, XIII, and XIV,[2a] as well as that of VI, are summarized in Table II.

Experimental Section

General Remarks. Boiling points are uncorrected. NMR spectra were run in $CDCl_3$ with added Me_4Si on a Varian A-60A instrument, and are reported in δ units. IR spectra were run on a Perkin-Elmer Model 257 instrument, and are reported in cm^{-1}. Low-resolution mass spectra were obtained on a Finnigan 3300 gas chromatograph/mass spectrometer; high-resolution mass spectra were from an AEI MS-902 instrument. Microanalysis was done by Galbraith Laboratories, Inc. "Nitrogen" refers to commercial "prepurified" grade. Analytical GC work was performed with a Varian 2100 instrument, preparative GC using a Varian 200 instrument; glass columns were used throughout.

4-Formyltricyclo[3.3.0.0^{2,6}]octan-3-one (II). Into a solution of 21 ml (125 mmol) of 2,2,6,6-tetramethylpiperidine in 200 ml of dry THF at 0 °C in a nitrogen-filled three-necked (nitrogen inlet, rubber septum, and 125-ml pressure-equalizing addition funnel topped with a straight-bore stopcock) 500-ml flask with magnetic stirring bar was dropped 45 ml of *n*-butyllithium in hexane (Ventron, 2.5 M, 113 mmol) over 15 min. After a further 1.25 h, the ice bath was replaced with a dry ice/ethanol bath, and 90 ml of additional dry THF was injected. Over the next 30 min was added 6.2 g (51 mmol) of I in 70 ml of THF, via the addition funnel, and the resulting solution was stirred for an additional 1.5 h before use. Another dry, nitrogen-filled flask (1000 ml) with magnetic stirrer and 500-ml jacketed addition funnel (capped with a rubber septum) was charged with 17 ml (210 mmol) of dry ethyl formate and 150 ml of dry THF. Both flask and funnel were then chilled with dry ice/ethanol. The ketone enolate solution was transferred (large-bore double-tipped flexible needle) to the cold addition funnel and added dropwise to the ethyl formate solution over the next 1.25 h. After a further 3 h, 100 ml of 10% aqueous HCl was added (froze to a slurry in the flask) and stirring continued without the dry ice bath. After reaching room temperature (ca. 45 min), the layers were separated, and the acidic aqueous layer extracted with 3 × 25 ml of ether. The combined organic phase was washed with 2 × 20 ml of saturated aqueous sodium chloride and evaporated down to a small volume of yellow liquid. This was dissolved in 100 ml of ether and extracted with 7 × 35 ml of 8% aqueous sodium hydroxide; the extracts were poured into 250 ml of cold 10% aqueous hydrochloric acid under 100 ml of ether. After separation, the acid layer was extracted with 3 × 100 ml of ether. After a final wash (saturated sodium chloride solution) the ethereal phase was dried over anhydrous sodium sulfate at −20 °C overnight. Filtration and evaporation followed by vacuum distillation gave 2.47 g (32%) of II: bp 60–65 °C (0.1 Torr); IR ($CDCl_3$) 2980 s, 2930 w, 2890 m, 2840 w, 2740 w, 1757 vs, 1710 vs, 1650 cm^{-1} w; NMR δ 1.95 (slightly broadened s, 4 H), a series of seven peaks at 2.25–3.10 (4 H), 3.52 (sl br s, 1 H), and 9.80 (d, J = 1.5 Hz, 1 H); mass spectrum (EI) *m/e* (rel intensity) 150 (2), 123 (3), 122 (36), 121 (20), 107 (23), 106 (22), 104 (19), 103 (22), 95 (12), 94 (74), 93 (84), 92 (11), 91 (86), 81 (54), 80 (36), 79 (80), 78 (73), 77 (100), 68 (41), 67 (26), 66 (54), 65 (38), 63 (14), 55 (33), 53 (31), 51 (25), 41 (12). Anal. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 71.92; H, 6.87.

4-Diazotricyclo[3.3.0.0^{2,6}]octan-3-one (III). Mixed together and allowed to stir for 13 h at room temperature were 1.59 g (10.6 mmol) of II, 8.0 g (ca. 25 mequiv of azide) of polymeric tosyl azide,[6] 40 ml of methylene chloride (AR, distilled from calcium hydride), and 12 ml of purified triethylamine. The mixture was then filtered and the solid reagent washed with several small portions of ether. The combined solution was evaporated, taken up again in ether. The combined solution was evaporated, taken up again in ether (leaving insoluble material behind), dried over anhydrous sodium sulfate, refiltered, and reevaporated to give 0.79 g (50%) of crude orange oil which slowly evolved gas bubbles when completely free of solvent. This material was stored in a few milliliters of ether at −20 °C before use: IR ($CDCl_3$) 3070 vw, 2980 m, 2890 w, 2090 vs, 1745 m, 1695 s, 1650 s, 1400 m, 1330 m, 1155 cm^{-1} m; NMR δ 1.80–2.0 (narrow m, ca. 4 H), 2.15 (d, J = 9 Hz, ca. 1 H), 2.90 (d, J = 9 Hz, ca. 1 H), and 3.2 (sl br s, ca. 2 H), significant contamination was indicated by a series of small absorptions in the ranges 0.9–1.7, 2.5–3.4, and 5.6–5.8.

Irradiation of III. Apparatus for the experiment consisted of a quartz immersion well in a 200-ml reaction vessel with two joints and a magnetic stirring bar. One joint was covered with a rubber septum pierced by a nitrogen inlet tube, and the other was vented to the hood by a bubbler type connection. The assembled apparatus was thoroughly flushed with nitrogen, then the vessel was cooled in dry ice and ca. 50 ml of dimethylamine (Matheson) was condensed in via a tube

Table II[a]

Registry no.	Compd	C-2	C-3	C-4	C-5	C-6	C-1	C-7	C-8	C-9
60803-19-2	II	64.9 (d, 160)	206.3 (s)	62.4 (dd, 135, 20)	47.6 (d, 150)	(53.0 (d, 155	53.3) d, 155)	(24.5 (tr, 130	25.6) tr, 128)	197.7 (dd, 180, 10)
15774-41-1	I	66.1 (d, 155)	213.2 (s)	38.3 (tr, 135)	46.3 (d, 160)	55.2 (d, 150)		25.6 (tr, 135)		
15774-44-4	XIV	56.8 (d, 140)	71.6 (d, 150)	36.3 (tr, 130)	(47.3 (d, 150	48.7 d, 145	51.2) d, 150)	(24.3) (tr, 135)		
15774-47-7	XIII	58.6 (d, 140)	60.0 (d, 155)	38.0 (tr, 130)	(49.5 (d, 150		52.0) d, 145)	(24.3 (tr, 130	25.1) tr, 130)	
250-21-5	XII	50.9 (d, 145)	25.5 (tr, 130)							
60803-20-5	VI	23.8		42.1	49.3	36.0		171.3	(34.7	36.5)

[a] Spectra were run in $CDCl_3$ using a Bruker HX-90 instrument in the FT mode. With the exception of VI, all were run both with and without broad-band proton decoupling; chemical shift reference was the center of the $CDCl_3$ triplet (taken as δ 76.9 from Me_4Si). In parentheses below each value is its multiplicity and C–H coupling constant (in Hz, ±5 Hz); sets in parentheses indicate uncertainty of individual assignments within the sets. Assignments were based on shifts, multiplicities, and coupling constants; where isochrony occurred, intensities were also taken into account, but isochronous signals were not duplicated in the tabulation.

through the septum. Anhydrous ether (150 ml) was syringed in, and the vessel allowed to come to room temperature as excess dimethylamine bubbled out (final volume was ca. 190 ml). Diazo ketone III (0.79 g, 5.3 mmol) in a few milliliters of ether was injected. With stirring, a slow nitrogen stream, and water cooling of the well condenser jacket (outlet temperature 10 °C), the solution was irradiated through Corex using a 450-W Hanovia lamp until small aliquots (withdrawn by syringe) no longer showed the diazo band at 2090 cm^{-1} (about 2 h). Evaporation to an orange, viscous oil was followed by preparative GC (6% SE-30 column) to give I (30 mg, ca. 3%), VII (194 mg, 22%; this also showed a single peak on a 6% Carbowax 20M column), and a mixture of VIII–XI (149 mg). This last fraction was separated further by a 3% FFAP column, giving pure VIII (trace), a mixture of IX and X (72 mg), and pure XI (37 mg, 4%). To get pure IX, the mixture of IX and X in ca. 2 ml of ether was treated with 4% bromine in carbon tetrachloride until the red-orange color persisted, then the mixture was quenched with excess saturated aqueous sodium bisulfite (the whole of this took only 20–30 s). Preparative GC then gave IX (30 mg, ca. 3%). Compound VII: IR (neat) 2970 m, 2930 vw, 2890 w, 2830 w, 2780 w, 1750 s, 1640 vw, 1160 m, 890 cm^{-1} w; NMR δ 1.88 (sl br s, 4 H), 2.30 (s, 2 H), 2.35 (s, 6 H), and 2.43, 2.66, 2.90, 3.03 (totaling 3 H); mass spectrum (EI) *m/e* (rel intensity) 166 (5), 165 (46), 137 (41), 136 (100), 122 (56), 94 (57), 93 (47), 92 (28), 91 (55), 82 (50), 79 (24), 77 (26), 71 (32), 70 (29), 68 (12), 67 (18), 66 (9), 65 (13), 58 (23), 57 (13), 56 (11), 55 (14), 53 (13), 46 (11), 45 (6), 44 (24), 42 (61), 41 (18). High-resolution mass spectrum: Calcd for $C_{10}H_{15}NO$ (M^+): 165.1152. Found: 165.1145. Calcd for $C_9H_{14}N^+$: 136.1125. Found: 136.1109. Compound VIII: mass spectrum (EI) *m/e* (rel intensity) 126 (2), 124 (1), 101 (6), 100 (100), 72 (18), 67 (15), 55 (22), 46 (10). This compound was unaffected by the conditions of bromination used to destroy X. Compound IX: IR (neat) 2960 m, 2880 w, 1640 s, 1495 w, 1455 w, 1410 m, 1400 m, 1160 cm^{-1} m; NMR described in the discussion; mass spectrum (EI) *m/e* (rel intensity) 166 (0.5), 165 (4), 164 (4), 150 (3), 137 (2), 121 (15), 120 (38), 119 (9), 103 (16), 98 (12), 93 (36), 92 (17), 91 (69), 87 (14), 80 (5), 79 (15), 78 (10), 77 (58), 73 (6), 72 (100), 68 (4), 67 (8), 66 (7), 65 (22), 55 (45), 45 (15), 44 (19). High-resolution mass spectrum: Calcd for $C_{10}H_{15}NO$ (M^+): 165.1152. Found: 165.1144. Calcd for $C_3H_6NO^+$: 72.0449. Found: 72.0453. Compound X (from NMR of mixture with IX): δ 5.8 (s, olefinic) and 2.9 and 3.0 (*N*-methyl); mass spectrum (EI) *m/e* (rel intensity) 166 (2), 165 (18), 150 (1), 101 (4), 100 (62), 99 (7), 98 (21), 93 (12), 72 (51), 66 (100), 55 (27), 46 (16), 45 (13), 44 (14). Compound XI: IR (neat) 3060 w, 2960 m, 2860 w, 1650 s, 1500 w, 1450 w, 1400 m, 1155 m, 1050 w, 720 cm^{-1} mw; NMR δ 2.13–2.50 (m, 4 H), 2.88 (s, 3 H), 2.95 (s, 3 H), 3.1–3.5 (m, 3 H), 5.73 (sl br s, 2 H); mass spectrum (EI) *m/e* (rel intensity) 165 (1), 101 (6), 100 (100), 99 (2), 94 (1), 93 (3), 92 (2), 91 (12), 79 (2), 78 (2), 77 (8), 72 (18), 66 (15), 55 (21), 46 (12); (CI, methane) *m/e* 194 (7) ($M + 29^+$), 167 (12), 166 (100), 165 (2), 164 (7), 121 (2), 101 (5), 100 (84), 93 (2), 72 (16), 66 (1). High-resolution mass spectrum: Calcd for $C_{10}H_{15}NO(M^+)$: 165.1152. Found: 165.1149. Calcd for $C_5H_{10}NO^+$: 100.0761. Found: 100.0757. Calcd for $C_3H_6NO^+$: 72.0449. Found: 72.0469.

Acknowledgment. The partial support of this research by a grant (MPS 73-04986) from the National Science Foundation is acknowledged with pleasure. We are also very grateful to Mr. Iwao Miura and Professor Koji Nakanishi of Columbia University for obtaining the ^{13}C spectrum of compound IX for us.

Registry No.—III, 60803-21-6; VII, 60803-22-7; IX, 60803-23-8; XI, 60803-24-9; ethyl formate, 123-38-6; tosyl azide, 938-10-3.

References and Notes

(1) National Science Foundation Graduate Fellow, 1973–1976.
(2) (a) J. Meinwald and B. E. Kaplan, *J. Am. Chem. Soc.*, **89**, 2611 (1967); (b) J. Meinwald and D. A. Aue, *Tetrahedron Lett.*, 2317 (1967); (c) J. Meinwald and D. N. Schmidt, *J. Am. Chem. Soc.*, **91**, 5877 (1969); (d) J. Meinwald and H. Tsuruta, *ibid.*, **91**, 5878 (1969); (e) D. N. Schmidt, Ph.D. Dissertation, Cornell University, 1970; (f) R. Srinivasan, *J. Am. Chem. Soc.*, **85**, 819 (1963).
(3) A. Padwa and W. Eisenberg, *J. Am. Chem. Soc.*, **94**, 5852 (1972).
(4) A few of many examples: (a) K. B. Wiberg, B. R. Lowry, and T. H. Colby, *J. Am. Chem. Soc.*, **83**, 3998 (1961); (b) P. E. Eaton and G. H. Temme III, *ibid.*, **95**, 7508 (1973); (c) F. T. Bond and C.-Y. Ho, *J. Org. Chem.*, **41**, 1421 (1976); (d) J. Meinwald and Y. C. Meinwald, *Adv. Alicyclic Chem.*, **1**, 1 (1966); (e) N. L. Allinger and T. J. Walter, *J. Am. Chem. Soc.*, **94**, 9267 (1972).
(5) For a review of this area, see M. Regitz, *Synthesis*, 351 (1972).
(6) (a) W. R. Roush, D. Feitler, and J. Rebek, Jr., *Tetrahedron Lett.*, 1391 (1974); (b) J. Rebek, Jr., and F. Gaviña, *J. Am. Chem. Soc.*, **97**, 3453 (1975). We prefer to wash the resin chlorosulfonation mix with inert organic solvents first, rather than to quench directly with water as described in this reference.
(7) C.-Y. Ho, Ph.D. Dissertation, University of California at San Diego, 1975.
(8) K. B. Wiberg, B. R. Lowry, and B. J. Nist, *J. Am. Chem. Soc.*, **84**, 1594 (1962).
(9) K. B. Wiberg and V. Z. Williams, Jr., *J. Org. Chem.*, **35**, 369 (1970).

Silver Ion Assisted Ring Expansions of Some Geminal Dibromobicyclo[*n*.1.0]alkanes. Evidence for Free Cationic Intermediates

Hubert J. J. Loozen,*[15] Jan W. de Haan, and Henk M. Buck

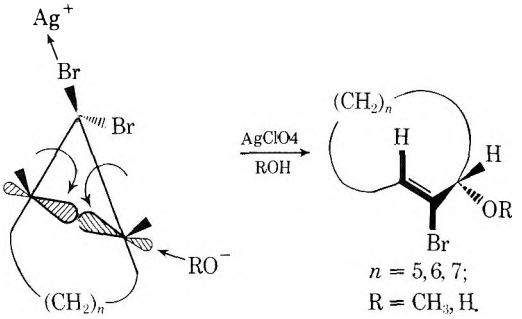
Department of Organic Chemistry, Eindhoven University of Technology, The Netherlands

Received February 9, 1976

Geminal dibromocyclopropanes, annelated to seven-, eight-, and nine-membered rings, represent well-adapted precursors for the construction of medium-sized rings via ring expansion. Though the exo bromine atom is lost, the products do not always possess the expected trans allylic configuration. Reaction of **1** and **2** with silver nitrate in acetonitrile gives the trans nitrate esters **6** and **7**. However, **3** gives exclusively the cis product **8**, and the nine-membered precursor **4** affords a mixture of trans and cis nitrate **9** and **10**. In connection with the results obtained from reaction of **1**–**4** with silver tosylate, it became apparent that, though the exo halogen atom was lost, both ring size and nucleophilicity of the counterion might be the final configuration determining parameters. In order to demonstrate this, compound **3** was solvolyzed with silver perchlorate in a number of alcohols with different nucleophilicity. The percentage of cis product proved to increase in the order $CH_3OH < C_2H_5OH < i\text{-}C_3H_7OH < t\text{-}C_4H_9OH$. A free trans cation which can isomerize to a cis cation is assumed to be the intermediate.

Silver ion promoted ring expansions of geminal dibromobicyclo[*n*.1.0]alkanes represent a useful approach for the construction of medium sized rings.[1a-h] The ring opening, when performed in the presence of strong nucleophiles (H_2O or CH_3OH), generally leads to cyclic structures with a trans geometry. The mechanism of formation, which has been discussed recently by Reese et al., is visualized in Scheme I.

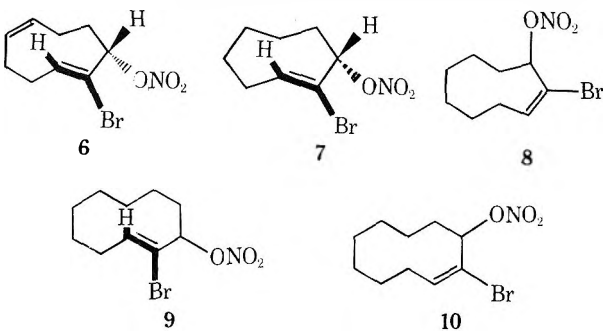
Scheme I

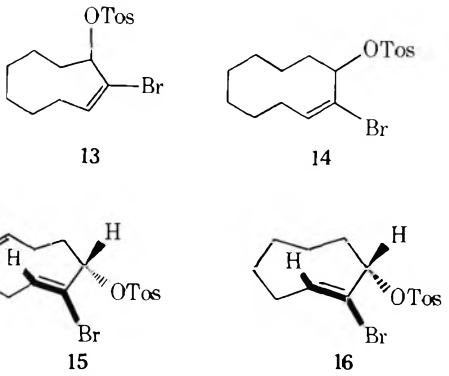


Essential features of this mechanism consist in a disrotatory ring opening, according to the rules of conservation of orbital symmetry, with departure of the exo bromine atom.[2-4]

In most cases only one diastereoisomer was formed. This could be explained by assuming that attack of the nucleophile should be concerted with the ring opening. From these observations the intermediacy of a free trans cation was made questionable.

Recently we presented a method which permits the stereospecific synthesis of medium-sized rings by the reaction of geminal dibromobicyclo[*n*.1.0]alkanes with silver tosylate in acetonitrile.[5] We observed that on reacting 9,9-dibromobicyclo[6.1.0]nonane (**3**) and 10,10-dibromobicyclo[7.1.0]decane (**4**) with silver tosylate only cis products were formed though the exo bromine atom was released; viz., *cis*-2-bromo-3-tosyloxycyclonon-1-ene (**13**) and *cis*-2-bromo-3-tosyloxycyclodec-1-ene (**14**), respectively. The formation of such cis products was rationalized by assuming the intermediacy of a free trans cation in both cases, which isomerizes rapidly to the cis cation before reacting with the weakly nucleophilic tosylate anion.





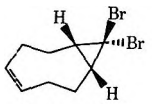
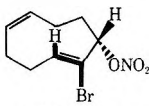
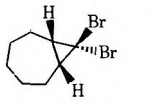
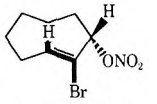
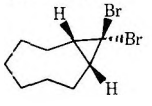
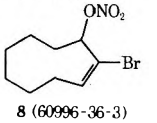
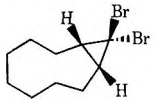
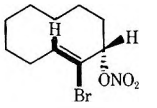
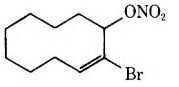
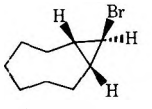
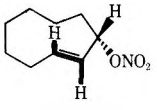
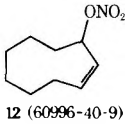
Ring expansion of 9,9-dibromobicyclo[6.1.0]non-4-ene (**1**) and of 8,8-dibromobicyclo[5.1.0]octane (**2**) with silver tosylate led to *trans,cis*-2-bromo-3-tosyloxycyclonona-1,6-diene (**15**) and *trans*-2-bromo-3-tosyloxycyclooct-1-ene (**16**), respectively. This result is not surprising since the full development of a trans cation in these latter systems would represent an energetically unfavorable situation and consequently the tosylate anion enters simultaneously with the ring opening.

A series of ring expansions we performed with silver nitrate, in order to investigate the scope and limitations of this reaction, corroborated the assumed tendency (vide supra). Reaction of the dibromides **1** and **2** led, as expected, to *trans,cis*-2-bromocyclonona-1,6-dien-3-yl nitrate (**6**) and *trans*-2-bromocyclooct-1-en-3-yl nitrate (**7**), respectively, whereas **3** gave the *cis*-2-bromocyclonon-1-en-3-yl nitrate (**8**).

In contrast to the silver tosylate promoted ring opening the reaction of **4** with silver nitrate afforded a 1:1 mixture of *trans*- and *cis*-2-bromocyclodec-1-en-3-yl nitrate (**9** and **10**), respectively. However, this could be reconciled easily with the proposed mechanism. The nitrate anion, which is a slightly better nucleophile than the tosylate anion, reacts more rapidly with the transient cation and thus suppresses partially the isomerization in the less strained ten-membered system (see Table I). The conformations of the newly formed double bonds were established in a chemical way, on synthesizing **6**–**10** by nitration of their corresponding alcohols with acetyl nitrate.[6a,b]

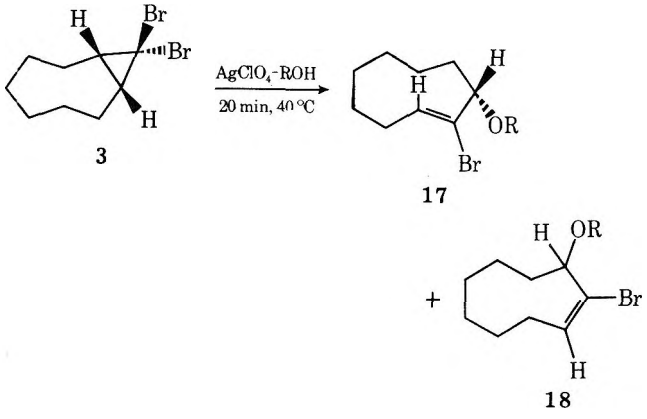
From all these observations it became apparent to us that both the nature of the initial bicyclic system and the nucleo-

Table I. Nitrate Esters

Substrates	Products (ratio)	NMR data ($CDCl_3$), δ	Yield, %[a]	Reaction time, h
 1 (54809-08-4)[b]	 6 (60996-34-1)	6 08 (dd, 1, olefin H, J = 8 and 6 Hz), 5.35 (m, 2, cis double bond), 5.14 (m, 1, methine H)	62	3
 2 (52750-35-3)	 7 (60996-35-2)	6.37 (t, 1, olefin H, J = 8 Hz), 5.76 (t, 1, methine H, J = 8 Hz)	71	4
 3 (32644-18-1)	 8 (60996-36-3)	6.33 (t, 1, olefin H, J = 9 Hz), 5.86 (m, 1, methine H)	78	4
 4 (51129-79-0)	 9 (1) (60996-37-4)  10 (1) (60996-38-5)	trans: 6.37 (t, 1, olefin H, J = 8 Hz), 5.21 (t, 1, methine H, J = 7 Hz) cis: 5.82–6.32 (m, 2, olefin H and methine H)	83	3
 5 (1551-94-6)	 11 (2) (60996-39-6)  12 (60996-40-9)	trans: 4.72–5.28 (m, 1, methine H), 5.36–6.03 (m, 2, olefin H), 0.70–2.60 (aliphatic H) cis: 5.20–6.08 (m, 3, methine H + olefin H), 1.05–2.20 (aliphatic H) [^{13}C (ppm downfield from external Me_4Si), 86.8 (methine C, trans), 82.9 (methine C, cis)]	72	0.5

[a] Yields were based on pure isolated products after chromatography. [b] Registry no.

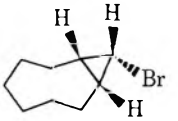
Table II

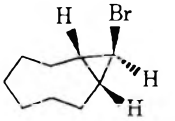


	R	17a–d (trans, %)	18a–d (cis, %)	Total yield, %
a	CH_3	90	10	81
b	C_2H_5	61	39	86
c	i-C_3H_7	47	53	85
d	t-C_4H_9	36	64	82

philicity of the attacking anion might be the main parameters in determining the percentage of cis and trans products in the silver ion assisted ring expansion reactions. In order to demonstrate this we performed a series of silver ion assisted alcoholysis reactions which unambiguously support this theorem.

Relying on the previously presented data it is clear that 9,9-dibromobicyclo[6.1.0]nonane (**3**) is the most interesting substrate to submit to the silver ion assisted ring opening, because it is the smallest ring in this series which obviously possesses the property of undergoing ring opening in a "semiconcerted" manner leading to a strained transient trans cation. Its lower homologue **2** has been shown to react always completely concerted, apparently without intermediate cations, leading to trans eight-membered systems. A number of ring expansions were performed by reacting **3** in a 1 M solution of silver perchlorate in a series of alcohols with varying nucleophilicity, viz., methanol, ethanol, 2-propanol, and *tert*-butyl alcohol. All these reactions were carried out at 40 °C with a twofold molar excess of silver perchlorate. After 20 min of reaction the starting material had disappeared (the reactions were monitored by TLC, using benzene as eluent). The results from the alcoholysis reaction of **3** have been presented in Table II. From these results it is readily recognized that decreasing nucleophilicity ($CH_3OH > C_2H_5OH > i$-$C_3H_7OH > t$-C_4H_9OH) leads to an increase of cis isomer in the final product. On performing the alcoholysis in *tert*-butyl alcohol the cis product even predominates. It should be mentioned that under the conditions applied for the ring opening of **3** the 9-*endo*-bromobicyclo[6.1.0]nonane (**19**) proved to be nearly


19


5

unreactive.[8] The results achieved with this number of alcohols undoubtedly give ample proof for our original idea of a free trans cation[5] (see Chart I).

Chart I

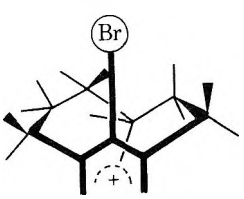
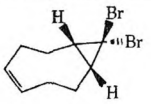
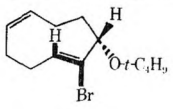
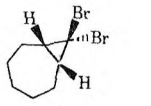
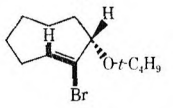
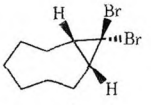
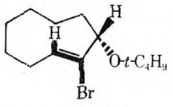
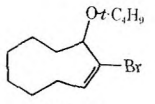
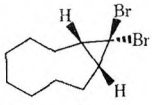
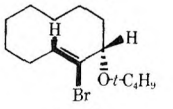
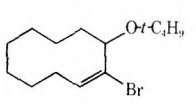
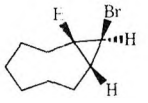
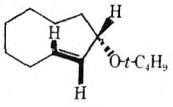
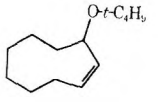


Table III. Solvolysis Reactions in 1 M $AgClO_4$ Solution in *tert*-Butyl Alcohol (40 °C)

Substrate	Products (ratio)	Yield, %	Reaction time, min
 1	 20	79	15
 2	 21	83	20
 3	 17d (36)  18d (64)	82	20
 4	 22 (80)  23 (20)	90	10
 5	 24 (90)  25 (10)	81	10

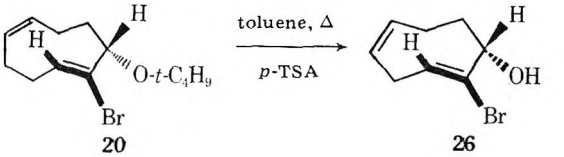
When 9-*exo*-bromobicyclo[6.1.0]nonane (**5**) was treated with silver perchlorate in *tert*-butyl alcohol at 40 °C a very rapid reaction took place, which led to the formation of nearly pure *trans*-3-*tert*-butoxycyclonon-1-ene (**24**); see Table III. Only a minor amount of the corresponding cis isomer was formed. This result is not surprising since the absence of the bulky bromine atom decreases the severe steric strain in the transient cation and thus diminishes the propensity for isomerization to the cis cation. It is interesting to note that a similar tendency is also observed in the ring expansion of **5** with silver nitrate. In this case predominantly *trans*-cyclonon-1-en-3-yl nitrate (**11**) is formed. A significant release of strain can also be effected by extension of the carbon chain by one carbon atom. So, on treatment of the next higher homologue **4** with silver perchlorate in *tert*-butyl alcohol mainly *trans*-2-bromo-3-*tert*-butoxycyclodec-1-ene (**22**) was formed. The corresponding cis isomer (**23**) represented only 20% of the product.

Finally, we wish to note that 8,8-dibromobicyclo[5.1.0]-octane (**2**) and 9,9-dibromobicyclo[6.1.0]non-4-ene (**1**) afforded only trans products on reaction with silver perchlorate in *tert*-butyl alcohol, viz., *trans*-2-bromo-3-*tert*-butoxycyclooct-1-ene (**21**) and *trans,cis*-2-bromo-3-*tert*-butoxycyclonona-1,6-diene (**20**), respectively. It was nearly self-evident that these reactions would proceed in a completely concerted manner.

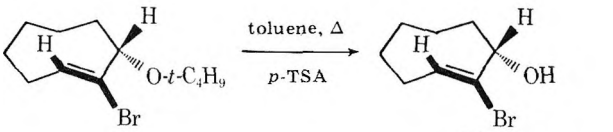
Structure Assignments. The configurations of products **17a–d** and **18a–d** arising from the ring expansion of **3** were determined with the aid of their ^1H and ^{13}C NMR spectra (see Table IV). In the proton spectrum the trans products **17a–d** exist as two rapidly equilibrating diastereoisomers (rotation of the trans double bond through the loop of the ring).[6b] Their spectra display typical double doublets for the olefinic region. The methine part of the spectrum shows a characteristic double doublet and a lower field multiplet. The corresponding cis structures **18a–d** can be detected readily by their typical olefinic triplet and by the signal of the methine proton: a multiplet which resonates always at lower field than the methine protons of the trans diastereoisomers. These observations are in good agreement with recently reported data for similar compounds.[1h] An additional and valuable method of determining the structures of the products consisted in comparison of the ^{13}C spectra. Of importance is the resonance of the allylic carbons. One of these, to which the alkoxy substituent is attached, may readily be found.

For the cis isomers this latter allylic carbon resonates generally at 5–10 ppm upfield relative to the allylic signal of the corresponding trans diastereoisomers.[9] In this way the mixtures **22, 23** and **24, 25** were analyzed unambiguously, as well as the mixture of *cis*- and *trans*-cyclonon-1-en-3-yl nitrate (**11** and **12**).

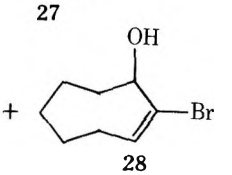
The structural assignments of the two trans compounds **20** and **21** were made in accordance with their ^1H NMR spectra. The coupling constants were in good agreement with the values measured in analogous compounds. Chemical evidence was obtained in the following way: on refluxing a solution of **20** in toluene containing a catalytic amount of *p*-toluenesulfonic acid for 10 min the parent alcohol **26** was obtained. In



20 **26**



21 **27**



28

a similar way the *tert*-butoxy group was removed from **21**. This afforded a 3:2 mixture of *trans*- and *cis*-2-bromocyclooct-1-en-3-ol (**27** and **28**, respectively).[10]

Experimental Section

General. The dibromides **1–4** were prepared by reaction of the appropriate olefins with dibromocarbene, generated from bromoform

and potassium *tert*-butoxide in pentane.[11] Cyclononene, required for the preparation of **4**, was obtained from 9,9-dibromobicyclo-[6.1.0]nonane (**3**) by conversion to cyclonona-1,2-diene and subsequent reduction.[12] 9-*exo*-Bromobicyclo[6.1.0]nonane (**5**) was obtained from the dibromide **3** by reduction with dimsyl anion in Me_2SO.[13] The corresponding 9-*endo*-bromobicyclo[6.1.0]nonane (**19**) was obtained via tri-*n*-butyltin hydride reduction of **3**.[14] ^1H NMR spectra were obtained on a Varian T-60 spectrometer and ^{13}C NMR spectra were measured on a Varian HA-100 apparatus at 25.12 MHz.

A typical experimental procedure for the preparation of the nitrate esters is exemplified with the preparation of **8**. The alcoholysis reactions were performed at 40 °C, starting with an initial 1 M concentration of silver perchlorate; a typical experiment is illustrated by the preparation of **21**.

***cis*-2-Bromocyclonon-1-en-3-yl Nitrate (8).** A solution of 2.82 g (0.01 mol) of 9,9-dibromobicyclo[6.1.0]nonane (**3**) and 3.38 g (0.02 mol) of silver nitrate in 20 ml of acetonitrile was refluxed with stirring for 4 h (progress of the reaction was monitored by TLC). After cooling the reaction mixture was poured onto 100 ml of saturated sodium chloride solution and 75 ml of ether. Stirring was continued for 10 min and the mixture was filtered through Celite. The organic layer was separated and washed twice with water. The product which remained after drying and concentrating was separated from some TLC immobile material by chromatography through a short silica gel column, using pentane as eluent. Upon bulb to bulb distillation 1.86 g (78%) of **8** was obtained as a colorless oil. NMR data are presented in the table; IR (neat) 2930, 2860, 1630, 1460, 1440, 1360, ,1320, 1290, 1270, 1160, 1020, 1005, 970, 962, 946, 920, 890, 845, 750 cm^{-1}.

Anal. Calcd for $C_9H_{14}NO_3Br$: C, 40.91; H, 5.30; N, 5.30. Found: C, 40.99; H, 5.36; N, 5.19.

Product **8** was obtained also by nitration of *cis*-2-bromocyclonon-1-en-3-ol. To 3 ml of acetic anhydride was added 265 mg (1.1 mmol) of $Cu(NO_3)_2 \cdot 3H_2O$. After the appearance of the typical precipitate of cupric acetate the mixture was stirred for an additional 15 min and then cooled to 0 °C. A solution of 210 mg (1 mmol) of *cis*-2-bromocyclonon-1-en-3-ol[5] in 2 ml of methylene chloride was added in 1 min. The mixture was stirred for an additional 5 min and then poured onto 20 ml of water. After neutralization with solid sodium bicarbonate the product was extracted with ether. The oil which remained after evaporation of the organic phase was chromatographed over a short silica gel column (pentane as eluent) and afforded 240 mg (91%) of **8**.

***trans,cis*-2-Bromocyclononа-1,6-dien-3-yl Nitrate (6).** This compound was prepared in 62% yield by refluxing a solution of 2.80 g (0.01 mol) of **1** and 3.38 g (0.02 mol) of silver nitrate in 20 ml of acetonitrile for 3 h. Some TLC immobile material was separated by chromatography through silica gel using pentane as eluent. Analytical material was obtained by microscale distillation. NMR data are presented in the table; IR (neat) 3000, 2925, 2860, 1625, 1540, 1530, 1440, 1360, 1295, 1270, 1260, 1215, 1192, 1170, 1078, 972, 955, 924, 900, 845, 787, 750, 748 cm^{-1}. Anal. Calcd for $C_9H_{12}BrNO_3$: C, 41.22; H, 4.58; N, 5.34. Found: C, 41.16; H, 4.69; N, 5.27.

***trans*-2-Bromocyclooct-1-en-3-yl Nitrate (7).** The nitrate was obtained in 71% yield as an oil from reaction of 2.68 g (0.01 mol) of **2** and 3.38 g (0.02 mol) of silver nitrate on refluxing 4 h in 20 ml of acetonitrile. The crude product was chromatographed through a short column of silica gel, using pentane as eluent, to remove some traces of TLC immobile material. NMR data are presented in the table; IR (neat) 2925, 2850, 1630, 1450, 1360, 1315, 1277, 1248, 1217, 1119, 1035, 1009, 990, 959, 892, 848, 750 cm^{-1}. Anal. Calcd for $C_8H_{12}BrNO_3$: C, 38.40; H, 4.81; N, 5.61. Found: C, 38.12; H, 4.59; N, 5.30.

2-Bromocyclodec-1-en-3-yl Nitrate (9 and 10). A mixture of 2.96 g (0.01 mol) of dibromide **4** and 3.38 g (0.02 mol) of silver nitrate in 25 ml of acetonitrile was refluxed for 3 h and worked up in the usual manner. After chromatography through a short column of silica gel (pentane) 2.72 g (83%) of a colorless oil was obtained which according to the NMR spectrum consisted of a 1:1 mixture of **9** and **10**. An analytical sample was obtained by evaporative bulb to bulb distillation. Anal. Calcd for $C_{10}H_{16}BrNO_3$: C, 43.17; H, 5.76; N, 5.04. Found: C, 43.01; H, 5.77; N, 5.12. The individual isomers were synthesized from the corresponding alcohols[5] as described for **8**. The NMR data of the individual isomers are presented in the table. IR (neat) for **10:** 2930, 2850, 1730, 1470, 1445, 1355, 1320, 1270, 1200, 945, 930, 845 cm^{-1}. IR (neat) for **9:** 2930, 2860, 1730, 1465, 1440, 1360, 1305, 1270, 955, 845 cm^{-1}.

Cyclonon-1-en-3-yl Nitrate (11 and 12). A solution of 2.03 g (0.01 mol) of **5** and 3.38 g (0.02 mol) of silver nitrate in 25 ml of acetonitrile was refluxed for 0.5 h. After workup in the usual manner, the resulting product was chromatographed over silica gel (hexane) and afforded 440 mg of *cis*-cyclonon-1-en-3-yl nitrate (**12**) (R_f 0.25) and 890 mg of *trans*-cyclonon-1-en-3-yl nitrate (**11**) (R_f 0.21). The total yield amounted to 72%. Analytical material was obtained by microdistillation. Anal. Calcd for $C_9H_{15}NO_3$: C, 58.38; H, 8.11; N, 7.57. Found: 58.60; H, 8.29; N, 7,31. The NMR data for the individual isomers are presented in Table I. IR (neat) for **11:** 2930, 2860, 1620, 1450, 1305, 1290, 1275, 1265, 975, 937, 855 cm^{-1}. ^{13}C spectrum ($CDCl_3$) 21.2, 23.6, 27.5, 31.7, 31.9, 33.4, 86.8, 128.0, 133.7 ppm. IR (neat) for **12:** 3020, 2930, 2860, 1620, 1450, 1300, 1270, 970, 945, 925, 855, 775, 740 cm^{-1}. ^{13}C spectrum ($CDCl_3$) 24.2, 26.6, 27.4, 28.9, 31.5, 82.9, 128.0, 134.7 ppm.

Table IV. NMR Data[a]

Compd[b]	^1H NMR, δ (CCl_4 solutions)	^{13}C NMR, ppm downfield from external Me_4Si in $C_2Br_2F_4$
17a, 18a	3.91 and 3.47 (m and dd, methine H-3, trans, J = 5 and 10 Hz), 4.20 (m, methine H-3, cis)	56.9 (CH_3O), 79.2 (C-3, cis), 85.9 and 87.2 (C-3, trans)
17b, 18b	3.62 and 4.02 (m and dd, methine H-3, trans, J = 5.5 and 10 Hz), 4.35 (m, methine H-3, cis)	64.7 (CH_3C_2O), 77.4 (C-3, cis), 84.1 and 85.4 (C-3, trans)
17c, 18c	4.11 (m, methine H-3, trans), 4.40 (m, methine H-3, cis), 6.20 (t, J = 0 Hz, olefin H-1, cis)	69.2 [$(CH_3)_2C$], 74.2 (C-3, cis), 81.3 and 82.7 (C-3, trans)
17d, 18d	3.72 and 4.07 (m and dd, trans, methine H-3, J = 5 and 10 Hz), 4.41 (m, cis, methine H), 6.02 (t, olefin H-1, J = 9 Hz, cis)	70.4 (C-3, cis), 74.7 [$(CH_3)_3C$], 78.1 and 79.3 (C-3, trans)
20	5.78 (t, 1, H-1, J = 8 Hz), 5.19 (m, 2, H-5 and H-6), 3.84 (m, 1, methine H-3)	
21	5.99 (dd, 1, H-1, J = 11 and 4.5 Hz), 3.96 (t, 1, H-3, J = 8 Hz)	75.1 [$C(CH_3)_3$], 78.7 (C-3, trans)
22, 23	6.24 (t, J = 8 Hz, trans, H-1), 5.82 (dd, H-1, cis, J = 12 and 6 Hz), 4.49 (m, H-3, cis), 3.99 (m, H-3, trans)	69.2 (C-3, cis), 75.0 [$C(CH_3)_3$], 77.6 (C-3, trans)
24, 25	3.59 (m, methine H, trans), 4.06 (m, methine H, cis), 5.21 (m, olefinic H)	68.9 (C-3, cis), 73.9 [$C(CH_3)_3$], 75.9 (C-3, trans)

[a] Only the most significant signals were tabulated, because in the methine region the signals are often overlapped by alkoxy protons, whereas in the olefinic region the protons of cis and trans structures coincide. [b] Registry no. are, respectively, 26994-06-9, 61045-43-0, 61045-44-1, 61045-45-2, 60996-41-0, 60996-42-1, 60996-43-2, 60996-44-3 60996-45-4, 60996-46-5, 60996-47-6, 60996-48-7, 60996-49-8, 60996-50-1.

***trans*-2-Bromo-3-*tert*-butoxycyclooct-1-ene (21).** To a solution of 4.14 g (0.02 mol) of silver perchlorate in 20 ml of *tert*-butyl alcohol (~15 g) was added to 40 °C with vigorous stirring 2.68 g (0.01 mol) of **2**. Precipitation of silver bromide began immediately. After 20 min the starting bromide had disappeared (as evidenced by the thin layer chromatogram, Merck silica gel plates, benzene as eluent). Then 20 ml of saturated sodium chloride solution was added. The mixture was stirred for about 5 min and filtered through Celite. After dilution with 100 ml of water the product was extracted twice with ether. Upon washing, drying, and evaporation of the solvent 2.16 g (83%) of pure **21** remained as a colorless oil.[10] The NMR data are presented in Table IV.

A solution of 1,3 g (0.005 mol) of **21** in 10 ml of toluene, containing about 100 mg of *p*-toluenesulfonic acid, was refluxed for 10 min. The mixture was washed twice with 10% Na_2CO_3 solution and once with

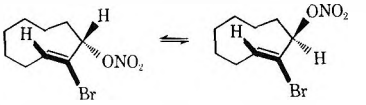
water. After drying and evaporation of organic phase 0.75 g (74%) of a 3:2 mixture of trans and cis alcohol **27** and **28**, respectively, was obtained. These two alcohols were separated by column chromatography (silica gel, chloroform–2% methanol as eluent): R_f (cis, **28**) 0.35; R_f (trans, **27**) 0 29. NMR ($CDCl_3$) for **27**: δ 4.18 (dd, 1, methine H-3, J = 10 and 5 Hz), 6.11 (dd, 1, olefin H-1, J = 10.5 and 4.5 Hz). NMR ($CDCl_3$) for **28**: δ 4.71 (dd, 1, methine H-3, J = 10 and 5 Hz), 6.21 (t, 1, olefin H-1, J = 8.5 Hz).

Acknowledgment. This investigation was supported in part by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for the Advancement of Pure Research (ZWO).

Registry No.—**27**, 61045-46-3; **28**, 60996-51-2; silver nitrate; 7761-88-8; *cis*-2-bromocyclonon-1-en-3-ol, 32726-58-2; *cis*-bromocyclodec-1-en-3-ol, 57090-98-9; *trans*-2-bromocyclodec-1-en-3-ol, 57090-97-8; *tert*-butyl alcohol, 75-65-0.

References and Notes

(1) (a) For a review see C. D. Gutsche and D. Redmore, "Advances in Alicyclic Chemistry; Carbocyclic Ring Expansion Reaction", Academic Press, New York, N.Y. 1968; (b) C. B. Reese and A. Shaw, *J. Am. Chem. Soc.*, **92**, 2566 (1970); (c) *Chem. Commun.*, 1365 (1970); (d) *ibid.*, 1367 (1970); (e) D. Duffin and J. K. Sutherland, *ibid.*, 626 (1970); (f) M. S. Baird and C. B. Reese, *Tetrahedron Lett.*, 4637 (1971); (g) G. H. Whitham and M. Wright, *J. Chem. Soc.*, 1173 (1969); (h) C. B. Reese and A. Shaw, *J. Chem. Soc., Perkin Trans. 1*, 2422 (1975), and references cited therein.
(2) R. B. Woodward and R. Hoffmann, *J. Am. Chem. Soc.*, **87**, 395 (1965).
(3) C. H. de Puy, R. G. Snack, and J. W. Hauser, *J. Am. Chem. Soc.*, **88**, 3343 (1966).
(4) Loss of the endo halogen atom occurs preferentially in those cases where the expanded ring would become too small to accommodate a trans double bond. Some relevant references are (a) P. v. R. Schleyer, W. F. Sliwinski, G. W. van Dine, U. Schollkopf, J. Paust, and K. Fellenberger, *J. Am. Chem. Soc.*, **94**, 125 (1972); (b) W. F. Sliwinski, T. M. Su, and P. v. R. Schleyer, *ibid.*, **94**, 133 (1972); (c) P. M. Warner, R. C. La Rose, R. F. Palmer, C. Lee, D. O. Ross, and J. C. Clardy, *ibid.*, **97**, 5507 (1975); (d) S. R. Sandler, *J. Org. Chem.*, **32**, 3876 (1967); (e) S. R. Sandler and P. S. Skell, *J. Am. Chem. Soc.*, **80**, 2024 (1958).
(5) H. J. J. Loozen, W. M. M. Robben, T. L. Richter, and H. M. Buck, *J. Org. Chem.*, **41**, 384 (1976).
(6) (a) T. Sato, T. Akima and K. Uno, *J. Chem. Soc. C*, 891 (1973). (b) The *trans*-cyclononene derivatives generally do exist as two rapidly equilibrating diastereoisomers which are readily recognized from their ^{1}H NMR spectra. This phenomenon has been discussed exhaustively in the literature; see



(a) A. C. Cope, K. Banholzer, H. Keller, B. A. Pawson, J. J. Whang, and H. J. S. Winkler, *J. Am. Chem. Soc.*, **87**, 3644 (1965); (b) G. Binsch and J. D. Roberts, *ibid.*, **87**, 5157 (1965). *trans*-Cyclonon-1-en-3-yl nitrate, which was prepared from the corresponding trans alcohol, could be characterized in this way.
The NMR spectrum (CCl_4) displayed an olefinic multiplet at δ 6.23, whereas the methine part was splitted in two signals, viz., a triplet at δ 5.33 (J = 5 Hz) and a double doublet at δ 5.02 (J = 10 and 4 Hz).
(7) Excess of silver perchlorate is necessary to obtain a high reaction rate and a quantitative conversion.
(8) Recently published data on the methanolysis of **19** showed that higher temperature and a longer reaction time were required to achieve ring expansion of this product; see ref 1b and 1h.
(9) J. W. de Haan and L. J. M. van de Ven, *Org. Magn. Reson.*, **5**, 147 (1972), and references cited therein.
(10) Trans eight-membered systems display thermal instability as has been mentioned already by others (ref 1b). We observed that **21** isomerized spontaneously on standing several days at room temperature.
(11) L. Skattebøl, *Acta Chem. Scand.*, **17**, 1683 (1963).
(12) P. D. Gardner and M. Narayana, *J. Org. Chem.*, **26**, 3518 (1961).
(13) C. L. Osborn, T. C. Shields, B.A. Shoulders, C. G. Cardenas, and P. D. Gardner, *Chem. Ind. (London)*, 766 (1965).
(14) D. Seyferth, H. Yamazaki, and D. Alleston, *J. Org. Chem.*, **28**, 703 (1963).
(15) Address correspondence to Organon International B. v., Research and Development Laboratories, RL 312, Dss. The Netherlands.

Specific Ortho Bromination.[1] 2. Aluminum Trichloride Catalyzed Transalkylation

Y. Halpern* and D. Meidar

Casali Institute of Applied Chemistry, the Hebrew University of Jerusalem, Jerusalem, Israel

Received April 6, 1976

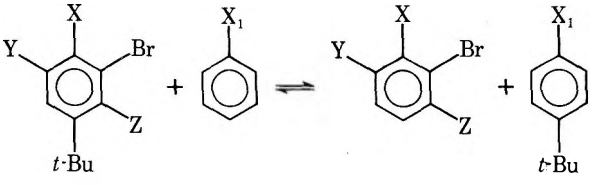
Transalkylation between 2-bromo-4-*tert*-butyl derivatives of substituted benzenes (donors) and various aromatics (acceptors) was found (under the conditions of this study) to be catalyzed by solid $AlCl_3$. The equilibrium constant of the reversible process was determined at different temperatures. The enthalpy of the reaction was calculated and discussed.

Direct bromination of monosubstituted aromatic compounds yields a mixture of the three possible monobrominated isomers. The separation of the isomers in most cases is difficult owing to their similarity in physical properties. In order to overcome this difficulty methods for an indirect bromination specifically at the ortho position have been developed.[1]

Tertiary butyl and other bulky hydrocarbons were used as blocking groups in the synthesis of ortho-disubstituted benzene derivatives. Various catalysts, temperatures, substrates, and solvents were used for the removal of the blocking groups.[2–8]

It has been reported[9–15] that bromine attached to benzene or substituted benzene shifts along the aromatic nuclei or even cleaves under alkylation reaction conditions.

We have recently reported that catalytic amounts of $AlCl_3$ promote the transfer of *tert*-butyl group from the donor to the acceptor, in a reversible process according to eq 1.[1]



(1)

Results and Discussion

At least 5 mol % of $AlCl_3$ is needed to disproportionate bromobenzene to benzene and dibromobenzene.[13] Our results show that transfer of *tert*-butyl group from the donor to the acceptor is accomplished with 1–2 mol % of $AlCl_3$ without concurrent bromine transfer.

Crump,[16] who investigated the $AlCl_3$-catalyzed isomerization of bromotoluenes, suggested that the $AlCl_3$ catalysis is heterogeneous in nature.

Table I. Yields of *o*-Bromotoluene, after Various Reaction Times, as a Function of Incubation Period[a]

Expt no	16	17	18	19	20	21
Incubation time, h	0	24	48	72	96	144
Reaction time, min	% yield					
5	38.3	38.0	27.0	1.4	0.1	0.1
10	82.8	82.0	47.0	5.5	0.1	0.1
15	88.0	87.0	62.0	10.0	0.1	0.1
20	88.3	88.1	73.0	17.0	0.1	0.1
30	88.6	88.4	85.7	32.2	0.1	0.1
45	88.7	88.5	88.7	60.0	0.1	0.1
60		89.0		79.5	0.1	0.1
90			88.7	86.2	0.3	0.1
150				87.5	0.5	0.1
240					1.0	0.7

[a] 2-Bromo-4-*tert*-butyltoluene, 3.8 ml (20 mmol); benzene, 7.1 ml (80 mmol); $AlCl_3$, 26.7 mg (0.2 mmol); T = 20 °C. Catalyst's particle size 50 μ.

Table II. Yields of o-Bromotoluene, after Various Reaction Times, as a Function of Incubation Period, Catalyst Particle Size 300 μ[a]

Expt no.	23	24	25	26	27	28
Incubation time, h	0	22	48	72	96	144
Reaction time, min	% yield					
5	1.4	17.1	15.5	7.0	3.3	0.1
10	8.8	37.0	31.5	11.9	8.0	0.1
15	19.5	52.5	46.8	19.0	13.7	0.1
20	39.3	66.3	61.6	31.3	19.3	0.1
30	78.3	81.6	80.5	56.5	32.8	0.1
45	87.7	87.4		79.2		0.1
60	88.0		88.7	87.2		0.1
90					81.3	0.1
120	88.6					0.1
150					87.2	0.3
240					87.4	0.6

[a] 2-Bromo-4-*tert*-butyltoluene, 3.8 ml (20 mmol); benzene, 7.1 ml (80 mmol); $AlCl_3$, 26.7 mg (0.2 mmol); T = 20 °C.

Other investigators[2,5,7] have reported that transfer of tertiary alkyl group from an aromatic hydrocarbon is accomplished with the soluble $AlCl_3$–CH_3NO_2 complex.

The results of our work show that no transalkylation takes place with the soluble $AlCl_3$–CH_3NO_2 or $AlCl_3$–Et_2O complexes even in large excess (150 mol %). Furthermore, no reaction takes place when a saturated solution of $AlCl_3$ in benzene (0.2% w/v[17]) is used as a catalyst. Addition of a small amount of solid $AlCl_3$ to this solution immediately promotes the transalkylation. The heterogeneity of the catalysis is depicted by the fact that the reaction proceeds only as long as solid $AlCl_3$ is present.

The influence of the catalyst's particle size and the incubation period (the time interval between mixing the catalyst with the acceptor and introducing the donor) on the reaction rate and induction period (Tables I and II) also indicates the heterogeneous nature of the catalyst. Two processes occur in the catalyst during the incubation period: (a) breakage of the particles; (b) dissolution (Table III). The result of the former is an increase of the catalyst's surface area while the latter decreases the amount of the active catalyst. Using a 300-μ particle size $AlCl_3$ an acceleration of the reaction rate is observed when the incubation period is increased up to 48 h,

Table III. Amount of Dissolved $AlCl_3$ in Benzene as a Function of Incubation Time

Incubation time, h	Liquid phase volume, ml	$AlCl_3$ introduced, mg	$AlCl_3$ dissolved, mg/ml	Total amount of $AlCl_3$ dissolved, mg
0.1	10.4	39.0	0.00	0.0
24	9.9	37.3	0.33	3.3
72	11.2	42.2	2.53	28.3
144	9.2	34.5	3.70	34.0

Table IV. Equilibrium Constants as a Function of the Temperature and ΔH in the Reaction between I as the Donor and Various Acceptors Catalyzed by $AlCl_3$

Acceptor	$K_{0°C}$	$K_{25°C}$	$K_{35°C}$	ΔH, kcal/mol
m-Xylene	0.26	0.26	0.27	+0.3 ± 0.3
Toluene	0.82	0.76	0.75	−0.8 ± 0.2
Benzene	2.91	2.14	1.84	−2.4 ± 0.4
Fluorobenzene	1.78	0.70	0.46	−6.9 ± 0.8
Chlorobenzene	4.10	1.54	1.00	−7.1 ± 0.7
Bromobenzene	5.31	1.78	1.12	−7.8 ± 0.7

Table V. Equilibrium Constants as a Function of the Temperature and ΔH in the Reaction between Various Donors and Benzene as Acceptors

Donor[a]	$K_{0°C}$	$K_{25°C}$	$K_{35°C}$	ΔH, kcal/mol
I	2.91	2.14	1.84	−2.4 ± 0.4
II	1.22	1.99	2.53	+3.8 ± 0.6
III	0.45	1.22	1.49	+5.1 ± 2.1
IV	3.45	2.27	2.08	−2.0 ± 0.3
V	8.93	4.53	3.67	−4.2 ± 0.3
VI	9.11	4.48	3.74	−4.0 ± 0.6

[a] Donors: I, 2-bromo-4-*tert*-butyltoluene; II, 2-bromo-4-*tert*-butylchlorobenzene; III, 1,2-dibromo-4-*tert*-butylbenzene; IV, 2-bromo-4-*tert*-butylethylbenzene; V, 1-bromo-2,6-dimethyl-3-*tert*-butylbenzene; VI, 2-bromo-1,6-dimethyl-4-*tert*-butylbenzene.

resulting from the increase of the catalyst's surface area. Longer incubation periods cause a decrease in reaction rate resulting from the reduction of the amount of active catalyst due to dissolution (Table II). No change in the reaction is observed with incubation periods up to 24 h when 50-μ (high surface area) particles are used. Longer incubation periods cause a decrease in reaction rate due to dissolution which decreases the amount of the solid catalyst (Table I).

The basicity of the bromo-substituted aromatic ring is lower than that of the hydrocarbon; hence a more acidic catalyst is needed to promote transalkylation in the case of the bromo-substituted compound. Any complexed $AlCl_3$ is a weaker Lewis acid than the uncomplexed salt.[18] This is the reason that complexed $AlCl_3$ catalyzes transalkylation from aromatic hydrocarbons[2,5,18] but a stronger catalyst like solid $AlCl_3$ is needed for transalkylation from brominated aromatic compounds.

It has been proved that after the reaction reaches a stage where no further change in the relative amounts of the reactants is observed, an equilibrium is reached. Addition of a new portion of reactants (after 1 h at equilibrium) causes the reaction to proceed until the initial equilibrium is reestablished. On the other hand, if the new portion of reactants is added after a long period (24 h) from the time the equilibrium is reached, the reaction does not proceed further, owing to deactivation of the catalyst.[19] At this stage a fatty brown layer

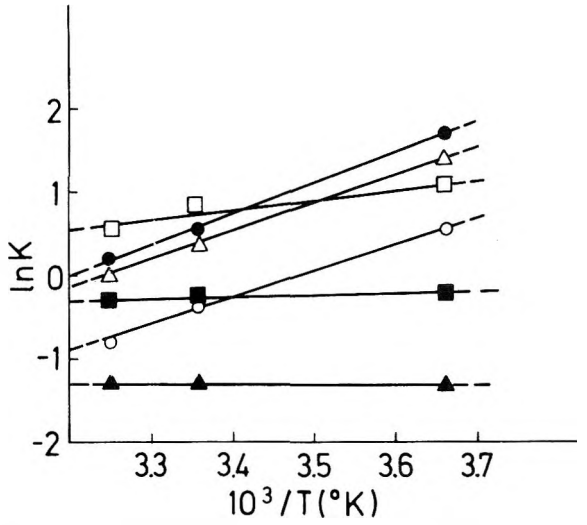


Figure 1. Ln K as a function of T^{-1} in the reaction between I as the donor and the following acceptors: ▲, m-xylene; △, chlorobenzene; ■, toluene; □, benzene; ●, bromobenzene; ○, fluorobenzene.

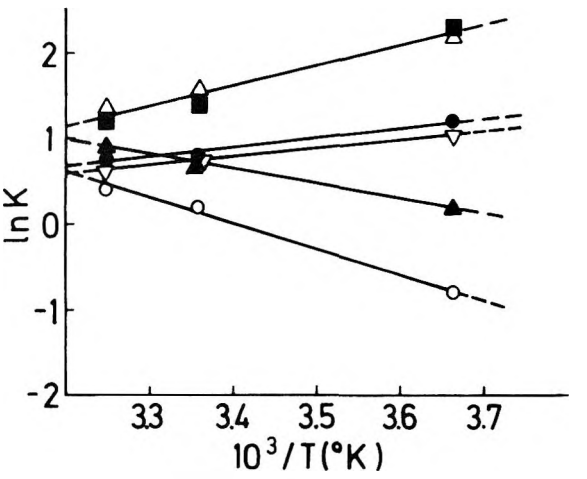


Figure 2. Ln K as a function of T^{-1} in the reaction between benzene as acceptor and the following donors: ▽, I; ▲, II; ○, III; ●, IV; ■, V; △, VI.

is separated from the reaction mixture.[19] Addition of another amount of solid catalyst reestablished the equilibrium.

Studying the reverse reaction (eq 1) with the same amount of catalyst shows that the reaction stops before it reaches equilibirum. Consecutive additions of small amounts of solid catalyst cause the reaction to continue until equilibrium is reached. Attempts to reach the equilibrium in one step, e.g., using a larger amount of solid catalyst, have been unsuccessful since side reactions (bromine migration) take place in addition to the desired transalkylation.

Equilibrium constants (K) and the calculated enthalpies of the reaction for different donor–acceptor systems are summarized in Tables IV and V.

Based on the calculated enthalpy of the reaction (Figure 1 and Table IV), it is possible to divide the acceptors into two major groups (a) acceptors involved in reactions with low (+0.3 to −2.4) ΔH values, e.g., m-xylene, toluene, and benzene; (b) those involved in reactions showing relatively high (−6.9 to −7.8) values of ΔH, e.g., fluoro-, chloro-, and bromobenzene.

This behavior stems from the fact that the acceptor does not influence the rate of the forward reaction and is responsible only for the reverse process where it serves as a "donor". High-basicity acceptors (group a) facilitate the reverse reaction which results in low ΔH. The oppostie effect occurs with low-basicity acceptors (group b). Furthermore, the ΔH value in each group is increased with decreased basicity of the acceptor: (a) m-xylene < toluene < benzene; (b) fluorobenzene < chlorobenzene < bromobenzene. Similar results which strengthen the above explanation are obtained from the experiments with various donors and benzene as an acceptor (Table V and Figure 2). The above results are particularly important for choosing the proper reaction temperature for a given donor–acceptor system in synthetic applications of the process.

Experimental Section

Materials. Benzene was spectrograde Merck reagent dried over sodium emulsion and freshly distilled through a 2-ft column, at an atmospheric pressure, into a vessel containing sodium wires.

Other aromatic compounds were Fluka pure reagents dried over molecular sieve type 4A, activated at 400 °C.

Solution of $AlCl_3$ in nitromethane, 1 M concentration, was "Cationics" product used with no further treatment.

The donors were prepared as described in a previous paper.[1]

$AlCl_3$ was Fluka white resublimed solid of 99% purity. It was crushed and passed through appropriate sieves in a glove bag over P_2O_5, under dry nitrogen atmosphere, and immediately transferred into a dried 50-ml ground glass stoppered Erlenmeyer with a side arm covered by a rubber septum.

Transalkylation Reactions. $AlCl_3$ (26.7 mg, 0.2 mmol) and 7.1 ml (80 mmol) of benzene (introduced into the Erlenmeyer) kept in a drybox under dry N_2 were shaken together (for a predetermined incubation period); 3.8 ml of 2-bromo-4-*tert*-butyltoluene (20 mmol) was added by means of a syringe and the mixture was shaken at a constant temperature in a shaking bath. Samples (25 μl) were withdrawn (at predetermined reaction times) through the septum by means of a 25-μl syringe and quenched in 1 ml of diethyl ether containing 0.05 mmol of durene [used as a gas chromatograph (GLC) internal standard]. Transalkylations with other donors and acceptors were carried out following the same procedure.

For equilibrium constant determination the same procedure was used, with different ratios of reactants and catalyst. Solution of $AlCl_3$ in benzene was prepared by shaking a large excess of powdered $AlCl_3$ in benzene for 24 h, filtering the mixture through a 10-μ sintered glass funnel in a glove bag under dry nitrogen.

The soluble $AlCl_3$ content of the benzene solution and reaction mixtures was determined by means of a Perkin-Elmer Model 403 atomic absorption spectrophotometer using the following procedure: 1 ml of the $AlCl_3$ solution was extracted into a known volume of twice distilled water for Al^+ determination. For Cl^- determination a known volume of 0.1 N $AgNO_3$ solution was used to precipitate all the Cl^- present in 1.0 ml of $AlCl_3$ solution and the excess Ag^+ was determined.

In order to examine the accuracy of $AlCl_3$ analysis, a solid sample of 41.9 mg of $AlCl_3$ was analyzed following the above procedure. The obtained result was 41.5 ± 0.5 mg of $AlCl_3$.

For GLC analysis a Varian Aerograph gas chromatograph series 2800 with a thermal conductivity detector coupled to a Pantos Model u-125 recorder and an Autolab Model 6300 digital integrator was used.

Acknowledgment. The authors wish to thank Professor M. Levy of the Weizmann Institute of Science for his helpful remarks and Mrs. R. Bilu of the Casali Institute for atomic absorption determinations.

Registry No.—I, 61024-94-0; II, 61024-95-1; III, 6683-75-6; IV, 57190-08-6; V, 61024-96-2; VI, 61024-97-3; m-xylene, 108-38-3; toluene, 108-88-3; bromobenzene, 108-86-1; chlorobenzene, 108-90-7; benzene, 71-43-2; fluorobenzene, 462-06-6; $AlCl_3$, 7446-70-0; o-bromotoluene, 95-46-5.

References and Notes

(1) Part 1: D. Meidar and Y. Halpern, *J. Appl. Chem. Biotechnol.*, in press.
(2) M. J. Schlatter, *J. Am. Chem. Soc.*, **76**, 4952 (1954).
(3) F. R. J. Willemse, J. Walters, and E. C. Kooyman, *Recl. Trav. Chim. Pays-Bas*, **90**, 5 (1971).
(4) F. R. J. Willemse, J. Walters, and E. C. Kooyman, *Recl. Trav. Chim. Pays-Bas*, **90**, 14 (1971).
(5) N. Yoneda, M. Yamagushi, and H. Ohtsuka, *Nippon Kagaku Kayshi*, 331 (1973).
(6) Y. Mite and N. Kametake, *Hydrocarbon Process*, **47**, 122 (1968).

(7) A. A. Khalaf and R. M. Roberts, *J. Org. Chem.*, **35**, 3717 (1970).
(8) V. N. Ipatieff and B. B. Cerson, *J. Am. Chem. Soc.*, **59**, 1417 (1937).
(9) M. Capisarow, *J. Chem. Soc.*, **119**, 442 (1921).
(10) F. Fairbrother and N. Scott, *Chem. Ind. (London)*, **998** (1953).
(11) G. J. P. Augustijn, E. C. Kooyman, and R. Louw, *Recl. Trav. Chim. Pays-Bas*, **82**, 965 (1962).
(12) G. J. P. Augustijn and E. C. Kooyman, *Recl. Trav. Chim. Pays-Bas*, **86**, 122 (1967).
(13) G. A. Olah, W. S. Tolgyesi, and R. E. A. Dear, *J. Org. Chem.*, **27**, 3441, 3449 (1962).
(14) G. A. Olah and H. W. Meyer, *J. Org. Chem.*, **27**, 3464 (1962).
(15) M. Tashiro, H. Watanabe, and O. Tsuge, *Org. Prep. Proceed. Int.*, **6**, 107 (1974).
(16) J. W. Crump and G. A. Gornowicz, *J. Org. Chem.*, **28**, 949 (1963).
(17) B. Menschutkin, *J. Russ. Phys.-Chem. Soc.*, **41**, 1089 (1909).
(18) G. A. Olah, S. Kobayshi, and M. Tashiro, *J. Am. Chem. Soc.*, **94**, 7448 (1972).
(19) Part 3: D. Meidar and Y. Halpern, in preparation.

Concerning the Mechanism of Trimethylaluminum Addition to Benzophenone

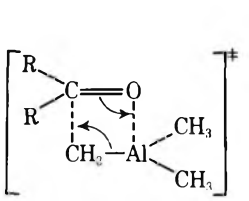
E. C. Ashby* and R. Scott Smith

School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332

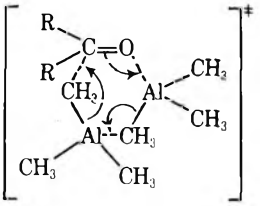
Received July 22, 1976

Because of the stereochemical significance of the reaction of $(CH_3)_3Al$ with substituted cyclohexanones in 2:1 ratio in benzene, an attempt was made to more clearly define the nature of the transition state involved in this reaction. In this connection, molecular weight and NMR studies were carried out on the systems $(CH_3)_3Al$–$O(C_2H_5)_2$, $(CH_3)_3Al$–$Ph_2C{=}O$, and $(CH_3)_2AlCl$–$Ph_2C{=}O$ in an attempt to distinguish among three suggested reaction pathways. One pathway involving the intermediate formation of two molecules of monomeric $(CH_3)_3Al$ bound to one molecule of $Ph_2C{=}O$ was eliminated by the data. All of the available data more strongly support a pathway involving cyclic six-center transition state.

The reaction between $(CH_3)_3Al$ and benzophenone in benzene is known to proceed by two distinct mechanistic pathways depending on the stoichiometric ratio of reactants.[1] At 1:1 ratio the reaction is first order in $(CH_3)_3Al$ and first order in ketone and is presumed to proceed via a four-center transition state (A) whereas in 2:1 ratio the reaction is second order in $(CH_3)_3Al$ and first order in ketone and is presumed to proceed via a six-center transition state (B). When the reaction is carried out in diethyl ether the kinetic order (first order in $(CH_3)_3Al$ and first order in ketone) is independent of the stoichiometric ratio of reactants and the mechanism has been represented as proceeding through transition state A.[2]



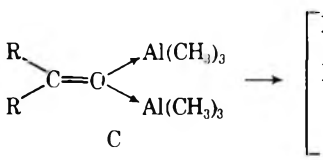
A



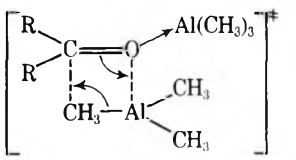
B

Since this reaction proceeds via two distinct mechanistic pathways in benzene and hence via two distinct transition states, it was presumed that the stereochemistry of the reaction at $(CH_3)_3Al$:ketone ratios of 1:1 and 2:1 would be different. In this connection, it was found that the reaction of $(CH_3)_3Al$ with 4-*tert*-butylcyclohexanone in 1:1 ratio in benzene resulted in 75% equatorial attack whereas the reaction in 2:1 ratio resulted in 90% axial attack. This is a rather dramatic and unprecedented stereochemical result and we have expended considerable effort in attempts to arrive at a satisfactory explanation.[3,4]

Recently, Kawasaki[5] has rationalized stereochemical data assuming transition state B and Starowieyski[6] has provided evidence for B by noting the stability of an acetophenone–$(AlCl_3)_2$ adduct. On the other hand, Mole[7] has suggested that the reaction in 2:1 ratio proceeds via the intermediate C leading to transition D. Because an understanding of the unusual stereochemical results of this reaction involving cyclohexanones necessitates an accurate picture of the transition state, we have set out to study the nature of the transition state involved in this reaction.



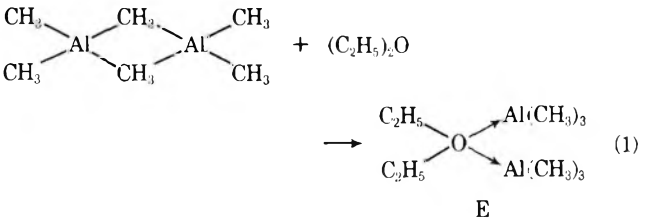
C



D

Results and Discussion

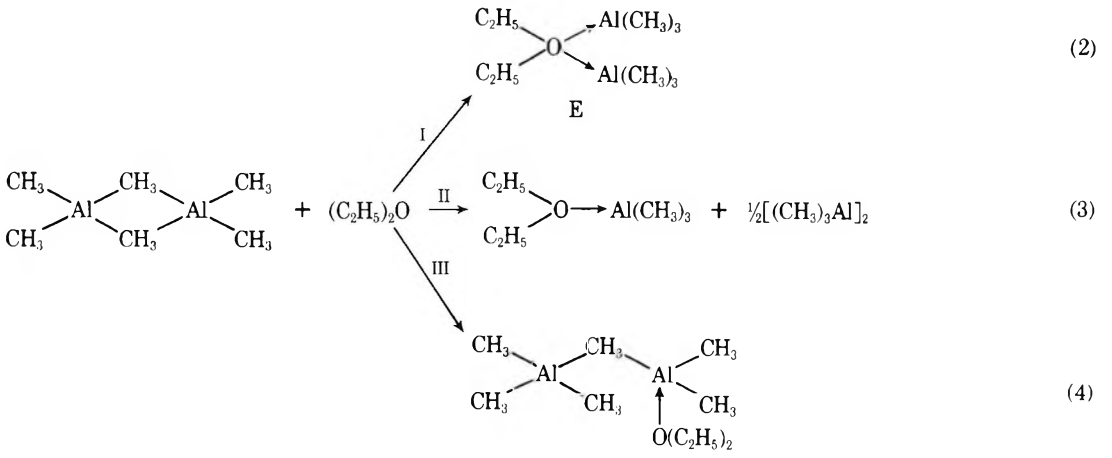
If Mole is correct about the intermediacy of C, then it should be possible to detect such an intermediate spectroscopically (NMR) or by observing the colligative properties of the solutions on mixing $(CH_3)_3Al$ and $Ph_2C{=}O$ in 2:1 ratio in hydrocarbon solvent. We have approached this study in two ways. (1) substituting diethyl ether for $Ph_2C{=}O$ (we have shown comparable basicities of diethyl ether and $Ph_2C{=}O$ toward $(CH_3)_3Al$[3]), we should observe a structure comparable to C (e.g., E) when $(CH_3)_3Al$ and diethyl ether are allowed to



(1)

E

react in 2:1 ratio provided that such a structure is present. Then (2) it should be possible to make a direct observation of C, provided that it is present in solution, by reaction of $(CH_3)_3Al$ and benzophenone in 2:1 ratio at sufficiently low temperatures where the addition reaction is very slow or nonexistent. Since the basicity of diethyl ether and benzophenone are approximately the same toward $(CH_3)_3Al$,[3] an analogy between the behavior of $(CH_3)_3Al$ and diethyl ether in 2:1 ratio and $(CH_3)_3Al$ and benzophenone in 2:1 ratio should



(2)

(3)

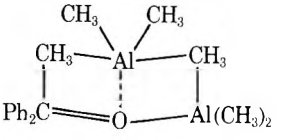
(4)

exist. The advantage of course, in studying the reaction of $(CH_3)_3Al$ with ether is that after complexation, no further reaction can take place (unlike the case with $Ph_2C{=}O$) thus making the system easier to study than the system involving benzophenone.

Reaction of $(CH_3)_3Al$ and Diethyl Ether in 2:1 Ratio. When $(CH_3)_3Al$ and diethyl ether are allowed to react in 2:1 ratio in toluene, three different reaction pathways are possible (I, II, and III). The product from pathway I (E) is easily distinguishable from the product of pathway II by both molecular weight measurements and NMR spectroscopy and from product III by NMR spectroscopy. The molecular weight in benzene of the 2:1 $(CH_3)_3Al$-$O(C_2H_5)_2$ mixture gave on four additions (0.04–0.15 M) the values 145.8, 143.1, 143.3, and 144.4. The molecular weight of the product expected for pathway II is 145 and for pathways I and III is 218. The molecular weight data then indicate that one-half of the $(CH_3)_3Al$ dimer is completely cleaved to the monoetherate when the $(CH_3)_3Al$:$O(C_2H_5)_2$ ratio is 2:1 and the other half remains in solution as unsolvated $(CH_3)_3Al$ dimer. These results were verified by 100-MHz FT ^1H NMR at −80 °C in toluene. The NMR data are consistent with a 2:1 mixture of $(CH_3)_3Al{\cdot}O(C_2H_5)_2$ and $(CH_3)_3Al$ dimer (ratio of methyl groups 3[$(CH_3)_3Al{\cdot}O(C_2H_5)_2$]:2(terminal methyls in $\frac{1}{2}[(CH_3)_3Al]$): 1(bridging methyls in $\frac{1}{2}[(CH_3)_3Al]_2$).

Reaction of $(CH_3)_3Al$ and Benzophenone in 2:1 Ratio. The above data indicate that diethyl ether coordinates so strongly with $(CH_3)_3Al$ dimer that it breaks all of the bridging methyl bonds in a molecule to which ether is attached (pathway II). If the analogy between the basicity of ether and benzophenone toward $(CH_3)_3Al$ is correct, then similar results should be observed with $Ph_2C{=}O$ as were observed with diethyl ether. Addition of $(CH_3)_3Al$ to benzophenone at −78 °C was found to be negligible over the period of time needed to obtain the NMR spectra. Integration of the spectrum for $(CH_3)_3Al$ dimer in toluene at −78 °C showed a 1:2 ratio of bridging to terminal methyl groups. When benzophenone was added to $(CH_3)_3Al$ in 1:2 ratio, the ratio of methyl groups now was 2:1. The low-field signal is due not only to the bridging methyl of the $\frac{1}{2}[Al(CH_3)_3]_2$ dimer remaining in solution, but also to the terminal methyl groups of $(CH_3)_3Al{\cdot}O{=}CPh_2$. Substantiation of this assignment was made by noting that the same low-field signal was observed for $(CH_3)_3Al{\cdot}O{=}CPh_2$ prepared by the reaction of $(CH_3)_3Al$ and $Ph_2C{=}O$ in 1:1 ratio. Thus it is clear that C is not an intermediate in the reaction, but that benzophenone (like diethyl ether) cleaves the $(CH_3)_3Al$ dimer completely when allowed to react in 1:2 ratio to form the monosolvate $(CH_3)_3Al{\cdot}O{=}CPh_2$ and $[(CH_3)_3Al]_2$ according to pathway II.

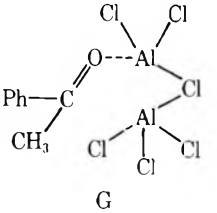
The question still remains, however, as to whether the initially formed $(CH_3)_3Al{\cdot}O{=}CPh_2$ is attacked by the second molecule of $(CH_3)_3Al$ via transition state B or D. As we have pointed out earlier,[3] there is not a great deal of difference between the two transition states if the transition state is represented by F. The major difference between B and D is



F

that the $(CH_3)_3Al$ in D is free to rotate while in B rigidity is imposed by a bridging methyl group. The important question from a stereochemical standpoint (nature of the transition state) is whether or not a methyl bridge bond is formed as the free monomeric $(CH_3)_3Al$ attacks the $Ph_2C{=}O{\cdot}Al(CH_3)_3$ complex. The formation of such a bond (B) would be energetically favored over D by 6 kcal. In addition, the large negative entropy of activation ($\Delta S^{\ddagger}$) for this reaction (−21.1 eu) supports a cyclic transition state.[3] Because evidence for pathway III involving ether or benzophenone was not found and since only a small concentration of the intermediate would be necessary to effect reaction, further effort was made to indicate the validity of this pathway.

Reaction of $(CH_3)_2AlCl$ with $Ph_2C{=}O$ in 2:1 Ratio. Starowieyski and co-workers[6] have presented evidence for a complex (G) in which one chlorine bridge remains intact when



G

$AlCl_3$ is admixed with acetophenone in 2:1 ratio. We had shown earlier[8] that $(CH_3)_2AlCl$ shows similar stereochemistry to $(CH_3)_3Al$ when allowed to react with 4-*tert*-butylcyclohexanone (91% axial attack in 2:1 ratio). By carrying out a study with $(CH_3)_2AlCl$ similar to that we have just described for $(CH_3)_3Al$, we felt that we should be able to observe pathway III (if indeed it exists) since Cl–Al bridge bonds are stronger than CH_3–Al bridge bonds. Also $(CH_3)_2AlCl$ would better resemble the actual situation with $(CH_3)_3Al$ than would $AlCl_3$ used in the study by Starowieyski. Since $(CH_3)_2AlCl$ shows the same unusual stereochemistry as $(CH_3)_3Al$ when allowed to react with 4-*tert*-butylcyclohexanone in benzene, the reaction is presumed to take place via the same transition state.

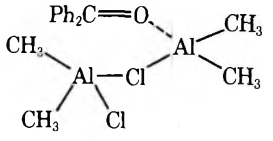
The 60-MHz ^1H NMR spectra for 1:1 and 2:1 ratios of $(CH_3)_2AlCl$:$O{=}CPh_2$ show clearly (Table I) that $(CH_3)_2AlCl$ and $Ph_2C{=}O$ in 2:1 ratio form the complex (H) containing two different methyl groups in 1:1 ratio since neither methyl group

Table I. ^{1}H NMR Data for Aluminum Alkyls and Complexes with Ether and Benzophenone in Toluene

Ratio (Al:O)	$(CH_3)_3Al$: $O(C_2H_5)_2$[a,c]	$(CH_3)_3Al$: $O{=}CPh_2$[b,c]	$(CH_3)_2AlCl$: $O{=}CPh_2$[b,c]
1:0	−2.09, −2.66 (1:2)	−2.08, −2.65 (1:2)	−2.42
1:1	−2.41	−2.07	−2.08
2:1	−2.07, −2.42, −2.65 (1:3:2)	−2.08, −2.65 (2:1)	−2.07, −2.2 (1:1)

[a] Solutions 1 M in $(CH_3)_3Al$. [b] Solutions 0.2 M in $Ph_2C{=}O$. [c] Measured from toluene methyl singlet.

corresponds to that of free $(CH_3)_2AlCl$ or $(CH_3)_2AlCl{\cdot}O{=}CPh_2$.



H

It is of course very difficult to obtain information concerning the exact structure of a transition state. However, in this study, it was possible to eliminate the intermediacy of complex C and to provide a modest amount of circumstantial evidence to support a six-center transition state in the reaction of $(CH_3)_3Al$ or $(CH_3)_2AlCl$ with benzophenone in 2:1 ratio in benzene. Because of the importance of the stereochemical outcome of organometallic addition reactions, a better understanding of the transition states in such reactions as discussed here should be of considerable value.

Experimental Section

Materials. Trimethylaluminum (Ethyl Corp.) was distilled under N_2 in a glove box. Diethyl ether was distilled under N_2 from $LiAlH_4$. Benzophenone was doubly distilled and stored in a desiccator over P_2O_5. Aluminum chloride was purified by sublimation under N_2 at 180 °C and transferred in a glove box. Benzene was distilled from $NaAlH_4$ under N_2 and toluene was distilled under N_2 from sodium.

Aluminum Alkyl Solutions. All aluminum alkyl solutions were standardized by total aluminum analysis (EDTA) and total methane after hydrolysis. The purity of each aluminum alkyl was further checked by NMR for the presence of aluminum alkoxides. The solutions were handled at the bench using standard Schlenk tube techniques.

Molecular Weight. Molecular weight measurements were carried out according to a procedure previously reported.[9] The k_f for benzene was determined experimentally using Me_3Al; $k_f = 5.163$. All solutions were prepared by weight and all additions were by weight.

NMR Samples. NMR samples for 100-MHz ^{1}H NMR were prepared in a glove box using 10% by volume of toluene-d_8 (Aldrich Chemical Co.) and then vacuum sealed. The NMR samples for 60-MHz ^{1}H NMR were prepared by addition of reagents to an NMR tube fitted with a serum cap and filled with nitrogen. The NMR tube was immersed in a dry ice–acetone bath before addition of Me_3Al or Me_2AlCl to the $Ph_2C{=}O$ which was added at room temperature.

NMR. ^{1}H NMR spectra (100 MHz) were recorded on a JEOL 100-MHz Fourier transform instrument. A Varian A-60D equipped with a low-temperature probe was used for obtaining 60-MHz NMR spectra. The $(CH_3)_3Al{\cdot}O{=}CPh_2$ (2:1) sample was checked for product formation by raising the probe temperature to where coalescence of the complex peaks would allow observation of product peaks.

Acknowledgment. We wish to acknowledge financial support of this work by the National Science Foundation, Grant MPS 7504127, and a generous gift of $(CH_3)_3Al$ by the Ethyl Corp.

Registry No.—$(CH_3)_3Al$, 75-24-1; $(CH_3)_2AlCl$, 1184-58-3; $O(C_2H_5)_2$, 60-29-7; $O{=}CPh_2$, 119-61-9; $(CH_3)_3Al{:}O(C_2H_5)_2$, 14878-85-4; $(CH_3)_3Al{:}O{=}CPh_2$, 60706-08-3; $(CH_3)_2AlCl{:}O{=}CPh_2$(1:1 ratio), 60706-09-4; $(CH_3)_2AlCl{:}O{=}CPh_2$(1:2 ratio), 60706-10-7.

References and Notes

(1) E. C. Ashby, J. Laemmle, and H. M. Neumann, *J. Am. Chem. Soc.*, **90**, 5179 (1968).
(2) E. C. Ashby and J. Laemmle, *J. Org. Chem.*, **33**, 3398 (1968).
(3) H. M. Neumann, J. Laemmle, and E. C. Ashby, *J. Am. Chem. Soc.*, **95**, 2597 (1973).
(4) J. Laemmle, E. C. Ashby, and P. V. Roling, *J. Org. Chem.*, **38**, 2526 (1973).
(5) T. Suzuki, T. Kobayashi, Y. Takegami, and Y. Dawasaki, *Bull. Chem. Soc. Jpn.*, **47**, 1971 (1974).
(6) K. B. Starowieyski, S. Pasynkiewicz, A. Sparzynski, and A. Chevojnowski, *J. Organomet. Chem.*, **94**, 361 (1975).
(7) E. A. Jeffery, T. Mole, and J. K. Saunders, *Aust. J. Chem.*, **21**, 649 (1968); E. A. Jeffery and T. Mole, *ibid.*, **23**, 715 (1970).
(8) E. C. Ashby and J. T. Laemmle, *J. Org. Chem.*, **40**, 1469 (1975).
(9) F. Walker and E. C. Ashby, *J. Chem. Educ.*, **45**, 654 (1968).

Studies on Selective Preparation of Aromatic Compounds. 13. Formation of Benzquinhydrone Type Complexes from 2-*tert*-Butylhalophenols in Alkaline Solution and Their Reduction with Zinc Powder in Acetic Acid Affording 4,4′-Dihydroxybiphenyls

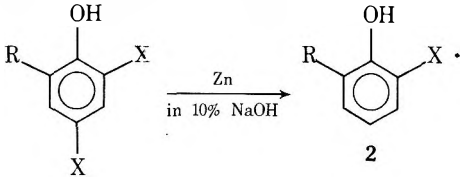
Masashi Tashiro* and Gouki Fukata

Research Institute of Industrial Science, Kyushu University Hakozaki, Higashi-ku, Fukuoka 812, Japan

Received July 2, 1976

Dark violet compounds (**3a–d**) were formed in good yields when a solution of 2-*tert*-butylhalophenols (**1e–h**) in 10% sodium hydroxide was warmed at 80 °C. However, 2,6-di-*tert*-butyl-4-bromophenol (**1i**) afforded 3,5,3′,5′-tetra-*tert*-butyldiphenoquinone (**4**) in the Claisen alkaline reagent. Compounds **3a–d** are quinhydrone type charge transfer complexes based on spectral and elemental data as well as their chemical conversion to 4,4′-dihydroxybiphenyls (**5a–d**) on reduction with zinc powder in acetic acid. Mechanisms for the formation of **3** are also discussed in this paper.

It has been previously reported that[1] some halophenols (**1**) were easily reduced with zinc powder in 10% sodium hydroxide solution to afford the reductive dehalogenated compounds (**2**) which were mainly *o*-halophenols, that is, the *p*-bromo or -iodo group was selectively reduced to give **2**. It was also found that in the case of 2-*tert*-butyl-4,6-dihalophenol (R = *t*-Bu) the rapid addition of zinc powder to an alkaline solution of **1** or addition of **1** to a suspension of zinc powder in alkaline solution was necessary to avoid the formation of dark violet compounds (**3**).



In order to clarify the structure and the mechanism for the formation of **3**, several halophenols were treated with 10% sodium hydroxide or the Claisen alkaline reagent.[2]

Results and Discussion

Treatments of 2,4,6-tribromo- (**1a**), 2,4-dibromo-6-methyl- (**1b**), 2,4-dichloro-6-*tert*-butyl- (**1c**), 2-*tert*-butyl-4-iodo- (**1d**), 2-chloro-6-*tert*-butyl- (**1e**), 2,4-dibromo-6-*tert*-butyl- (**1f**), 2-bromo-6-*tert*-butyl-4-iodo- (**1g**), 2-*tert*-butyl-4,6-dibromo- (**1h**), and 2,6-di-*tert*-butyl-4-bromophenol (**1i**) with 10% sodium hydroxide or the Claisen alkaline reagent[2] were carried out at 80 °C and the results are summarized in Table I and Scheme I. The latter condition was only used in the case of **1i**,

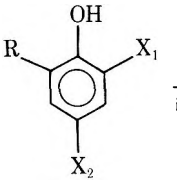
Table I. Treatment of 1 with Alkaline Solution at 80 °C[a]

Run	Substance	Time, min	Product (%)
1	**1a**	60	No reaction
2	**1b**	60	No reaction
3	**1c**	60	No reaction
4	**1d**	60	No reaction
5	**1e**	5	**3a** (99.7)
6	**1f**	5	**3b** (91.6)
7	**1g**	15	**3c** (99.5)
8	**1h**	5	**3d** (85.7)
9[b]	**1i**	60	**4** (95)

[a] The 10% sodium hydroxide solution was used unless otherwise indicated. [b] The Claisen alkaline solution was used.

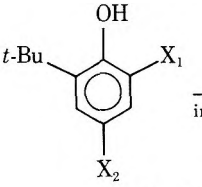
Scheme I

Group A

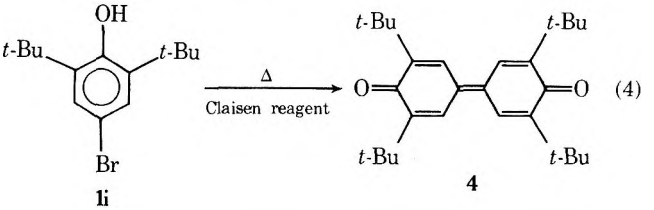


a, R = X_1 = X_2 = Br
b, R = CH_3, X_1 = X_2 = Br
c, R = *t*-Bu, X_1 = X_2 = Cl
d, R = *t*-Bu; X_2 = I; X_1 = H

Group B



e, X_1 = X_2 = I
f, X_1 = Br; X_2 = I
g, X_1 = X_2 = Br
h, X_1 = Cl; X_2 = I

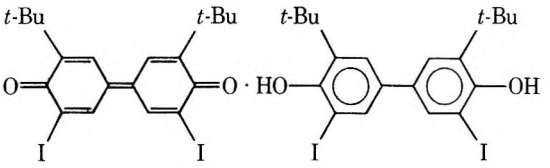


which was not soluble in 10% sodium hydroxide solution. These reactions took place at room temperature, although the reaction time was longer than at 80 °C.

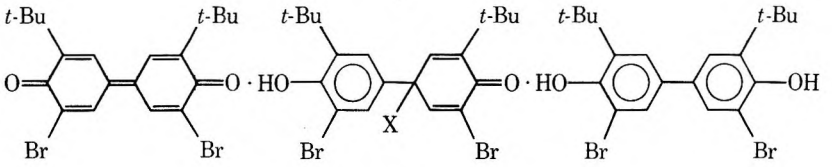
The data of Table I show that the phenols (**1**) can be classified into three groups (A, B, and C) as shown in Scheme I; group A (**1a–d**) did not react, group B (**1e–h**) afforded good yields of **3a–d**, respectively, group C (compound **1e**) gave 3,5,3′,5′-tetra-*tert*-butyl-4,4′-diphenoquinone (**4**), a product formed in the oxidation of 2,6-di-*tert*-butylphenol.[3-6]

Formation of **3** from **1** in alkaline solution requires the following three factors: (1) the alkyl group ortho to the hydroxy group should be *tert*-butyl but not methyl, (2) X_2 should be bromo or iodo but not chloro group, and (3) X_1 should be chloro, bromo, or iodo group but not hydrogen.

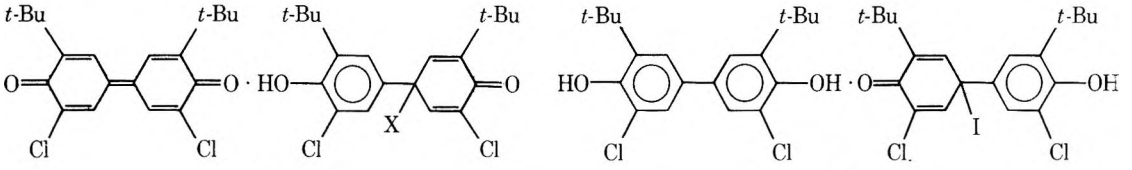
Scheme II



3a



3b, X = I
c, X = Br



3d$_1$ **3d**$_2$

Table II. IR Spectra of 3[a]

Run	Substance	$\nu_{C=O}$, cm^{-1}	ν_{OH}, cm^{-1}
1	**3a**	1610	3440
2	**3b**	1620	3460
3	**3c**	1620	3460
4	**3d**	1620	3420

[a] IR spectra were measured as KBr pellets.

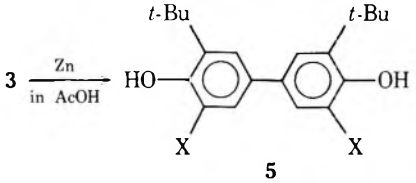
Table III. Reduction of 3 with Zinc Powder in AcOH at 20 °C

Run	3	Time, min	Product (%)
1	**a**	5	**5a** (75.5)
2[a]	**a**	60	**5d** (63)
3	**b**	30	**5b** (85.9)
4	**c**	30	**5b** (87.6)
5	**d**	30	**5c** (86)

[a] Reaction temperature 100 °C.

The infrared spectra of **3** are summarized in Table II. As is shown in Table II, all of **3** have quinoidal carbonyl and phenolic hydroxy groups. The ultraviolet spectra of **3** show strong absorptions in the visible region (see Experimental Section).

When compounds **3a–d** were treated with zinc powder in acetic acid, the corresponding 4,4′-dihydroxybiphenyls (**5**)



(5)

5

a, X = I
b, X = Br
c, X = Cl
d, X = H

were obtained in good yield (Table III).

It should be noted that the reduction of **3b** and **3c** afforded the same product, 3,3′-dibromo-5,5′-di-*tert*-butyl-4,4′-dihydroxybiphenyl (**5b**). The reduction of **3a** at 100 °C gave 3,3′-di-*tert*-butyl-4,4′-dihydroxybiphenyl (**5d**) but not 3,3′-di-*tert*-butyl-5,5′-diiodo-4,4′-dihydroxybiphenyl (**5a**), which was obtained by the reduction of **3a** at 20 °C for 5 min. The above result suggests that the iodo group of **5a** is easily reduced to afford **5d**. Indeed, **5d** was obtained in good yield by the reduction of **5a** at 100 °C with zinc powder in acetic acid.

However, in contrast to results with **5a**, compounds **5b** and **5c** did not yield **5d** under the same conditions used to reduce **5a**.

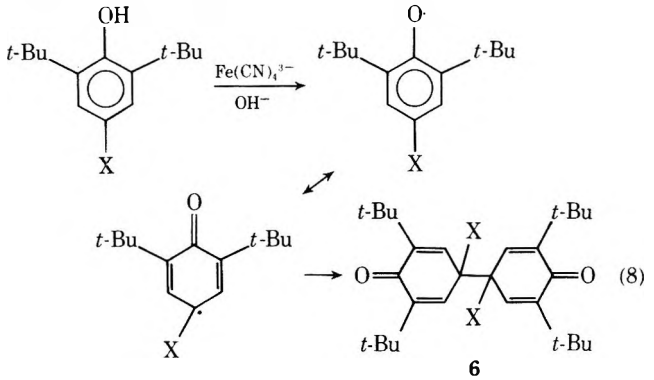
$$\mathbf{5a} \xrightarrow[\text{in AcOH}]{\text{Zn}} \mathbf{5d} \quad (6)$$

$$\mathbf{5b\text{–}c} \xrightarrow[\text{in AcOH}]{\text{Zn}} \mathbf{5d} \quad (7)$$

Compounds **3a** and **5a** might be good starting compounds in the preparation of **5d**, a compound which could not be prepared in the usual manner.[7]

Based on the results described above and the spectral data as well as elemental analyses of **3**, compounds **3a–d** are proposed to be quinhydrone type charge transfer complexes (Scheme II).

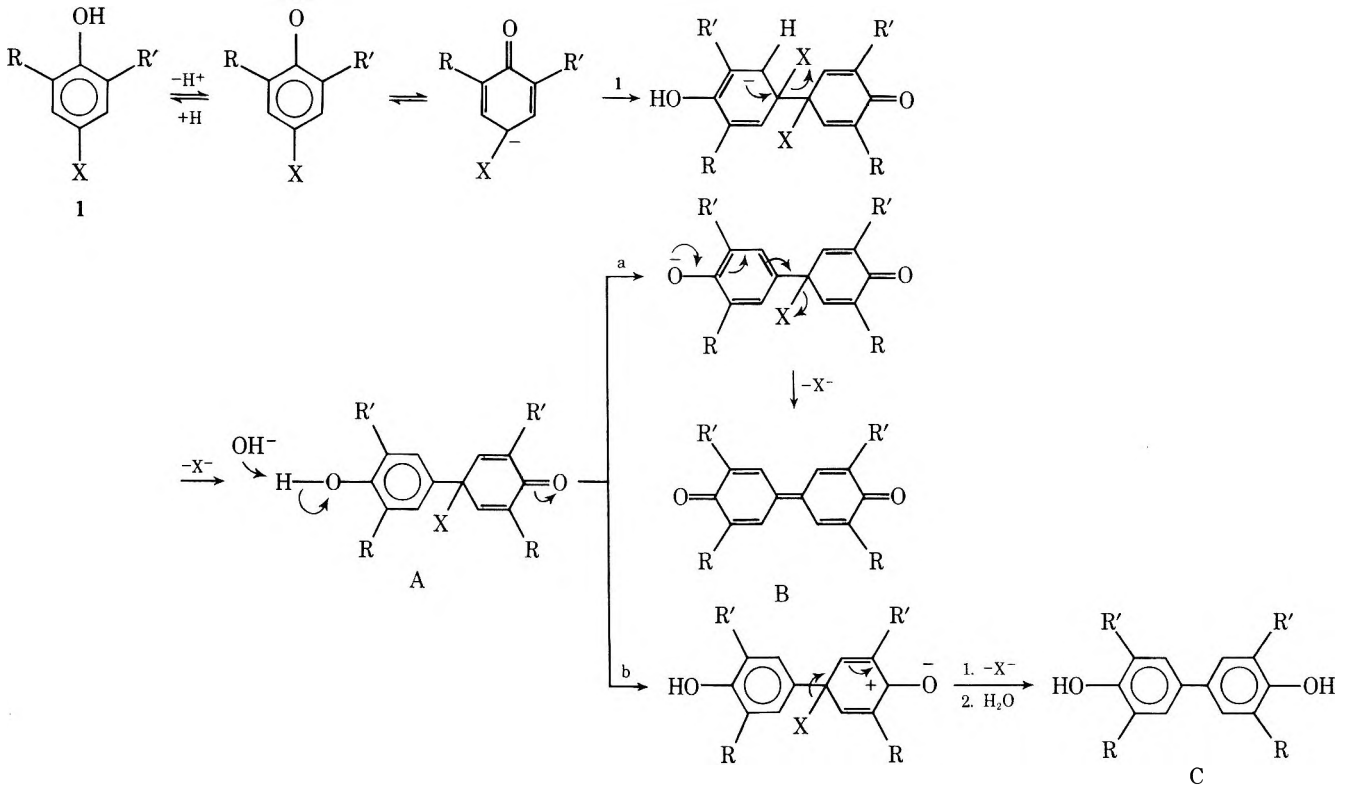
The ^{13}C NMR spectrum of **3c** shows a signal at 37.8 ppm which can be assigned to an sp^3 carbon atom bonded to a bromine atom. This signal could not be observed in the ^{13}C NMR spectrum of **3a**. These results also support the proposed structure of **3**. Unfortunately, it could not be determined whether structure **3d**$_1$ or **3d**$_2$ is correct based on the available data. The conversion of **1** to **3** took place even under a nitrogen atmosphere. Recently the formation of 1,1′-dihalo-3,5,3′,5′-tetra-*tert*-butyl-2,5,2′,5′-biscyclohexadien-4,4′-one (**6**) in the



(8)

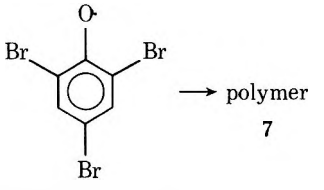
6

Scheme III



oxidation of 2,6-di-*tert*-butyl-4-halophenol with alkaline ferricyanide was reported by Cook.[8]

It was also reported that[8] 2,4,6-tribromophenoxy radical afforded polymer **7**.



(9)

As described above, the reported product **6** was not obtained in the treatment of **1i** with the Claisen alkaline reagent. Also compound **1a** was recovered in quantitative yield and did not give the reported polymer **7**.

The ionic mechanisms shown in Scheme III for the formation of **3** and **4** might be reasonable. The different combination of A, B, and C might afford the alternative type charge transfer complexes **3a–d** and **4**. In the case of **4**, the steric

$$\mathbf{B} + \mathbf{C} \longrightarrow \mathbf{3a} \quad (10)$$

$$\mathbf{A} + \mathbf{B} + \mathbf{C} \longrightarrow \mathbf{3b, 3c} \quad (11)$$

$$\left.\begin{matrix}\mathbf{A} + \mathbf{B} \\ \text{or} \\ \mathbf{A} + \mathbf{C}\end{matrix}\right\} \longrightarrow \mathbf{3d} \quad (12)$$

$$\mathbf{B} \longrightarrow \mathbf{4} \quad (13)$$

hindrance of two *tert*-butyl groups might preclude such complexation and yield only B (**4**).

Experimental Section

All melting points are uncorrected. IR spectra were measured as KBr pellets on a Nippon Bunko IR-S spectrophotometer and NMR spectra were determined at 60 MHz with a Hitachi R-20 NMR spectrometer using Me_4Si as an internal reference.

Treatment of 2,4,6-Tribromo- (1a),[8] 2,4-Dibromo-6-methyl- (1b),[9] 2,4-Dichloro-6-*tert*-butyl- (1c),[10] and 2-*tert*-Butyl-4-iodophenol (1d)[1] with 10% Sodium Hydroxide. After a solution of 5 g of **1** (**1a–d**) in 50 ml of 10% sodium hydroxide was heated at 80 °C for 60 min, the reaction mixture was acidified with 10% hydrochloric acid and extracted with benzene. The extract was dried over sodium sulfate and evaporated in vacuo to afford the starting material **1** in almost quantitative yields, respectively.

Formation of 3a from 2-*tert*-Butyl-4,6-diiodophenol (1e). After a solution of 5 g (12.5 mmol) of **1e** in 50 ml of 10% sodium hydroxide was heated at 80 °C for 5 min, the precipitated dark violet product was collected by filtration and washed with a large amount of water and then with a small amount of ether to afford 3.4 g (99.7%) of **3a**: mp 122–140 °C dec; IR (KBr) 3440 (OH), 1610 cm^{-1} (C=O); UV λ_{max} (EtOH) 322 nm (log ϵ 4.73), 255 (4.36), 290 (4.23), 428 (4.71), 444 (4.65), 475 (4.53).

Anal. Calcd for $C_{40}H_{46}O_4I_4$: C, 43.74; H, 4.22. Found: C, 43.48; H, 4.20.

Formation of 3b from 2-Bromo-6-*tert*-butyl-4-iodophenol (1f). When a solution of 3.55 g (10 mmol) of **1f**[1] in 50 ml of 10% sodium hydroxide was heated at 80 °C for 5 min, similarly 2.4 g (91.6%) of **3b** was isolated: mp 110–135 °C dec; IR (KBr) 3460 (OH), 1620 cm^{-1} (C=O); UV λ_{max} (EtOH) 220 nm (log ϵ 4.90), 240 (4.62), 270 (4.56), 417.5 (5.09), 428 (5.12), 435 (5.11).

Anal. Calcd for $C_{60}H_{69}O_6Br_6I$: C, 48.28; H, 4.66. Found: C, 48.32; H, 4.49.

Formation of 3c from 2,4-Dibromo-6-*tert*-butylphenol (1g). Similarly 2.5 g (8 mmol) of **1g**[11] was treated at 80 °C for 15 min and worked up as described above to afford 1.95 g (99.5%) of dark brown product (**3c**): mp 85–100 °C dec; IR (KBr) 3460 (OH), 1620 cm^{-1} (C=O); UV λ_{max} (EtOH) 220 nm (log ϵ 4.95), 240 (4.79), 270 (4.55), 417.5 (4.99), 428 (5.04), 435 (5.21).

Anal. Calcd for $C_{60}H_{69}O_6Br_7$: C, 49.85; H, 4.81. Found: C, 49.98; H, 4.61.

Formation of 3d from 2-Chloro-6-*tert*-butyl-4-iodophenol (1h). Similarly 0.5 g (1.6 mmol) of **1h**[1] was treated at 80 °C for 5 min and worked up as described above to afford 0.3 g (85.7%) of **3d**: mp 90–105 °C dec; IR (KBr) 3420 (OH), 1620 cm^{-1} (C=O); UV λ_{max} (EtOH) 220 nm (log ϵ 4.75), 240 (4.41), 260 (4.27), 270 (4.24), 280 (4.22), 412 (4.79), 426 (4.85), 432 (4.74).

Anal. Calcd for $C_{40}H_{45}O_4Cl_4I$: C, 55.96; H, 5.28. Calcd for $C_{40}H_{47}O_4Cl_4I$: C, 55.83; H, 5.51. Found: C, 56.51; H, 5.32.

Reduction of 3a. A. At 20 °C. To a solution of 2 g (1.8 mmol) of **3a** in 40 ml of acetic acid was added at 20 °C 4 g of zinc powder. The reduction mixture was stirred for 5 min and the unreacted zinc powder was filtered off. To the filtrate was added 80 ml of water, affording 1.56 g (75.5%) of **5a**, mp 85–89 °C dec, as a colorless, crystalline powder ($AcOH-H_2O$): IR (KBr) 3550 (shoulder), 3480 cm^{-1} (OH); NMR ($CHCl_3$) δ 1.45 [18 H, s, $(CH_3)_3$], 5.52 (2 H, s, OH), 7.35 (2 H, d, J = 2.2 Hz), 7.64 (2 H, d, J = 2.2 Hz, aromatic protons).

Anal. Calcd for $C_{20}H_{24}O_2I_2$: C, 43.66; H, 4.40. Found: C, 43.46; H, 4.60.

B. At 100 °C. A solution of 1 g (0.9 mmol) of **3a** in 40 ml of acetic acid was treated with 2 g of zinc powder at 100 °C for 60 min and worked up as described above, 0.40 g of the crude of **5d**. The purification of the crude product was carried out by column chromatography on silica gel using chloroform, affording 0.34 g (63%) of **5d**: mp 181–183 °C (lit.[7] mp 181–183 °C); colorless plates (petroleum ether); IR (KBr) 3550, 3440 cm^{-1} (OH); NMR ($CDCl_3$) δ 1.45 [18 H, s, $(CH_3)_3$], 4.78 (2 H, s, OH), 6.67 (2 H, d, J_{ac} = 7.61 Hz), 7.15 (2 H, d, J_{ab} = 2.21 Hz), 7.36 (2 H, dd, J_{ab} = 2.25 Hz, J_{ac} = 7.65 Hz, aromatic protons).

Reduction of 5a. To a solution of 0.55 g (1.0 mmol) of **5a** was added 1 g of zinc powder. The reaction mixture was heated at 100 °C for 60 min, and worked up as described above. The compound **5d** was obtained in 70% yield, mp 181–183 °C.

Reduction of 3b. A solution of 2.4 g (1.6 mmol) of **3b** in 50 ml of acetic acid was treated with 4.5 g of zinc powder at 20 °C for 30 min and worked up as described above to give 1.89 g (85.9%) of **5b**: mp 55–59 °C; colorless, crystalline powder ($AcOH-H_2O$); IR (KBr) 3530 cm^{-1} (OH); NMR ($CDCl_3$) δ 1.42 [18 H, s, $(CH_3)_3$], 5.80 (2 H, s, OH), 7.31 (2 H, d, J = 2.25 Hz), 7.74 (2 H, d, J = 2.25 Hz, aromatic protons).

Anal. Calcd for $C_{20}H_{24}O_2Br_2$: c, 52.65; H, 5.30. Found: C, 52.87; H, 5.44.

Reduction of 3c. A solution of 1.95 g (1.3 mmol) of **3c** in 40 ml of acetic acid was treated with 4 g of zinc powder and worked up as described above. Similarly 1.02 g (87.6%) of **5b** was obtained.

Reduction of 3d. Similarly 85 mg (86%) of **5c** was obtained from 100 mg (0.1 mmol) of **3d** with 200 mg of zinc powder in 5 ml of acetic acid. **5c**: mp 54–58 °C; colorless, crystalline powder; IR (KBr) 3540 cm^{-1} (OH); NMR ($CDCl_3$) δ 1.45 [18 H, s, $(CH_3)_3$], 5.86 (2 H, s, OH), 7.20–7.45 (4 H, m, aromatic protons).

Anal. Calcd for $C_{20}H_{24}O_2Cl_2$: C, 65.40; H, 6.59. Found: C, 65.03; H, 6.52.

Formation of 3,5,3′,5′-Tetra-*tert*-butylphenoquinone (4) from 2,6-Di-*tert*-butyl-4-bromophenol (1i). A solution of 5 g (17.5 mmol) of **1i** in 30 ml of the Claisen alkali reagent was heated at 80 °C for 60 min and worked up as described above to give 3.4 g (95%) of **4** as orange needles, mp 241–243 °C (lit. mp 240–241 °C).

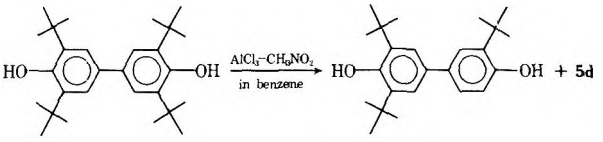
Preparation of 2-*tert*-Butyl-4,6-diiodophenol (1e). To a solution of 11 g (73.2 mmol) of 2-*tert*-butylphenol in 30 ml of acetic acid was added at 40 °C a solution of 25 g (154 mmol) of ICl in 20 ml of acetic acid. After the reaction mixture was heated at 70 °C for 5 min, it was poured into a large amount of water and extracted three times with 100 ml of benzene. The extract was dried over sodium sulfate and evaporated in vacuo to leave the dark brown residue which was chromatographed on silica gel using benzene as an eluent affording 20 g (68%) of **1e** as colorless needles (EtOH): mp 55.5–57.5 °C; IR (KBr) 3500 cm^{-1} (OH); NMR ($CDCl_3$) δ 1.35 [9 H, s, $(CH_3)_3$], 5.50 (1 H, s, OH), 7.43 (1 H, d, J = 2.25 Hz), 7.80 (1 H, d, J = 2.25 Hz, aromatic protons).

Anal. Calcd for $C_{10}H_{12}OI_2$: C, 29.87; H, 3.01. Found: C, 29.42; H, 2.29.

Registry No.—**1a**, 118-79-6; **1b**, 609-22-3; **1c**, 13395-86-3; **1d**, 60803-25-0; **1e**, 60803-26-1; **1f**, 60803-27-2; **1g**, 15460-12-5; **1h**, 60803-28-3; **1i**, 1139-52-2; **3a**, 60828-71-9; **3b**, 60803-32-9; **3c**, 60803-34-1; **3d**$_1$, 60803-37-4; **3d**$_2$, 60803-39-6; **5a**, 60828-70-8; **5b**, 60803-31-8; **5c**, 60803-38-5; **5d**, 60803-40-9; 2-*tert*-butylphenol, 88-18-6.

References and Notes

(1) Part 12: M. Tashiro and G. Fukata, *J. Org. Chem.*, in press.
(2) L. Claisen, *Justus Liebigs Ann. Chem.*, **418**, 89 (1919).
(3) H. Dietl and H. S. Young, *J. Org. Chem.*, **37**, 1672 (1972).
(4) L. H. Vogt, Jr., J. G. Wirth, and H. L. Finkbeiner, *J. Org. Chem.*, **34**, 273 (1969).
(5) M. S. Kharasch and B. S. Joshi, *J. Org. Chem.*, **22**, 1439 (1957).
(6) H. Hunt and F. A. Cassis Jr., *J. Am. Chem. Soc.*, **73**, 3179 (1951).
(7) The preparation of **5d** was only reported in the partial transalkylation reaction of 3,5,3′,5′-tetra-*tert*-butyl-4,4′-dihydroxydiphenyl. M. Tashiro and G. Fukata, *Org. Prep. Proced. Int.*, in press.
(8) G. D. Cook and D. G. Imour, *J. Org. Chem.*, **25**, 1429 (1960).
(9) E. E. Turner, *J. Chem. Soc.*, 514 (1929).
(10) T. Zincke and N. Junney, *Justus Liebigs Ann. Chem.*, **398**, 354 (1913).
(11) I. Brown, G. Eglinton, and M. Martin-Smith, *Spectrochim. Acta*, **18**, 1593, 1601 (1962).



Transfer Hydrogenation and Transfer Hydrogenolysis. 13. Hydrogen Transfer from Cyclic Amines to Aromatic Nitro Compounds Catalyzed by Noble Metal Salts

Hideaki Imai,* Takeshi Nishiguchi, and Kazuo Fukuzumi

Department of Applied Chemistry, Faculty of Engineering, Nagoya University, Chikusa-ku, Nagoya, Japan

Received June 15, 1976

Noble metal salts were found to catalyze the homogeneous transfer hydrogenation of nitrobenzenes to anilines in good yields using indoline as a hydrogen donor. Tetrahydroquinoline, piperidine, and pyrrolidine also showed relatively high hydrogen donating ability. $RuCl_3 \cdot H_2O$ and $RhCl_3 \cdot 3H_2O$ had high and $PdBr_2$ and $PdCl_2$ moderate catalytic activity. A mechanistic pathway is proposed in which the initial formation of Rh(I) species, the coordination of nitrobenzene to Rh(I) species, and the hydrogen transfer from indoline to nitrobenzene on the metal are involved. Nitrosobenzene was detected as an intermediate.

It has been reported that the reduction of a nitro group by molecular hydrogen is catalyzed by several heterogeneous[1] and homogeneous catalysts.[2] However, the catalytic reduction of a nitro group by the hydrogen transfer from organic compounds (transfer hydrogenation) has been scarcely reported. So far as we know, the only example seems to be that cyclohexene reduced nitrobenzenes to the corresponding anilines in the presence of Pd–carbon,[3] and the mechanism of the reduction was hardly discussed.

During the course of the systematic study of transfer hydrogenations, we found that aromatic nitro compounds were reduced to the corresponding amines in the presence of noble metal salts under mild reaction conditions. So we undertook this study to enlarge the scope of the transfer hydrogenation of nitroaryls and to discuss the mechanism of the reaction.

Results and Discussion

Catalytic Activity. In the reaction system in which indoline (1.5 mol $l.^{-1}$), nitrobenzene (0.5 mol $l.^{-1}$), and a soluble catalyst (0.08 mol $l.^{-1}$) or a metallic palladium catalyst (20 g/l.) were heated in toluene at 80 °C for 4 h, the activity of several catalysts was examined. Although some of the noble metal

Table I. Rate of Reduction of Monosubstituted Nitrobenzenes[a]

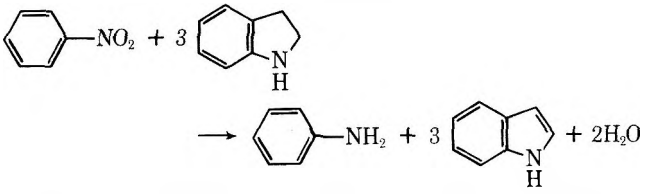
Registry no.	Hydrogen acceptor	Rate, mol $l.^{-1}$ min^{-1}
100-00-5	*p*-Nitrochlorobenzene	33.9×10^{-4}
100-19-6	*p*-Nitroacetophenone	32.0×10^{-4}
98-95-3	Nitrobenzene	23.4×10^{-4}
88-73-3	*o*-Nitrochlorobenzene	11.0×10^{-4}
121-73-3	*m*-Nitrochlorobenzene	6.7×10^{-4}
554-84-7	*m*-Nitrophenol	6.3×10^{-4}
100-02-7	*p*-Nitrophenol	5.2×10^{-4}
100-17-4	*p*-Nitroanisole	5.0×10^{-4}
99-99-0	*p*-Nitrotoluene	4.3×10^{-4}
100-01-6	*p*-Nitroaniline	4.2×10^{-4}
99-08-1	*m*-Nitrotoluene	4.0×10^{-4}
88-72-2	*o*-Nitrotoluene	3.1×10^{-4}
88-75-5	*o*-Nitrophenol	1.7×10^{-4}

[a] $RhCl_3 \cdot 3H_2O$ (0.08 mol $l.^{-1}$), indoline (1.5 mol $l.^{-1}$), and the hydrogen acceptor (0.5 mol $l.^{-1}$) were heated in dioxane at 80 °C.

salts scarcely dissolved in toluene at room temperature, they dissolved in the solvent at the reaction temperature in the presence of the reactants. In these conditions, the amount of metallic palladium in 5% Pd–carbon, 50% Pd–asbestos, or Pd black is about 0.12, 1.2, or 2.3 times as much as that in palladium salts, respectively. Under this condition, $RuCl_3 \cdot H_2O$ (88%) and $RhCl_3 \cdot 3H_2O$ (82%) showed high catalytic activity. $PdBr_2$ (50%) and $PdCl_2$ (20%) showed moderate and $ReCl_5$ (5%), $(NH_4)_2PdCl_4$ (3%), and K_2PtCl_4 (2%) low catalytic activity. Here, the percentages shown in parentheses are the yield of aniline. K_2PtCl_6, $FeCl_2 \cdot 2H_2O$, $CoCl_2 \cdot 6H_2O$, $NiCl_2 \cdot 6H_2O$, $RhCl(PPh_3)_3$, $RhH(PPh_3)_4$, $RuCl_2(PPh_3)_3$, and $RuH_2(PPh_3)_4$ hardly catalyzed the reduction. Pd black, Pd–carbon, and Pd–asbestos gave yields of 52, 18, and 6%, respectively. A rather good reproducibility of the results was confirmed. It is noteworthy that the triphenylphosphine complexes which exhibited high catalytic activity in the transfer hydrogenation of olefins and carbonyl compounds[4-7] showed no activity. Perhaps this fact is explained by the inference that nitrobenzene, which is strongly polarized,[8] has strong coordinating power and several nitrobenzene molecules occupy the coordination sites of the catalysts to make the coordination of indoline difficult. In any experiments described hereafter, $RhCl_3 \cdot 3H_2O$ was used as a catalyst.

Hydrogen Donors. We have previously reported that ethers,[4,7] amines,[5] alcohols,[6] and hydrocarbons[7] donated their hydrogen atoms to olefins and aldehydes in the presence of phosphine complexes or Pd–carbon. When the reduction of nitrobenzene was carried out in toluene at 120 °C for 4 h in the presence of $RhCl_3 \cdot 3H_2O$, indoline was found to have an excellent hydrogen donating ability (97%). Secondary cyclic amines, such as tetrahydroquinoline (57%), 3-pyrroline (45%), piperidine (28%), and pyrrolidine (23%), functioned as fair hydrogen donors. Here, the percentages shown in parentheses are the yield of aniline. In the reaction of indoline and tetrahydroquinoline the stoichiometric amounts of indole and quinoline were detected, respectively. *N*-Methylpiperidine, *N*-methylpyrrolidine, 2,5-dihydrofuran, tetralin, and cyclohexene hardly showed hydrogen donating ability. Tri-*n*-propylamine, cyclohexylamine, 2-propanol, methanol, cyclohexanol, 1-phenylethanol, dioxane, tetrahydrofuran, and indan showed no hydrogen donating ability. Since nitrobenzene seems to have strong coordinating power by the high degree of N–O bond polarization,[8] the hydrogen donors with strong coordinating power may be effective for the reduction of nitrobenzene. At least partly, the higher hydrogen donating ability of secondary cyclic amines is explained by this inference.

When indoline (1.5 mol $l.^{-1}$), nitrobenzene (0.5 mol $l.^{-1}$), and $RhCl_3 \cdot 3H_2O$ (0.08 mol $l.^{-1}$) were heated in toluene at 80 °C for 4 h, aniline was obtained in 82% yield (0.41 mol $l.^{-1}$) along with the dehydrogenation product, indole (1.30 mol $l.^{-1}$), and survived indoline (0.19 mol $l.^{-1}$) and nitrobenzene (0.09 mol $l.^{-1}$) also were detected in the reaction mixture. This result is summarized as follows. (1) The amount of indole was equal to the theoretical one within experimental errors, because 1.31 mol $l.^{-1}$ of hydrogen is needed to form 0.41 mol $l.^{-1}$ of aniline and to reduce 0.08 mol $l.^{-1}$ of a Rh(III) species to a Rh(I) species. (2) The total amount of indoline and indole was nearly equal to the amount of the charged indoline. (3) The total amount of aniline and nitrobenzene was equal to the amount of the charged nitrobenzene. Other products, such as azo and azoxy compounds, were not detected by GLC and TLC analysis. These results show that the following reaction proceeded without remarkable side reactions.



Reaction Solvents. When ethanol, *N*,*N*-dimethylformamide, ethyl acetate, benzene, dioxane, chlorobenzene, toluene, and methanol were used as solvents, the yield of aniline was not so varied. This fact may be explained by the presumption that indoline and nitrobenzene coordinate rather strongly on catalytic species. However, the reduction proceeded rather slower in *N*,*N*-dimethylacetamide and much slower in dimethyl sulfoxide and benzonitrile. These compounds may coordinate so strongly as to prevent the coordination of the hydrogen donor. When the reaction was carried out in water, a black, tarry material was formed and no aniline was detected.

Effect of Additives. The addition of sodium borohydride to the reaction system promoted the reduction of nitrobenzene. The hydride donated the hydrogen atoms catalytically, because it could not reduce nitrobenzene without a catalyst. Therefore, sodium borohydride was found to be an excellent hydrogen donor. Water, which is one of the products, and anhydrous sodium sulfate, which is a dehydrating agent, did not affect the reduction. The addition of hydrochloric acid moderately retarded the reduction. Perhaps, the acid deactivates the hydrogen donor by salt formation and the catalyst by coordination. Although the removal of hydrogen chloride seems to be necessary in order to activate $RhCl_3$ as described later, the addition of the amines having no hydrogen donating ability, such as *n*-propylamine, tri-*n*-octylamine, *N*,*N*-dimethylaniline, and pyridine, decreased the yield of aniline. The addition of triphenylphosphine and triphenyl phosphite also retarded the reaction. These inhibitors coordinate to the metal and make the coordination of indoline difficult. The addition of potassium hydroxide, which has been reported to promote the reduction of nitro compounds by molecular hydrogen,[2b] inhibited the transfer hydrogenation completely, because the addition caused the precipitation of metallic rhodium.

Substituent Effect. Initial rates of the reduction of monosubstituted nitrobenzenes were measured in dioxane, which has higher dissolving ability than toluene (Table I). Roughly speaking, the substances having electron-withdrawing substituents were reduced more rapidly than those having electron-donating ones.[1c] In order to interpret this result, the coordination ability of nitrobenzenes was evaluated. The visible spectrum of the methanol solution of $RhCl_3 \cdot 3H_2O$ showed an absorption peak at 510 nm (ϵ 160) and the strength of the peak decreased gradually after the addition of nitro-

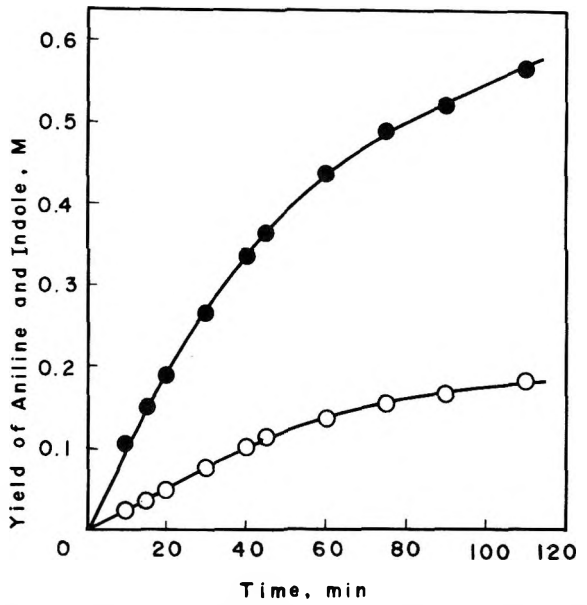


Figure 1. Plot of the yield of aniline and indole vs. reaction time. $RhCl_3 \cdot 3H_2O$ (0.04 mol $l.^{-1}$), indoline (1.5 mol $l.^{-1}$), and nitrobenzene (0.5 mol $l.^{-1}$) were heated in methanol at 70 °C. (○), aniline; (●), indole.

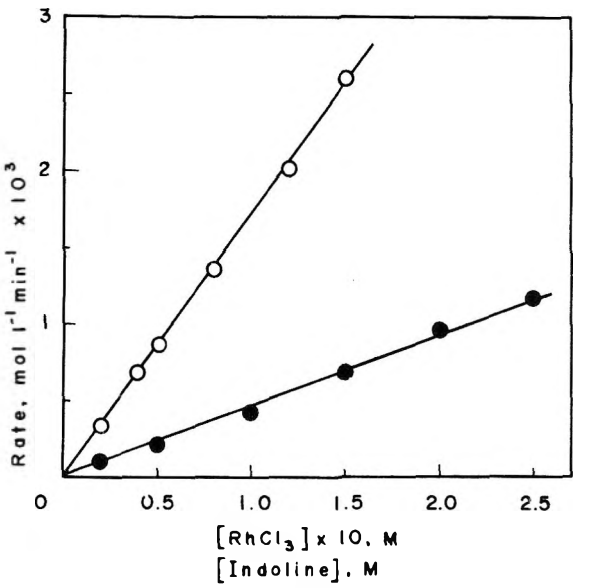


Figure 2. Dependence of rate of reduction of nitrobenzene (0.5 mol $l.^{-1}$) on the concentration of the catalyst (○) (1.5 mol $l.^{-1}$ indoline) and indoline (●) (0.04 mol $l.^{-1}$ $RhCl_3 \cdot 3H_2O$) in methanol at 60 °C.

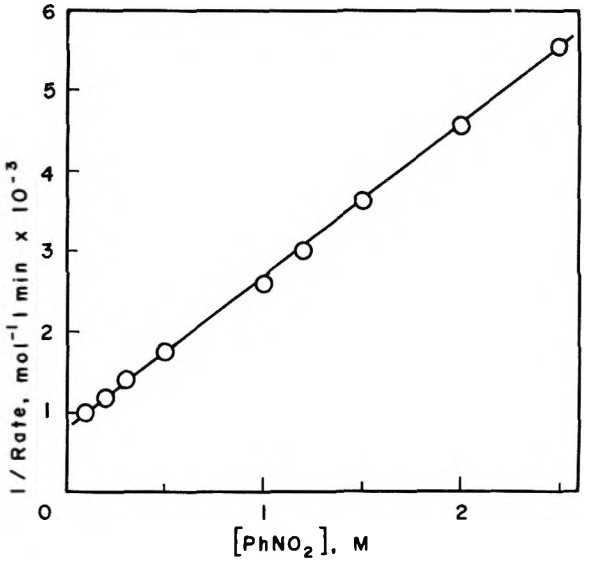


Figure 3. Dependence of rate of reduction of nitrobenzene on the concentration of nitrobenzene. $RhCl_3 \cdot 3H_2O$ (0.04 mol $l.^{-1}$), indoline (1.5 mol $l.^{-1}$), and nitrobenzene were heated in methanol at 60 °C.

benzenes. The nitrobenzenes having *p*-Cl, *p*-$COCH_3$, H, *p*-CH_3, or *p*-OCH_3 as a substituent showed almost the same initial rate of the disappearance of the peak and nearly equal final strength of the peak. This result suggests that the coordinating powers of nitrobenzenes were not so different. The substituent effect in the reduction of nitrobenzenes might be caused by the ease of the hydrogen transfer from a metal hydride intermediate to the coordinated nitrobenzenes and/or by the ability of the complexes coordinated by nitrobenzenes to accept hydrogen atoms from indoline.

Aliphatic nitro compounds were not reduced under these reaction conditions. Partly reduced derivatives, nitrosobenzene and phenylhydroxylamine, were reduced to aniline much faster under the condition in Table I with rates of 1.26×10^{-2} and 1.23×10^{-2} mol $l.^{-1}$ min^{-1}, respectively. Hydrazobenzene and azobenzene could be reduced to aniline under the same condition with rates of 8.5×10^{-3} and 5.9×10^{-3} mol $l.^{-1}$ min^{-1}, respectively.

Kinetic Study

A kinetic study was carried out using methanol as solvent. Figure 1 shows an example of the yield of aniline and indole against time plots, and indicates that the reproducibility of the reaction was fairly good because the data shown in the figure were obtained by different runs (see Experimental Section). The yield of aniline was proportional to reaction time until about 0.10 mol (20%) and the initial rate of the reduction of nitrobenzene was derived from the linear part. The rate showed the first-order dependence on the concentration of the catalyst and that of indoline (Figure 2). The initial rate decreased with the increase of the concentration of nitrobenzene, and the reciprocal of the rate against the concentration of nitrobenzene was linear with a positive intercept on the *y* axis (Figure 3). The data in Figure 3 may be accommodated by the relationship

$$1 \Big/ \frac{d[PhNH_2]}{dt} = a[PhNO_2] + b \qquad (1)$$

where *a* and *b* are constants.

Based on the results described above, the rate of the reduction can be described by the expression

$$\frac{d[PhNH_2]}{dt} = k \frac{[Rh]_0[indoline]}{1 + K[PhNO_2]} \qquad (2)$$

where the rate constant, *k*, had the value of 0.08 mol^{-1} l. min^{-1}, and the constant, *K*, had that of 1.5 mol^{-1} l. Since the dimension of *K* does not contain time, *K* is inferred to be an equilibrium constant or a ratio of rate constants.

Initial rates were measured at temperatures ranging from 40 to 100 °C and the Arrhenius plot showed a good linear relationship, indicating that the kinetics of the system and are not so complicated. From the plot, the activation energy of 14.4 kcal mol^{-1} was obtained.

Discussion of Mechanism

It has been reported that $RhCl_3$, which was used as a catalyst, is reduced to a Rh(I) species in the reduction of unsaturated compounds by molecular hydrogen.[9] In our system too, Rh(I) species are assumed to be active catalytic species by the following observations: (1) Indoline was dehydrogenated to indole by heating with $RhCl_3$ in the absence of a hydrogen acceptor and the reaction mixture did not show the absorption peak at 510 nm which may be assignable to a Rh(III) species, while the peak remained unchanged in the mixture which had

not been heated. (2) The amount of indole in a reaction mixture was larger than the one calculated from the yield of aniline and nearly equalled the one needed to reduce both nitrobenzene and $RhCl_3$.

We should like to propose the following reaction process for the transfer hydrogenation of nitrobenzene.

$$Rh^{III}Cl_3 + \text{indoline} \rightarrow Rh^{I}Cl + \text{indole} + 2HCl \quad (3)$$

$$Rh^{I}Cl + PhNO_2 \rightarrow Rh^{I}Cl(PhNO_2) \quad (4)$$

$$Rh^{I}Cl(PhNO_2) + 3\ \text{indoline} \rightarrow Rh^{I}Cl + PhNH_2 + 3\ \text{indole} + 2H_2O \quad (5)$$

According to this suggestion, $RhCl_3$ is activated to a Rh(I) species by indoline (eq 3), nitrobenzene coordinates to the Rh(I) species (eq 4), and then the coordinated nitrobenzene is reduced to aniline by the hydrogen donor (eq 5). As described before, the coordination of nitrobenzenes to $RhCl_3$ was confirmed by the spectroscopic study.

$$Rh^{III}Cl_3 + PhNO_2 \overset{K'}{\rightleftarrows} Rh^{III}Cl_3(PhNO_2) \quad (6)$$

The rate expression, eq 2, suggests that this step is not involved in the catalytic cycle of the reduction and K' in eq 6 corresponds to K in eq 2, because the term $[PhNO_2]$ appears only in the denominator of eq 2. Further, eq 2 indicates that the coordination of nitrobenzenes to $RhCl_3$ and Rh(I) species occurs in parallel and that the formation of Rh(I) species from the Rh(III) species in eq 3 is depressed by the coordination of nitrobenzene to $RhCl_3$.

In the process of the hydrogen transfer shown in eq 5, 3 mol of indoline is necessary for the reduction of 1 mol of nitrobenzene. Therefore, three hydrogen transfer steps from indoline will be involved, as shown in Scheme I.

Scheme I

$$PhNO_2 \xrightarrow[-\text{indole}\ -H_2O]{\text{indoline}} PhNO \xrightarrow[-\text{indole}]{\text{indoline}} PhNHOH \xrightarrow[-\text{indole}\ -H_2O]{\text{indoline}} PhNH_2$$

In the reduction of nitrobenzene, nitrosobenzene was detected, but phenylhydroxylamine was not. Since nitrosobenzene and phenylhydroxylamine were reduced to aniline about five times as fast as nitrosobenzene, the deoxygenation of nitrobenzene to nitrosobenzene is considered to be the rate-determining step.

Experimental Section

Materials. Rhodium trichloride, ruthenium trichloride, palladium bromide, palladium chloride, rhenium pentachloride, ammonium palladous chloride, potassium chloroplatinate, palladium black, palladium carbon, and palladium asbestos were purchased and used without purification. Amines, alcohols, ethers, and hydrocarbons were purified by distillation and dried by the usual methods. Nitrobenzene, *p*- and *m*-nitrotoluene, and *o*- and *m*-nitrochlorobenzene were purified by distillation. Other nitrobenzenes, nitrosobenzene, azobenzene, and hydrazobenzene were purified by recrystallization. Phenylhydroxylamine was synthesized by the method reported in the literature.[10]

An Example of Transfer Hydrogenation. Nitrobenzene (30.8 mg, 0.25 mmol), indoline (89.3 mg, 0.75 mmol), and $RhCl_3 \cdot 3H_2O$ (10.5 mg, 0.04 mmol) were put into a Pyrex tube which had been sealed at one side. Into the mixture, toluene was added and the total volume of the solution was made 0.5 ml. The tube was sealed under vacuum with two freeze–pump–thaw cycles at 10^{-3} Torr on a vacuum line with liquid nitrogen bath. The sealed tube was heated for 4 h in a polyethylene glycol bath kept at 80 ± 1 °C. To determine the amount of aniline formed, the reaction mixture was submitted to GLC analysis which was performed at 130 °C using 2 m × 6 mm stainless steel column packed with 15% of Silicone DC 11 on Diasolid L and 25 μl of benzene as an internal standard. The amount of indole and indoline was measured by the use of a 2 m × 6 mm column packed with 10% diethylene glycol succinate on Diasolid L and of dibenzyl ether as an internal standard. Then the reaction mixture was treated by TLC technique in order to isolate the produced amines. The isolated products were identified by comparison with authentic samples in the IR spectra.

The other transfer hydrogenations were carried out in a similar way. However, in the reactions catalyzed by the heterogeneous catalysts the sealed tubes were heated with continuous oscillation.

An example of Kinetic Runs. Five samples, prepared by the method described above, were heated in a polyethylene glycol bath kept at 60 ± 1 °C for 10, 20, 30, 45, and 60 min, respectively. The reaction mixtures were submitted to GLC analysis.

Registry No.—Aniline, 62-53-3; indole, 120-72-9; indoline, 496-15-1; $RhCl_3$, 10049-07-7.

References and Notes

(1) (a) R. B. Wagner and H. D. Zook, "Synthetic Organic Chemistry", Wiley, New York, N.Y., 1953, p 654; (b) R. E. Lyle and J. L. LaMattina, *Synthesis*, 726 (1974); (c) K. Kondo, N. Sonoda, and H. Sakurai, *J. Chem. Soc., Chem. Commun.*, 42 (1975); (d) R. Baltzly, *J. Org. Chem.*, **41**, 920 (1976); (e) *ibid.*, **41**, 928 (1976); (f) *ibid.*, **41**, 933 (1976).

(2) (a) Tse-Lok Ho and C. M. Wong, *Synthesis*, 45 (1974); (b) J. F. Knifton, *J. Org. Chem.*, **40**, 519 (1975); (c) *ibid.*, **41**, 1200 (1976).

(3) (a) R. P. Linstead, E. A. Braude, P. W. D. Mitchell, K. R. H. Wooldrige, and L. M. Jackman, *Nature (London)*, **169**, 100 (1952); (b) E. A. Braude, R. P. Linstead, and K. R. H. Wooldridge, *J. Chem. Soc.*, 3586 (1954); (c) I. D. Entwistle, R. A. W. Johnstone, and T. Jeffery Povall, *J. Chem. Soc., Perkin Trans 1*, 1300 (1975).

(4) T. Nishiguchi and k. Fukuzumi, *J. Am. Chem. Soc.*, 96, 1893 (1974).

(5) (a) T. Nishiguchi, K. Tachi, and K. Fukuzumi, *J. Org. Chem.*, **40**, 237 (1975); (b) *ibid.*, **40**, 240 (1975); (c) T. Nishiguchi, H. Imai, Y. Hirose, and K. Fukuzumi, *J. Catal.*, **41**, 249 (1976).

(6) (a) H. Imai, T. Nishiguchi, and K. Fukuzumi, *J. Org. Chem.*, **39**, 1622 (1974); (b) *ibid.*, **41**, 665 (1976); (c) H. Imai, T. Nishiguchi, M. Kobayashi, and K. Fukuzumi, *Bull. Chem. Soc. Jpn.*, **48**, 1585 (1975).

(7) H. Imai, T. Nishiguchi, and K. Fukuzumi, *J. Org. Chem.*, **41**, 2688 (1976).

(8) E. S. Gould, "Mechanism and Structure in Organic Chemistry", Holt, Rinehart and Winston, New York, N.Y., 1959, p 69.

(9) (a) B. R. James and G. L. Rampel, *Discuss. Faraday Soc.*, **46**, 48 (1968); (b) B. R. James and G. L. Rampel, *Can. J. Chem.*, **44**, 233 (1966); (c) B. R. James and F. T. T. Ng, *J. Chem. Soc., Dalton Trans.*, 355 (1972).

(10) "Organic Syntheses", Collect Vol. I, Wiley, New York, N.Y., 1956, p 445.

Addition–Displacement Reactions of Electron-Deficient Aromatics. Formation of Indole, Benzoquinoline, and Quinoline or Isoquinoline Derivatives

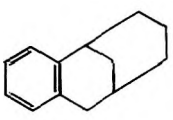
Raymond R. Bard and Michael J. Strauss*

Department of Chemistry, University of Vermont, Burlington, Vermont 05401

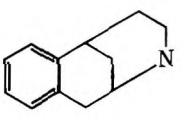
Received April 20, 1976

Reactions of amidines with electron-deficient benzenes and naphthalenes are shown to yield heteroaromatic compounds. These reactions are in contrast to those yielding meta-bridged products which can form from similar substrates. N-Methylated α-phenylacetamidines were reacted with *sym*-trinitrobenzene to give substituted indoles, with 1,3,6,8-tetranitronaphthalene to give benzoquinoline derivatives, and with 3,5-dinitrobenzophenone to produce a substituted quinoline or isoquinoline derivative.

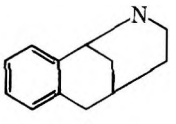
We have previously reported the formation of highly functionalized derivatives of the bicyclic ring systems **1–5**,



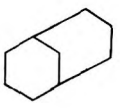
1



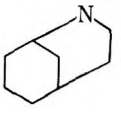
2



3



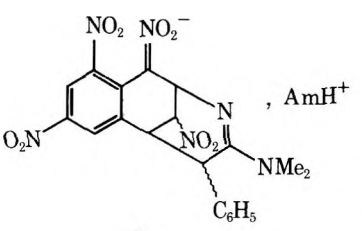
4



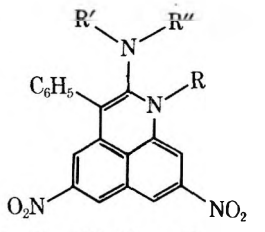
5

which result from meta bridging of nitronaphthalenes and nitrobenzenes with carbanions and amidines.[1-6] We and others have also reported the observation that a carbonyl-containing substituent in the electron-deficient benzene substrate results in either meta-bridged bicyclics (**4**) or naphthalenes depending on the nature of the attacking nucleophile.[7,8] We now report other modes of cyclization involving intramolecular nitrite displacement or intramolecular nucleophilic addition which lead to indole, isoquinoline or quinoline, and benzoquinoline derivatives. We also report a new oxidative mechanism for meta bridging. These reactions extend the utility of synthetic methods involving neighboring group interaction in ortho-substituted nitrobenzenes, an area recently reviewed by Preston and Tennant.[9]

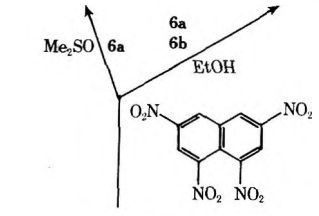
The reactions of amidines with nitronaphthalenes and nitrobenzenes leading to bridged adducts containing the ring systems **2**, **3**, and **5** were in most cases carried out in Me_2SO.[2,3,5,6] In several instances however, changing the solvent to ethanol results in an entirely different product. For example, reaction of α-phenyl-*N*,*N*-dimethylacetamidine (**6a**) with 1,3,6,8-tetranitronaphthalene in Me_2SO affords the red-orange bicyclic adduct **2a**.[2,6] The same reaction in ethanol yields purple crystals of a different product which analyzes correctly for a 1:1 adduct of amidine and aromatic minus $H_2N_2O_4$. A parent peak in the mass spectrum at *m/e* 376 supports the loss of two nitro groups, and the ^1H NMR spectrum and elemental analyses (see Experimental Section) substantiate the structure as benzoquinoline **7a**. Preparation of **7a** from C-1 deuterated 1,3,6,8-tetranitronaphthalene provides a product with diminished ^1H NMR intensities for the two aromatic peri protons at δ 8.22 and 9.40. Double nitrite displacement is not entirely unexpected. The peri nitro groups in 1,3,6,8-tetranitronaphthalene are in very close proximity and the resulting nonbonded repulsions would be expected to distort the planarity of the π system.[10] One other double displacement of two peri nitro groups has been reported.[11] Both nitro groups in 1,8-dinitronaphthalene are displaced photochemically in chloroform–HCl to afford 1,8-dichloronaphthalene. 1,3,6,8-Tetranitronapthalene after 100 h at pH 10.6 reacts to yield more than 1 equiv of nitrite ion.[12a]

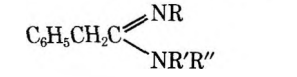


2a

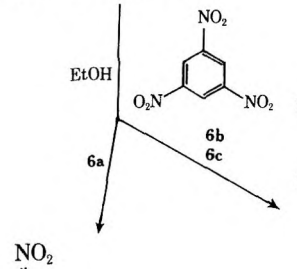


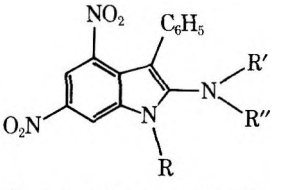
7a, R = H; R′ = R″ = Me
b, R = R′ = Me; R″ = H



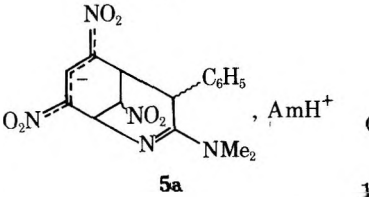


6a, R = H; R′ = R″ = Me
b, R = R′ = Me; R″ = H
c, R = R′ = R″ = Me

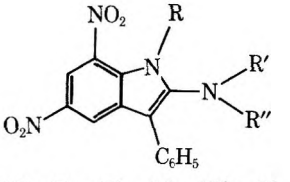




8b, R = R′ = Me; R″ = H
c, R = R′ = R″ = Me



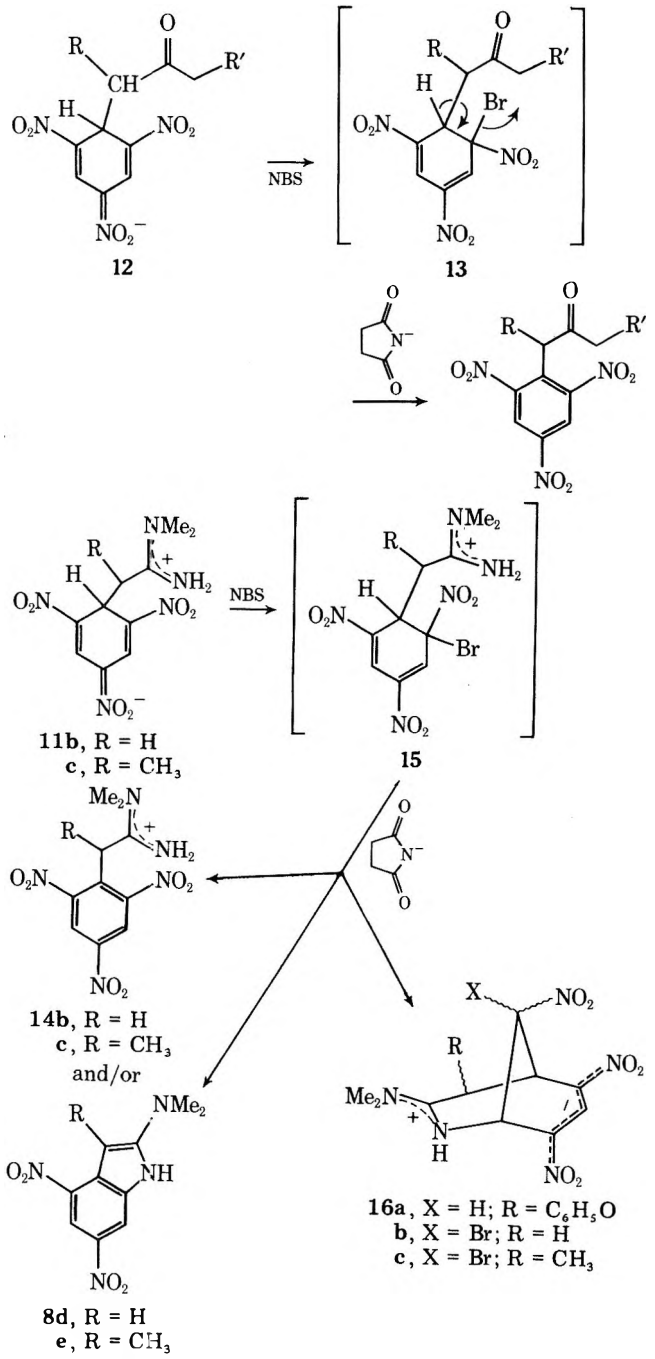
5a



10b, R = R′ = Me; R″ = H
c, R = R′ = R″ = Me

Reaction of 1,3,6,8-tetranitronaphthalene with α-phenyl-*N*,*N*′-dimethylacetamidine (**6b**) yields the *N*,*N*′-dimethyl analogue **7b**. The structure is again confirmed by the elemental analyses, ^1H NMR, and mass spectra, further substantiating the loss of both peri nitro groups (see Experimental Section).

We have previously found that α-phenyl-*N*,*N*-dimethylacetamidine (**6a**) reacts with *sym*-trinitrobenzene (TNB) to give the bridged adduct **5a**, analogous to the bridged adduct **2a**, formed from 1,3,6,8-tetranitronaphthalene and **6a** in Me_2SO.[2,6] Surprisingly, **5a** is formed from **6a** and TNB even



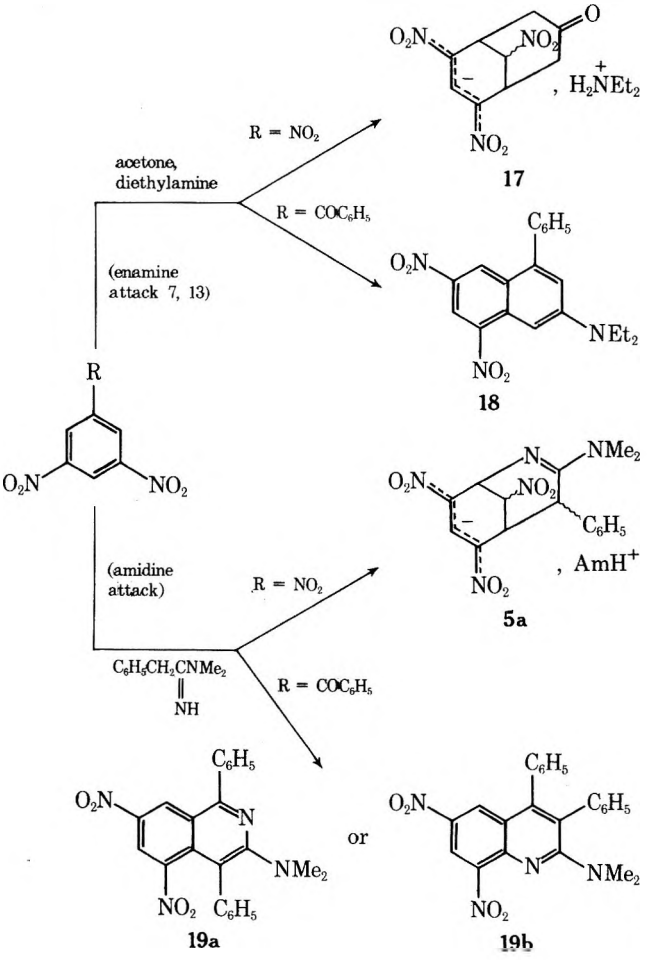
in ethanol, whereas **7a** is the only isolable product in this protic solvent with the naphthalene substrate. In order to more fully characterize the spectrum of amidine reactivity with TNB, the *N,N'*-dimethyl- and *N,N,N'*-trimethyl-α-phenylacetamidines **6b** and **6c** were reacted with this aromatic in ethanol. A dramatic difference in reactivity between these amidines and the *N,N*-dimethyl derivative **6a** was observed. With **6b**, red crystals of a product analyzing correctly for $C_{16}H_{14}N_4O_4$ were obtained. In chloroform this product shows strong maxima at 335 and 449 nm. The ^1H NMR spectrum shows two doublets (J = 3 Hz) at δ 8.36 and 8.75, which are consistent with an unsymmetrical 1,2,3,5-substituted benzene. The loss of a nitro group, indicated by the elemental analyses, and the previous observations of addition[2,6] and nitrite displacement reactions involving amidines and nitroaromatics (vide supra) provide substantial evidence for indole **8b** or **10b**. A five-proton multiplet for the phenyl at δ 7.37, a three-proton singlet at δ 3.86 for the indole *N*-methyl, and a three-proton doublet at δ 2.92 for the exocyclic *N*-methyl comprise the rest of the spectrum (the NH absorption overlaps the aromatic multiplet).

With the trimethylamidine **6c** an analogous compound is formed (**8c** or **10c**). The complete ^1H NMR spectrum, as well as pertinent UV, IR, mass spectral, and electronic absorptions, are summarized in the Experimental Section.

Interestingly, when the filtrate from the reaction of **6c** and TNB is reduced in volume and chromatographed, the material obtained shows a ^1H NMR spectrum consistent with two isomers in a ratio of 4:1. The resonances of the major isomer are identical with those of the isolated crystalline product. Those of the minor isomer are similar to those of the product isolated from the reaction of **6b** and TNB. The minor product could not be isolated in pure form.

In an attempt to form products analogous to **8** via a different route, the well-characterized zwitterionic amidinium σ complexes **11b** and **11c**[2] were reacted with *N*-bromosuccinimide. Ketonic σ complexes like **12** undergo oxidation to the corresponding picryl ketone with this reagent,[12b] presumably via formation of **13**, followed by elimination of HBr. The reaction with **11** did not follow this course, however. Instead of products like **8** or **14**, a dark red, crystalline material was isolated which was shown to contain bromine. For example, reaction of **11b** with NBS yields a compound which analyzes correctly for $C_{10}H_{12}N_5O_6Br$. The visible and ^1H NMR spectra of this material are consistent with **16b**. Comparisons with ^1H NMR and visible spectra of **16a**, prepared by a different method,[6] provide definitive evidence for structure **16b**. The reaction of **11c** with NBS yields the analogous bridged ion **16c**. It is possible that elimination of HBr from **15** occurs less rapidly than intramolecular cyclization to **16**. The different behavior of the presumed intermediates **13** and **15** may also be related to the acidity of the C–H and N–H protons in the exocyclic side chains. Proton abstraction from carbon (in **13**) and nitrogen (in **15**) must precede cyclization.[3]

The reactivity of α-phenyl-*N,N*-dimethylacetamidine (**6a**) and enamines toward symmetrically substituted di- and



trinitrobenzenes shows interesting similarities. We have previously shown that the enamine of acetone and diethylamine forms a meta-bridged product **17** with *sym*-trinitrobenzene,[13] but forms the ortho substituent cyclized product, naphthalene **18**, with 3,5-dinitrobenzophenone.[7] Also, the bridged adduct **5a** results from reaction of **6a** with *sym*-TNB.[2,6] We now show that reaction of 3,5-dinitrobenzophenone with this amidine yields a highly functionalized nitroquinoline or nitroisoquinoline.

Reaction of 3,5-dinitrobenzophenone and α-phenyl-*N,N*-dimethylacetamidine (**6a**) yields red crystals of a compound with visible maxima similar to those of **18** (see Experimental Section). The ^{1}H NMR spectrum of this product is similar to that of **18** with two coupled doublets for the nitroaromatic ring protons at δ 8.62 and 9.06 (1 H each), two five-proton multiplets at δ 7.48 and 7.53 for the two phenyl groups, and a six-proton singlet at δ 2.90 for the *N*-methyls. The elemental analyses further substantiate structure **19**. An unequivocal distinction between **19a** and **19b** cannot be made.

Experimental Section

All melting points are uncorrected. ^{1}H NMR spectra were run on JEOL C-60-HL and MH-100 spectrometers with Me_4Si as an internal reference. Visible and ultraviolet spectra were recorded on a Perkin-Elmer Model 402 UV–visible spectrophotometer. Infrared spectra were recorded on a Perkin-Elmer Model 237B infrared spectrophotometer. Mass spectra were obtained on a Perkin-Elmer RMU-6D mass spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and G. I. Robertson Laboratories, Florham Park, N.J.

Amidines. α-Phenyl-*N,N*-dimethylacetamidine was prepared as reported previously.[2] α-Phenyl-*N,N'*-dimethylacetamidine was prepared by two methods.

Method A. A solution of 14.9 g of α-phenyl-*N*-methylacetamide in 150 ml of methylene chloride was added to 100 ml of a 1 M methylene chloride solution of triethyloxonium tetrafluoroborate and the mixture was stirred for 24 h. After reduction to ⅓ the original volume 22 ml of 5.45 M methylamine in ethanol was added and the resulting mixture was stirred for 72 h. The solvent was then removed under vacuum to give an oil which was added to 8 M NaOH, followed by extraction with chloroform. The extracts were dried over Na_2SO_4 and the chloroform removed by distillation. Fractional distillation of the residue yielded 10.2 g of amidine, bp 94 °C (0.13 mm). The ^{1}H NMR spectrum ($CDCl_3$) showed singlets at δ 2.76 (6 H, NMe), 3.44 (2 H, CH_2), 4.12 (1 H, NH, br), and a multiplet at δ 7.02 (5 H, C_6H_5). The IR spectrum showed strong bands at 3250 and 1615 cm^{-1}.

Method B. With vigorous stirring, 32 g of ethyl α-phenylacetimidate hydrochloride was added to a solution of 21.1% methylamine in 100 ml of ethanol. After 3 days the solution volume was reduced under vacuum and the residue was added to an additional 100 ml of 21.1% methylamine solution and stirred for 3 more days. The solvent was then removed under vacuum and the residue was stirred with anhydrous ether. The resulting solid was recrystallized from ethanol to give a white, crystalline product with mp 208–210 °C (lit.[14] 210 °C). The free base was obtained by treating the hydrochloride salt with an equimolar amount of sodium ethoxide in ethanol, filtering off the sodium chloride, and fractionally distilling the filtrate.

α-Phenyl-*N,N,N'*-trimethylacetamidine was prepared by adding 50 ml of 1 M triethyloxonium tetrafluoroborate in methylene chloride to a rapidly stirred solution of 7.45 g of α-phenyl-*N*-methylacetamide in 75 ml of the same solvent. The mixture was stirred for 24 h and the volume was then reduced to 40 ml. The remaining solution was then mixed with 11 ml of 5.21 M dimethylamine in anhydrous ethanol and stirred for 3 days. Removal of the solvent afforded a viscous oil which was treated with 8 M NaOH and extracted with chloroform. The extracts were dried over sodium sulfate and the chloroform was removed by distillation. The residue was fractionally distilled to afford 6.3 g of product, bp 61–63 °C (0.025 mmHg). The ^{1}H NMR spectrum ($CDCl_3$) showed singlets at δ 2.86 (6 H, NMe_2), 3.06 (3 H, C=NMe), 3.81 (2 H, CH_2), and a multiplet at δ 7.31 (5 H, C_6H_5). The IR showed a strong band at 1625 cm^{-1}.

Preparation of 7a. Mixing 30 ml of ethanol containing 0.49 g of α-phenyl-*N,N*-dimethylacetamidine with 350 ml of ethanol containing 0.31 g of 1,3,6,8-tetranitronaphthalene resulted in a dark purple solution. After standing for 21 days at room temperature the resulting purple crystals were filtered, washed with ethanol and ether, and dried at 60 °C (1 mmHg) for 12 h. The resulting product (0.16 g, 41%) had mp 297–299 °C and analyzed correctly for $C_{20}H_{16}N_4O_4$: C, 63.83; H, 4.29; N, 14.89. Found: C, 63.90; H, 4.51; N, 14.79. In Me_2SO **7a** shows absorption maxima at 411 and 585 nm. Strong IR absorption bands (KBr) occur at 3340, 1635, 1585, 1550, and 1525 cm^{-1}. A parent peak at *m/e* 376 appears in the mass spectrum, along with M + 1 and M + 2 peaks at 377, 378, and peaks at 346 (−NO), 330 ($-NO_2$), 284 ($-2NO_2$), 213, and 193. The ^{1}H NMR spectrum (Me_2SO-d_6) shows absorptions at δ 3.07 (6 H, s), 7.62 (5 H, m), 8.21 (1 H, s, br), 8.27 (1 H, s, br), 8.87 (1 H, d, J = 3 Hz), 9.42 (1 H, d, J = 3 Hz), 11.77 (1 H, br).

Preparation of 7b. This compound was obtained in 72% yield from reaction of 1,3,6,8-tetranitronaphthalene and α-phenyl-*N,N'*-dimethylacetamidine in the same fashion as **7a**. The crystalline product obtained in 71% yield had mp 276–278 °C and analyzed correctly for $C_{20}H_{16}N_4O_4$: C, 63.83; H, 4.29; N, 14.89. Found: C, 63.89; H, 4.34; N, 14.84. In Me_2SO **7b** shows visible absorption maxima at 407 and 659 nm. Strong IR bands (KBr) occur at 3420, 1630, 1565, 1530 cm^{-1}. A parent peak appears at *m/e* 376 in the mass spectrum. The ^{1}H NMR spectrum (Me_2SO-d_6) shows absorptions at δ 2.76 (3 H, d, J = 3 Hz), 3.70 (3 H, s), 7.28 (1 H, br), 7.65 (5 H, m), 8.22 (1 H, br), 8.31 (1 H, br), 8.88 (1 H, d, J = 2 Hz), and 9.30 (1 H, d, J = 2 Hz).

Reaction of TNB and 6c. A mixture of 0.83 g of α-phenyl-*N,N,N'*-trimethylacetamidine and 0.69 g of *sym*-trinitrobenzene in 50 ml of absolute ethanol was allowed to stand at room temperature for 3 days. The resulting orange solid was filtered off and recrystallized from chloroform–methanol to afford a crystalline solid which after drying at 70 °C (0.1 mmHg) for 4 h yielded 0.19 g of crystalline product which melted at 226–227 °C. An additional 0.3 g of powdery product was obtained by evaporating the solvent from the filtrate and chromatographing the residue on a silica gel column with chloroform. The crystalline material analyzed correctly for $C_{17}H_{16}N_4O_4$: C, 60.00; H, 4.74; N, 16.46. Found: C, 60.01; H, 4.69; N, 16.72. In chloroform it shows visible maxima at 346 and 428 nm. Strong IR bands (KBr) occur at 2935, 2850, 2935, 1605, 1540, 1520, and 1495 cm^{-1}. A parent peak appears at *m/e* 340 in the mass spectrum along with M + 1 and M + 2 peaks at *m/e* 341 and 342, and peaks at *m/e* 310 (−NO), 295 ($-NHMe_2$), 278, 263, 248, 233, and 218. The ^{1}H NMR spectrum ($CDCl_3$) shows absorptions at δ 2.66 (6 H, s), 3.76 (3 H, s), 7.18 (2 H, m), 7.31 (3 H, m), 8.33 (1 H, d, J = 2 Hz), and 8.48 (1 H, d, J = 2 Hz).

Reaction of TNB and 6b. This reaction was carried out in a fashion similar to the reaction of TNB and **6c** using 0.74 g of aromatic and 1.12 g of **6b**. After removal of solvent from the reaction mixture the residual oil was purified by column chromatography (silica gel–chloroform) to yield a solid which was recrystallized from methanol–chloroform to yield red crystals. These were washed with cold methanol and dried at 80 °C (0.1 mmHg) for 4 h to yield 0.21 g of product, mp 191 °C, which analyzed correctly for $C_{16}H_{14}N_4O_4$: C, 58.89; H, 4.32; N, 17.17. Found: C, 59.10; H, 4.36; N, 16.99. In chloroform **10** shows visible maxima at 335 and 449 nm. The ^{1}H NMR spectrum ($CDCl_3$) shows absorptions at δ 2.92 (3 H, d, J = 6 Hz), 3.86 (3 H, s), 4.36 (1 H, bd), 7.37 (5 H, m), 8.36 (1 H, d, J = 3 Hz), and 8.75 (1 H, d, J = 3 Hz).

Preparation of 16b. A solution of 0.19 g of NBS in 30 ml of ethanol was added dropwise, over a period of 2 h, to a rapidly stirred solution of 0.33 g of the σ complex **11b** in 100 ml of ethanol. After stirring for an additional 4 h the resulting red, crystalline material was filtered, washed with additional ethanol and ether, and then vacuum dried at 60 °C to give 0.18 g of **16b**, mp 222–224 °C. In Me_2SO **16b** shows maxima at 300 and 491 nm. It analyzes correctly for $C_{10}H_{12}N_5O_6Br$: C, 31.76; H, 3.20; N, 18.52. Found: C, 31.50; H, 3.33; N, 18.30. The ^{1}H NMR spectrum (Me_2SO-d_6) shows absorptions at δ 3.05 (3 H, s), 3.10 (3 H, s), 3.31 (2 H, m), 4.51 (1 H, m), 5.59 (1 H, d), 8.50 (1 H, s), and 10.22 (1 H, br). IR absorptions (KBr) occur at 3400–2200, 1640, 1565, 1530, 1385, and 1335 cm^{-1}.

Preparation of 16c. This compound was prepared in a fashion similar to that used for **16b**, at 0 °C. The crystalline product obtained in 50% yield had mp 172–173 ° and analyzed correctly for $C_{11}H_{14}N_5O_6Br$: C, 33.69; H, 3.60; N, 17.86. Found: C, 33.80; H, 3.87; N, 17.97. The ^{1}H NMR spectrum (Me_2SO-d_6) showed absorptions at δ 1.22 (3 H, d), 3.13 (6 H, s), 3.67 (1 H, m), 4.42 (1 H, br s), 5.94 (1 H, br s), 8.42 (1 H, s), and 10.16 (1 H, br), In Me_2SO **16c** shows maxima at 300 and 493 nm.

Preparation of 19. This compound was prepared by mixing 1.46 g of 3,5-dinitrobenzophenone with 1.71 g (mmol) of α-phenyl-*N,N*-dimethylacetamidine and heating the mixture to 60 °C with stirring. After 20 min the mixture was cooled and allowed to stand at room temperature for 48 h. Addition of 10 ml of ethanol and filtration of

the resulting solution resulted in a red powder, which was recrystallized from chloroform–methanol. The resulting red crystals (1.5 g, 68%) had mp 243–245 °C and analyzed correctly for $C_{23}H_{18}N_4O_4$: C, 66.66; H, 4.38; N, 13.52. Found: C, 66.80; H, 4.40; N, 13.27. The mass spectrum had a parent peak at *m/e* 414, M + 1 and M + 2 peaks at *m/e* 415 and 416, and peaks at *m/e* 413, 398, 397, 385, 384, 370, 368, 350, 339, 337, and 323. The IR spectrum (KBr) showed strong bands at 2920, 1600, 1575, 1565, 1530, 1385, 1335, and 1315 cm^{-1}. Strong visible maxima appeared at 476, 426, and 280 nm in Me_2SO, 478, 420, and 250 nm in chloroform, and 456, 412, and 247 nm in methanol. The ^1H NMR spectrum (Me_2SO-d_6) showed absorptions at δ 2.90 (6 H, s), 7.53 (5 H, m), 7.78 (5 H, m), 8.62 (1 H, d, J = 3 Hz), and 9.06 (1 H, d, J = 3 Hz). In $CDCl_3$ the spectrum showed absorptions at δ 2.95 (6 H, s), 7.66 (5 H, m), 7.96 (5 H, m), 8.76 (1 H, d, J = 3 Hz), and 9.22 (1 H, d, J = 3 Hz).

Acknowledgments. The authors wish to thank the National Institute on Drug Abuse and the Special Action Office for Drug Abuse Prevention for support of this work.

Registry No.—**6a,** 56776-16-0; **6b,** 52066-17-8; **6c,** 60719-04-2; **7a,** 60719-05-3; **7b,** 60719-06-4; **8b/10b,** 60719-26-8; **8c/10c,** 60719-27-9; **11b,** 56776-17-1; **11c,** 56776-18-2; **16b,** 60719-07-5; **16c,** 60719-08-6; **19a,** 60719-09-7; **19b,** 60719-10-0; α-phenyl-*N*-methylacetamide, 6830-82-6; methylamine, 74-89-5; ethyl α-phenylacetimidate hydrochloride, 5442-34-2; dimethylamine, 124-40-3; 1,3,6,8-tetranitronaphthalene, 28995-89-3; TNB, 99-35-4; NBS, 128-08-5; 3,5-dinitrobenzophenone, 51911-74-1.

References and Notes

(1) M. J. Strauss, *Acc. Chem. Res.*, **7,** 181 (1974).
(2) R. R. Bard and M. J. Strauss, *J. Am. Chem. Soc.*, **97,** 3789 (1975).
(3) M. J. Strauss, H. F. Schran, and R. R. Bard, *J. Org. Chem.*, **38,** 3394 (1973).
(4) M. J. Strauss, *Chem. Rev.*, **70,** 667 (1970).
(5) M. J. Strauss and S. P. B. Taylor, *J. Org. Chem.*, **38,** 856 (1973).
(6) M. J. Strauss and R. R. Bard, *J. Org. Chem.*, **41,** 2421 (1976).
(7) M. J. Strauss, *J. Org. Chem.*, **39,** 2653 (1974).
(8) S. R. Alpha, *J. Org. Chem.*, **38,** 3136 (1973).
(9) P. N. Preston and G. Tennant, *Chem. Rev.*, **72,** 627 (1972).
(10) V. Balasubramaniyan, *Chem. Rev.*, **6,** 567 (1966).
(11) G. Frater and E. Havinga, *Recl. Trav. Chim. Pays-Bas,* **89,** 277 (1970).
(12) (a) J. H. Fendler, E. J. Fendler, and L. M. Casilio, *J. Org. Chem.*, **36,** 1749 (1971); (b) A. Reznick and M. J. Strauss, *Tetrahedron Lett.*, 4439 (1970).
(13) M. J. Strauss and H. Schran, *J. Am. Chem. Soc.*, **91,** 3974 (1969).
(14) P. Reynaud, *C. R. Acad. Sci., Ser. C,* **262,** 665 (1966).

Structural Studies of Organosulfur Compounds. 2.[1] Conformational Analysis of 2-Methoxy-*trans*-hexahydro-1,4-benzoxathianes

Slayton A. Evans, Jr., *Barry Goldsmith, Robert L. Merrill, Jr., and Robert E. Williams

William Rand Kenan, Jr., Laboratories of Chemistry, The University of North Carolina, Chapel Hill, North Carolina 27514

Received September 20, 1976

The 2-methoxy substituent in the 1,4-oxathiane prefers the *equatorial* conformation where the $\Delta G°$'s range from −0.23 to −0.49 kcal/mol (axial ⇄ equatorial), in a number of solvents as determined by direct acid catalyzed equilibration of the diastereoisomeric 2-methoxy-*trans*-hexahydro-1,4-benzoxathianes.

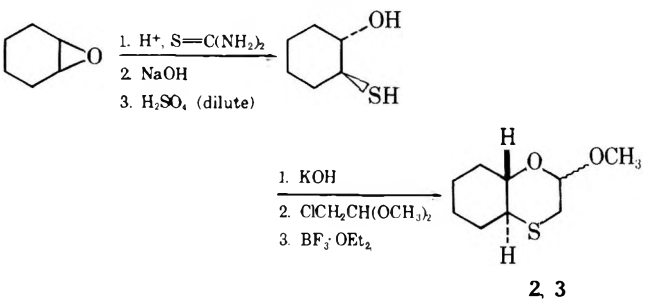
Recent reports indicate that the 2-methoxyl group in 1,4-oxathiane (1) may be slightly axial (56%)[2] or predominantly equatorial (75%)[3] in acetonitrile where presumably the anomeric effect,[4] van der Waals steric interactions, and the recently coined "hockey sticks" effect[2] collectively control its conformational preference. The conflicting results of these investigations[2,3] and other recent studies involving conformational predictions in some nucleoside derivatives of 1,4-oxathiane[5] have suggested the need for quantitative determinations of conformational energies of C-2 and possibly C-3 substituents in the 1,4-oxathiane system.

While conformational preferences of substituents derived from time-averaged intensive parameters (e.g., coupling constants and chemical shifts) of conformationally mobile systems and model systems are greatly influenced by the limitations of the models, direct chemical equilibrations of the appropriate model diastereoisomers (if practical) and direct observation of the conformers of conformationally mobile systems by NMR techniques are generally preferred[6] (Figure 1). However, solvent-dependent investigations are hampered by the inaccessibility of suitable solvents for low-temperature NMR determinations. In this report, we chose to put the conformational preference of the 2-methoxyl group in the 1,4-oxathiane system on a firm basis by determining its conformational free energy in a number of solvents by direct chemical equilibration of model diastereoisomers.

Results and Discussion

The diastereoisomers of 2-methoxy-*trans*-hexahydro-1,4-benzoxathiane (**2** and **3**) were envisioned as ideal models for the two chair conformations of 2-methoxy-1,4-oxathiane (1) since they would ensure conformational rigidity of the 1,4-oxathiane ring and allow for minimum distortions in the ring system. The compounds, **2** and **3,** were prepared by reacting a basic solution of *trans*-2-mercaptocyclohexanol, prepared from the addition of thiourea to cyclohexene oxide, with chloroacetaldehyde dimethyl acetal to afford the open chain acetal followed by condensation with boron trifluoride etherate (Scheme I). Separation of the stereoisomers was accomplished with spinning band column distillations, low-temperature crystallizations, and preparative gas chromatography (see Experimental Section).

Scheme I



2, 3

The stereochemistry of the C-2 methoxyl group in **2** and **3** was ascertained by ^1H NMR coupling constants and both proton and carbon chemical shifts. For example, the sample exhibiting the low-field "triplet" pattern for C-2 H at δ 4.75 ppm is suggestive of nearly equivalent vicinal couplings between the C-2 proton and the geminal C-3 protons. Application of the Karplus relationship to these couplings aided in

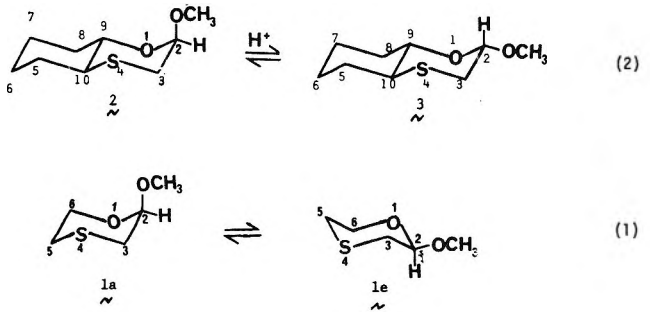


Figure 1.

Table I. Proton Chemical Shifts of *trans*-Hexahydro-1,4-benzoxathianes[a]

Compd	-OC-9 H	-S-C-10 H	C-3 H_e	C-3 H_a
trans-Hexahydro-1,4-benzoxathiane (**4**)[b]	3.28	2.65	2.37	3.10
2(a)-Methoxy-*trans*-hexahydro-1,4-benzoxathiane (**2**)	3.75	2.66	2.56	3.15
2(e)-Methoxy-*trans*-hexahydro-1,4-benzoxathiane (**3**)	3.41	2.56	2.51	2.75

[a] All NMR parameters were obtained as dilute solutions of the samp in deuteriochloroform ($CDCl_3$) with tetramethylsilane as internal reference. Chemical shifts (δ) are given in parts per million. [b] Unpublished observations with D. M. Frieze.

identifying the C-2 methoxyl group as axial. This "triplet" pattern was resolved, with an in-house modification of LACOON III,[7] into two coupling components of $^3J_{ee}$ = 1.93 and $^3J_{ea}$ = 2.45 Hz which could also be identified in the AB portion (C-3) of the NMR spectrum. The substance exhibiting the low-field doublet of doublets pattern at δ 4.55 ppm for C-2 H was assigned the other isomer, **3**. The magnitude of the C-2–C-3 vicinal coupling constants (J_{aa} = 8.63 and J_{ae} = 2.37 Hz)[7] supported this assignment.

Steric shifts arising from repulsive van der Waals interactions have been used extensively in NMR spectroscopy to support stereochemical assignments. In ^{1}H NMR this corresponds to downfield shifts of the interacting protons,[8] and in ^{13}C NMR upfield shifts of the appropriate carbon atoms.[9] Drieding molecular models show that when the C-2 methoxyl group and the C-9 proton are axial, they should experience severe nonbonding interactions. We noted that the C-9 proton in **2** is substantially deshielded (δ 3.75 ppm) on comparison with the same proton in both **1** and **4** (see Table I). On the other hand, the ^{13}C NMR spectra (Figure 2) show that C-9 of **2** experiences a substantial upfield shift of 9.78 ppm when compared to the C-9 atom in **3** (δ 82.37 for **3** and δ 72.59 ppm for **2**). In these anancomeric compounds, the C-2 atom of **2** responds similarly to the increase in steric congestion by exhibiting a higher field shift (δ 94.99 ppm) than the same carbon in **3** (δ 102.26 ppm) in accordance with previous observations on systems having similar functional groups.[12]

The chemical shifts of the axial and equatorial C-3 protons were also useful in corroborating the configurational assignment of the C-2 methoxyl group. In **3** and **4** the identity of the axial proton at C-3 is easily established since it should exhibit a relatively large coupling contribution from its axial neighbor at C-2 (8.83 Hz for **3** and 11.2 Hz for **4**). However, this scheme is not readily applicable in acetal **2** and since J_{ae} and J_{ee} are nearly identical assignments based on this coupling constant data would be less than conclusive.[13] The chemical shift of C-3

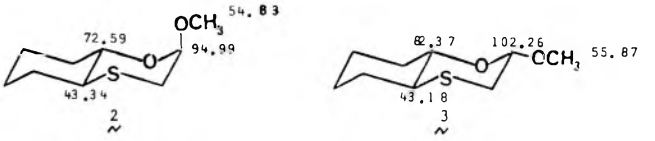


Figure 2. Partial assignments of carbons in **2** and **3**.

Table II. Solvent Dependent Conformational Free Energies of the 2-Methoxyl Group in 2-Methoxy-*trans*-hexahydro-1,4-benzoxathiane (Axial ⇄ Equatorial)[a]

Solvent (ϵ)	K_{eq}	$-\Delta G_{30°C}$, kcal/mol
C_6H_{12} (2.02)	2.29 ± 0.04	0.49 ± 0.01
C_6H_6 (2.28)	1.94 ± 0.06	0.39 ± 0.02
CH_2Cl_2 (9.08)	1.47± 0.02	0.23 ± 0.01
CH_3CN (36.5)	1.61 ± 0.07	0.28 ± 0.03
CCl_4 (2.24)	1.94 ± 0.09	0.39 ± 0.03

[a] See Experimental Section for details of acid-catalyzed equilibration and methods of analytical analyses.

H_a (δ 3.10 ppm) in **4** is similar to that exhibited by the C-3 H_a (δ 3.15 ppm) in **2** which seems quite reasonable since the proton antiperiplanar to the methoxyl group may not be expected to be greatly influenced by the anisotropy of the methoxyl group. Similarly, the chemical shift of the C-3 H_e in **2** (δ 2.56 ppm) would be expected to remain unchanged in **3** since the anisotropic influence of the synclinal (gauche) methoxyl group would be approximately the same in each case. Thus, the C-3 proton at δ 3.15 ppm in **2** is assigned the axial conformation which is removed from the diamagnetic shielding environment of the axial methoxyl group. Collectively, these observations serve to confirm the 1,3-axial/equatorial relationship of the C-2 methoxyl group and the C-9 axial proton in **2** and **3**, respectively.

The diastereoisomers, **2** and **3**, were equilibrated by methods similar to those previously described for acid-catalyzed equilibrations of substituted 1,3-dioxanes.[15] The conformational free energy data in Table II clearly indicate that the 2-methoxyl group prefers the *equatorial* conformation in all of the solvents used in this study. These results disagree with those obtained by Zefirov et al.,[2] but support the findings of Buck et al.[3] The equatorial preference varies significantly with solvent but does not appear to correlate with solvent E_T (30) values[16] and only slightly with solvent dielectric (and only when acetonitrile is excluded).[17] These data indicate that the 1,3-nonbonding heteroatom interactions (presumably, hockey sticks effect[2]) between sulfur and oxygen appear to override the anomeric effect between the two acetal oxygens. Although this result is perhaps suggestive of an electronic perturbation involving sulfur and oxygen, it is substantially larger than originally viewed.[2]

Finally, conformational entropies (ΔS) for systems similar to those described here are often assumed to be zero (and in a number of cases this seems justified[18]), and it was of interest to examine ΔH and ΔS in view of the relatively small values for the conformational free energies obtained for the above equilibrium.[19] Acid-catalyzed equilibrations were performed for **2** ⇄ **3** at 22, 40, 60, and 80 °C, and a least-squares refinement of the equilibrium data gave ΔH and ΔS values for the equilibrium in cyclohexane solvent of −0.41 ± 0.03 kcal/mol and 0.25 ± 0.09 eu, respectively. Although ΔS is positive and small, perhaps implying a bit less rotational freedom in the axial conformation than in the equatorial, it is clear that ΔH dominates the conformational free energy.

The electrostatic contribution to ΔH appears to be quite visible as shown by the solvent dependence of the ΔG's. The data suggest that dipole–dipole interactions are more severe

in the axial isomer **2** and hence subject to some diminution in the more polar solvents making the axial form more favored. However, the fact that the ΔG's do not correlate well with E_T (30) values or solvent dielectric data may simply reflect solvent-induced differences in intramolecular dipolar interactions ($\Delta H_{dipolar}$) and energies of solvation (ΔH_{solv}) which represent significant components of $\Delta H_{electrostatic}$.[20]

In summary, sulfur clearly plays a unique role in determining the conformational preference of the C-2 methoxyl group in 1,4-oxathiane, particularly since in the absence of the sulfur atom in structurally similar systems (i.e., 2-methoxytetrahydropyrans), the axial methoxyl group is greatly preferred owing to the anomeric effect.[21]

Experimental Section

Melting points were obtained in a Mel-Temp melting point apparatus with an open capillary tube, and are uncorrected.

Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and Integral Microanalytical Laboratories, Inc., Raleigh, N.C.

Proton magnetic resonance (^{1}H NMR) spectra were recorded on JEOL Model C-60 HL and Varian Model XL-100-12 NMR spectrometers. Carbon magnetic resonance (^{13}C NMR) FT spectra were recorded on a Varian Model XL-100-12 NMR spectrometer controlled by a 620/f computer. All FT spectra were obtained at ambient temperature (ca. 30 °C) and Fourier transforms were based upon 8K data points. The proton and carbon chemical shifts of samples as 5–30% (wt/wt %) deuteriochloroform ($CDCl_3$) solutions are presented in parts per million (δ) downfield from internal tetramethylsilane (Me_4Si), and these values are considered accurate to ±0.01 ppm unless otherwise indicated. The coupling constants are given in hertz and are accurate to ±0.1–0.2 Hz unless otherwise specified. All relevant proton signals were simulated with an in-house modification of a LACOON III program.[7] ^{1}H NMR coupling patterns are designated as s = singlet, dd = doublet of doublets, bb = broad bands, and t = triplet.

Infrared spectra were obtained from samples as neat films and solutions, and were recorded on Perkin-Elmer Models 257 and 421 spectrophotometers with polystyrene (1601.4 cm^{-1}) as reference. Absorption intensities are shown as s = strong, w = weak, and m = medium.

Gas–liquid partition chromatography (GLC) analyses were performed on a Hewlett-Packard Model 5750B research gas chromatograph. A Varian Aerograph Series 2700 instrument was used for preparative separations.

***trans*-2-Mercaptocyclohexanol.** Thiourea (40.0 g, 500 mmol) was added to a solution of sulfuric acid (25.9 ml, 0.5 equiv, 500 mmol) in 300 ml of water while stirring at 0–5 °C (ice bath). Cyclohexene oxide (49.0 g, 500 mmol) was added dropwise to the acidic solution over a 90-min period with constant (vigorous) stirring. The suspension was allowed to warm to ambient temperature for ca. 1 h, then cooled to 0–5 °C, and the *S*-(*trans*-2-hydroxycyclohexyl)thiuronium sulfate was suction filtered. The aqueous filtrate was treated with 100–200 g of ammonium sulfate and additional thiuronium sulfate salt precipitated from the aqueous solution. The combined salts were dried in a vacuum desiccator to give 102 g (75%) or recrystallized from 50% ethanol to give 68–82 g (50–60%) of pure material, mp 312–314 °C (lit.[21] mp 310–325 °C).

A portion of the thiuronium sulfate (30.0 g, 110 mmol) was added to a solution of sodium hydroxide (9.2 g, 220 mmol) in 140 ml of water at 0–5 °C (ice bath). The resulting solution was allowed to stir at room temperature for 10 min, then poured over acidic ice water (ca. 5.3 ml, 110 mmol of sulfuric acid). The organic material was extracted with ethyl ether (3 × 100 ml) and the ethereal solution was dried ($MgSO_4$) and concentrated to dryness (rotary evaporator) to afford an oil (10.5 g, 70–72%). The oil was distilled under reduced pressure to give two major components. The low-boiling component (bp 29–37 °C, 0.035 Torr) was identified as cyclohexene sulfide (7.2 g, 69%) from comparison with published infrared data[22] and the remaining 3.3 g (31%) of the high-boiling component (bp 48–49 °C, 0.015 Torr) was identified as *trans*-2-mercaptocyclohexanol [lit.[23] bp 97–99 °C (15 mm)]: IR (neat film) 3400 (broad, OH), 2570 (weak, SH), 1504, 1120 (s), and 970 cm^{-1} (s).

***trans*-2-(Thioacetaldehyde dimethyl acetal)cyclohexanol.** A solution of *trans*-2-mercaptocyclohexanol (52.8 g, 400 mmol) in 200 ml of ethanol was added to a solution of potassium hydroxide (26.3 g, 400 mmol) in 500 ml of ethanol. The solution was stirred for 15 min, then a solution of chloroacetaldehyde dimethyl acetal (49.8 g, 400 mmol) in 100 ml of ethanol was added in one portion. The resulting solution was refluxed (16 h) and cooled to ambient temperature and the KCl was removed by filtration. The resulting filtrate was concentrated to dryness (rotary evaporator), diluted with water (150 ml), and washed with ether (3 × 100 ml). The combined ethereal solutions were dried ($MgSO_4$) and concentrated to dryness (rotary evaporator) to give an amber oil which was distilled under reduced pressure to afford a colorless oil (63 g, 71%): bp 97–99 °C (0.035 Torr); IR (neat film) 3450 (broad band, OH), 1452 (s), 1128 (s), 1071 (vs), and 970 cm^{-1} (s). On standing this material slowly cyclized to give an approximately equal distributon of **2** and **3**.

***trans*-2-Methoxyhexahydro-1,4-benzoxathianes.** A solution of *trans*-2-(thioacetaldehyde dimethyl acetal)cyclohexanol (61 g, 286 mmol) in 300 ml of anhydrous ether was stirred overnight with 4 ml of BF_3·OEt_2. The ethereal solution was washed with water (2 × 100 ml), dried ($MgSO_4$), and concentrated to dryness (rotary evaporator) to give a colorless oil. Distillation of the oil under reduced pressure gave 46.3 g (76% yield) of a colorless oil, bp 73–75 °C (0.05 Torr).

The approximately 50:50 mixture of stereoisomers (by ^{1}H NMR) was partially separated by distillation on a Nester-Faust adiabatic annular Teflon spinning band column. The equatorial isomer **3** could be obtained pure by distillation [bp 60–61 °C (0.25 Torr) which crystallized on standing] while the axial isomer **2** could only be obtained as a highly enriched mixture favoring the axial isomer. GLC separations of the mixtures on a 6 ft × 0.375 in. Al column packed with 20% FFAP on Chromosorb W (45/60 mesh) at 125 and 160 °C gave pure samples of both the axial and equatorial sulfides, **2** and **3**. The equatorial isomer could also be obtained in pure form by low-temperature crystallization from the pure mixture at ca. 0–5 °C. Continuous removal of the crystalline solid eventually gave a solution mixture composed of ca. 70% **2** and 30% **3**.

2(e)-Methoxy-*trans*-hexahydro-1,4-benzoxathiane (3): mp 42.5–44.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.02–2.04 (bb, 8 H, CH_2), 2.51 (dd, J_{gem} = 13.02, J_{ae} = 2.37 Hz, 1 H, SCH), 2.52 (bb, 1 H, SCH), 2.75 (dd, J_{gem} = 13.02, J_{aa} = 8.63 Hz, 1 H, SCH), 3.45 (bb, 1 H, OCH), 3.48 (s, 3 H, OCH_3), and 4.55 ppm (dd, J_{ae} = 2.37, J_{aa} = 8.63 Hz, 1 H, –OC**H**OCH_3); IR (CCl_4) 1450 (s), 1362 (s), 1338 (s), 1174 (s), 1152 (s), 1120 (s), 1065 (s), 985 (s), and 850 cm^{-1} (m).

Anal. Calcd for $C_9H_{16}O_2S$: C, 57.41; H, 8.56. Found: C, 57.37; H, 8.62.

2(a)-Methoxy-*trans*-hexahydro-1,4-benzoxathiane (2): mp 9.0–30.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.10–1.98 (bb, 8 H, CH_2), 2.56 (dd, J_{gem} = 13.62, J_{ae} = 2.45 Hz, 1 H, SCH), 2.66 (bb, 1 H, SCH), 3.15 (dd, J_{gem} = 13.62, J_{ee} = 1.93 Hz, 1 H, SCH), 3.44 (s, 3 H, OCH_3), 3.74 (bb, 1 H, OCH), and 4.75 ppm ("t", J_{ae} = 2.45, J_{ee} = 1.93 Hz, 1 H, OCH-OCH_3); IR (CCl_4) 1448 (s), 1351 (s), 1130 (s), 1054 (s), and 987 cm^{-1} (s).

Anal. Found: C, 57.49; H, 8.60.

Equilibrations. Equilibrium concentrations were obtained by equilibrating weighted mixtures of **2** and **3** from both sides in five solvents at 30.0 °C in sealed ampules with Amberlyst-15 (a polystyrenesulfonic acid resin). GLC analyses were performed on primarily 6 ft and 10 ft × 0.125 in. (i.d.) stainless steel columns with 10% FFAP on Chromosorb W AW-DMCS (60–80 mesh) at 120–130 °C and 6 ft and 12 ft × 0.125 in. (i.d.) stainless steel columns with 10% XE-60 Nitrile on Chromosorb W HP AW DMCS (100–120 mesh) at 120–200 °C. Response ratios were measured from the areas obtained from weighed sample mixtures.

Acknowledgments. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, the North Carolina Board of Science and Technology, and the University Research Council (UNC) for support of this research. We also thank Dr. David L. Harris for recording both noise-decoupled and off-resonance decoupled ^{13}C NMR spectra.

Registry No.—**2**, 60861-03-2; **3**, 60895-17-2; cyclohexene oxide, 286-20-4; *S*-(*trans*-2-hydroxycyclohexyl)thiuronium sulfate, 60861-05-4; *trans*-2-mercaptocyclohexanol, 60861-06-5; *trans*-2-(thioacetaldehyde dimethyl acetal)cyclohexanol, 60861-07-6.

References and Notes

(1) For part 1, see D. M. Frieze and S. A. Evans, *J. Org. Chem.*, **40**, 2690 (1975).
(2) N. S. Zefirov, V. S. Balgoveshchensky, I. V. Kazimirchik, and N. S. Surova, *Tetrahedron*, **27**, 3111 (1971).
(3) K. W. Buck, F. A. Fahim, A. B. Foster, A. R. Perry, N. H. Qadir, and J. M. Webber, *Carbohydr. Res.*, **2**, 14 (1966); see also D. J. Watkin and T. A. Hamor, *J. Chem. Soc. B*, 1692 (1971).

(4) For a recent discussion of the generalized and reverse anomeric effects, see W. F. Bailey and E. L. Eliel, *J. Am. Chem. Soc.*, **96**, 1798 (1974).
(5) W. A. Szarek, D. M. Vyas, and B. Achmatowicz, *Tetrahedron Lett.*, 1553 (1975); W. A. Szarek, D. M. Vyas, A. M. Sepylchre, S. D. Gero, and G. Lukacs, *Can. J. Chem.*, **52**, 2041 (1974); W. A. Szarek, D. M. Vyas, and B. Achmatowicz, *J. Heterocycl. Chem.*, **12**, 123 (1975).
(6) F. R. Jensen, C. H. Bushweller, and B. H. Beck, *J. Am. Chem. Soc.*, **91**, 344 (1969).
(7) We thank our colleague, Professor Charles N. Reilley, of this department for the use of this program.
(8) For numerous examples, see L. M. Jackman and S. Sternhell, "Applicatcns of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2d ed, Pergamon Press, 1969, p 71.
(9) The γ-gauche effect or γ-steric shift effect is referred to in this context for the synclinal arrangement of substituent and carbon atom which results in an upfield shift of that carbon relative to the shielding of a corresponding carbon in the antiperiplanar conformation.[10] A recent report has cautioned the extrapolation of this generalization to complex systems since 1,3-syn axial substituents in some six-membered rings (e.g., steroids) exhibit appreciable downfield shifts (often referred to as δ effects).[11]
(10) See J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972.
(11) S. H. Grover, J. P. Guthrie, J. B. Stothers, and C. T. Tann, *J. Magn. Reson.*, **10**, 227 (1973).
(12) J. D. Roberts, F. J. Weigert, J. I. Kroschwitz, and H. J. Reich, *J. Am. Chem. Soc.*, **92**, 1338 (1970).
(13) Vicinal coupling constants are sensitive to the electronegativity of the attached substituents and (this sensitivity is also angular dependent)[14] arguments of angular dependencies based on a small difference in two coupling constants must be viewed as speculative. See for examples T. P. Forrest, *J. Am. Chem. Soc.*, **97**, 2628 (1975).
(14) H. Booth, *Tetrahedron Lett.*, 411 (1965).
(15) E. L. Eliel, *Rev. Pure Appl. Chem.*, **25**, 509 (1971).
(16) C. Reichardt, *Justus Liebigs Ann. Chem.* **752**, 64 (1971).
(17) E. L. Eliel and O. Hofer, *J. Am. Chem. Soc.*, **95**, 8041 (1973).
(18) J. J. Uebel and J. C. Martin, *J. Am. Chem. Soc.*, **86**, 4618 (1964).
(19) An example of where ΔG is controlled primarily by ΔS has been reported by B. Rickborn and F. R. Jensen, *J. Org. Chem.*, **27**, 4606 (1962).
(20) It has been pointed out that differences in intramolecular dipolar interactions and solvation energies between conformers or diastereoisomers can make substantial contributions to the conformational free energy(ies) of the substituent(s). See M. K. Kaloustian, *J. Chem. Educ.*, **51**, 777 (1974).
(21) R. U. Lemieux, *Rev. Pure Appl. Chem.*, **25**, 527 (1971), and references cited therein.
(22) C. J. Pouchert, "The Aldrich Library of Infrared Spectra", Aldrich Chemical Co., Milwaukee, Wis., 1975, p 142G.
(23) F. G. Bordwell and H. M. Andersen, *J. Am. Chem. Soc.*, **75**, 4959 (1953).

Heterocycles from *N*-Ethoxycarbonylthioamides and Dinucleophilic Reagents. 2. Five-Membered Rings Containing Two Heteroatoms at 1,3 Positions

Babu George and Eleftherios Paul Papadopoulos*

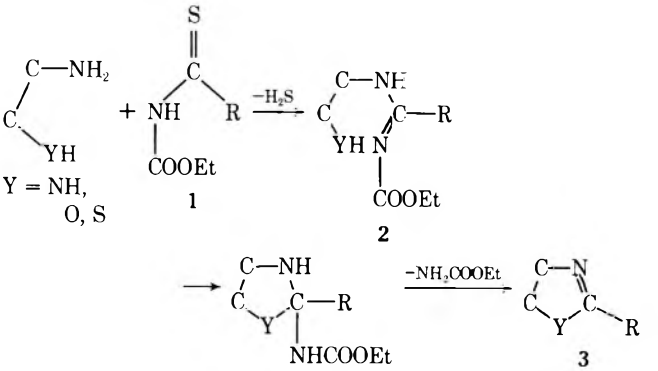
Department of Chemistry, The University of New Mexico, Albuquerque, New Mexico 87131

Received July 27, 1976

The reaction of *N*-ethoxycarbonylthioamides (1) with 1,2-diamines, amino alcohols, or aminomercaptans yields five-membered heterocyclic rings containing the thiocarbonyl carbon atom of 1 flanked by the two heteroatoms of the dinucleophilic reagent.

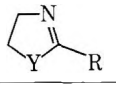
A recent study has shown that *N*-ethoxycarbonylthioamides (1) react with reagents possessing two adjacent nucleophilic sites (NH_2, NHR, OH) at both thiocarbonyl and carbonyl groups to form five-membered, carbonyl-containing heterocyclic rings. Thus reactions with hydrazines and hydroxylamines yield dihydro-1,2,4-triazolones and 1,2,4-oxadiazolones, respectively.[1] In view of these results, it was of interest to investigate the behavior of 1 toward reagents containing two nucleophilic groups separated by two or more positions. Were these reactions to proceed in the same manner as the previous ones, seven-membered or larger rings would be the anticipated products. A related study, however, has revealed that *S*-methyl derivatives of carbamates obtained by addition of alcohols to alkoxycarbonyl isothiocyanates react with 1,2- and 1,3-dinucleophilic reagents without participation of the ester group. Such reactions involving aliphatic 1,2- or 1,3-diamines result in formation of 2-alkoxycarbonyl derivatives of cyclic guanidines, whereas those with *o*-phenylenediamine lead to *N*-alkoxycarbonyl-2-aminobenzimidazoles.[2] On the other hand, it has long been known that primary thioamides react with ethylenediamine to form 2-substituted 4,5-dihydrothiazoles with elimination of H_2S and NH_3.[3]

Our investigation has shown that reactions of *N*-ethoxycarbonylthioamides (1) with 1,2-dinucleophilic reagents H_2NCCYH (Y = NH, O, S), in refluxing ethanol or tetrahydrofuran, proceed in complete analogy with the behavior of primary thioamides. The ester group is neither attacked by the reagent nor retained as side chain of the heterocyclic product. Instead, it is found in the reaction by-product, ethyl carbamate. On the basis of previous experience,[1] initial interaction between the thiocarbonyl of 1 and amino group of the reagent would be expected to result in elimination of H_2S and formation of a substituted amidine (2) as an intermediate. It now appears that this is followed by intramolecular addition of the second nucleophilic group YH to the C=N of 2 and elimination of ethyl carbamate. A five-membered, heterocyclic ring (3) is thus formed which is made up of the N–C–C–Y chain of the reagent and the thiocarbonyl carbon atom of 1.



This is a general reaction that *N*-ethoxycarbonylthioamides (1) undergo upon treatment with substances containing two primary amino, or a primary amino and a hydroxyl or mercapto groups on adjacent carbon atoms. Thus, treatment of 1 with 1,2-diaminoethane, 2-aminoethanol, and 2-aminoethanethiol yields 2-substituted 4,5-dihydroimidazoles (4), -oxazoles (5), and -thiazoles (6), respectively. Similarly, reactions with *o*-phenylenediamine, *o*-aminophenol, and *o*-aminothiophenol lead to 2-substituted benzimidazoles (7), benzoxazoles (8), and benzothiazoles (9) (Scheme I).

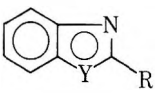
Table I.[a] 4,5-Dihydroimidazoles (4), -oxazoles (5), and -thiazoles (6)



Registry no.	Y	R	Yield,[b] %	Mp (bp), °C
59-98-3	NH	$PhCH_2$[c,d]	51[e]	66–67[f,g]
13623-58-0	NH	4-MeC_6H_4[h]	97[i]	181.5–183[j,k]
6302-84-7	NH	4-$MeOC_6H_4$[c]	85[l]	137–139[m,n]
60705-30-8	NH	2-Pyrrolyl[h]	84[l]	212–213[o]
45753-18-2	NH	2-Thienyl[c]	87[l]	175–177[p]
10431-98-8	O	Et[d,h]	50[q]	(124–126)[r]
10200-70-1	O	4-MeC_6H_4[c]	85[l]	72–73.5[s,t]
13676-94-3	O	4-$MeOC_6H_4$[c]	90[l]	62.5–63.5[f,u]
60705-31-9	O	2-Pyrrolyl[h]	73[l]	165–166[o]
60705-32-0	O	2-Thienyl[c]	39[v]	58–60[w]
13084-31-6	S	4-MeC_6H_4[x]	90[y]	41.5–42.5[z,aa]
2519-93-9	S	4-$MeOC_6H_4$[x]	93[y]	53.5–54.5[s,bb]
60705-33-1	S	2-Pyrrolyl[x]	66[y]	93–95[o]
60705-34-2	S	2-Thienyl[x]	94[y]	40.5–41.5[w]

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all new compounds listed in this table. [b] Crude or partially purified material with melting point lower than that of the pure compound by 1–10 °C. [c] Reaction run in THF. [d] Equimolar amounts of reactants used. [e] A cold solution of the reaction residue in absolute Et_2O was saturated with dry HCl and the precipitated hydrochloride salt was recrystallized from MeOH–Et_2O and then treated with NaOH–H_2O. Extraction of the resulting mixture with Et_2O followed by evaporation of the dried ($MgSO_4$) ethereal solution yielded the product. [f] Recrystallized from petroleum ether (bp 35–60 °C). [g] Lit. mp 66–68 °C: P. Oxley and W. F. Short, *J. Chem. Soc.*, 497 (1947). [h] Reaction run in EtOH. [i] The reaction residue was washed with cold Et_2O. [j] Sublimed. [k] Lit. mp 183 °C: A. J. Hill and S. R. Aspinall, *J. Am. Chem. Soc.*, 61, 822 (1939). [l] The reaction residue was washed with cold water. [m] Recrystallized from EtOAc–petroleum ether (bp 60–75 °C). [n] Lit. mp 140 °C: ref in *g*. [o] Recrystallized from H_2O. [p] Recrystallized from benzene. [q] A petroleum ether (bp 35–60 °C) extract of the reaction residue was evaporated and the new residue was distilled. [r] Lit. bp 129–130 °C: W. Seeliger and W. Thier, *Justus Liebigs Ann. Chem.*, 698, 158 (1966). [s] Recrystallized from hexane. [t] Lit. mp 67–68 °C: ref in *r*. [u] Lit. mp 63 °C: P. Rehländer, *Chem. Ber.*, 27, 2154 (1894). [v] Following washing with cold water, the reaction residue was boiled with two 100-ml portions of petroleum ether (bp 30–65 °C) and the decanted solution was chilled in dry ice–acetone to yield the product. [w] Recrystallized from pentane. [x] Reaction run in MeOH with MeONa used to liberate $HSCH_2CH_2NH_2$ from its hydrochloride salt. [y] The reaction residue was washed with cold, dilute NaOH–H_2O and then with cold water. [z] Recrystallized from EtOH–H_2O. [aa] Lit. mp 42.5–43.5 °C: Y. Iwakura, A. Nabeya, and T. Nishiguchi, *J. Org. Chem.*, 32, 2362 (1967). [bb] Lit. mp 54.5 °C: ref in *u*.

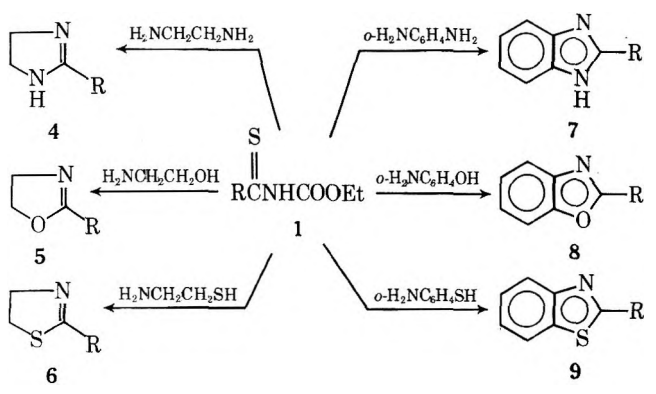
Table II.[a] Benzimidazoles (7), Benzoxazoles (8), and Benzothiazoles (9)



Registry no.	Y	R	Yield,[b] %	Mp (bp), °C
1848-84-6	NH	Et[c,d]	88[e]	172–174[f,g]
120-03-6	NH	4-MeC_6H_4[c,d]	85[h]	275–276[i,j]
2620-81-7	NH	4-$MeOC_6H_4$[k]	80[l]	226–227[i,m]
3878-23-7	NH	2-Pyrrolyl[c]	92[e]	274–275[n]
3878-18-0	NH	2-Thienyl[k]	95[e]	332–334[i,o]
835-71-2	O	4-MeC_6H_4[c]	90[l]	114–114.5[n,p]
838-34-6	O	4-$MeOC_6H_4$[k]	93[l]	99.5–101[i,q]
54584-08-6	O	2-Pyrrolyl[c]	71[l]	149–149.5[n]
23999-63-5	O	2-Thienyl[k]	75[l]	103–105[n,r]
936-77-6	S	Et[d,k]	46[s]	(129–130, 18 Torr)[t]
16112-21-3	S	4-MeC_6H_4[k]	95[l]	85–86[i,u]
6265-92-5	S	4-$MeOC_6H_4$[k]	83[l]	121–122[n,v]
54584-09-7	S	2-Pyrrolyl[c]	67[h]	158–160[n]
34243-38-4	S	2-Thienyl[k]	92[l]	98–100[n,w]

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all new compounds listed in this table. [b] Crude or partially purified material with melting point lower than that of the pure compound by 1–10 °C. [c] Reaction run in EtOH. [d] Equimolar amounts of reactants used. [e] The reaction residue was washed with water. [f] Recrystallized from water. [g] Lit. mp 172 °C: E. L. Hőlljes, Jr., and E. C. Wagner, *J. Org. Chem.*, 9, 31 (1944). [h] The reaction mixture was concentrated to a small volume, chilled, and filtered to yield the product. [i] Recrystallized from EtOH. [j] Lit. mp 266–269 °C: ref in *g*. [k] Reaction run in THF. [l] The reaction residue was washed with cold, dilute NaOH–H_2O and then with water. [m] Lit. mp 227 °C: T. Bacchetti and A. Alemagna, *Atti Accad. Naz. Lincei, Rend., Cl. Sci. Fis. Mat. Nat.* 28, 824 (1960); *Chem Abstr.*, 56, 7304*f* (1962). [n] Recrystallized from EtOH–H_2O. [o] Lit. mp 334 °C: W. Ried and P. Stahlhofen, *Chem. Ber.*, 90, 815 (1957). [p] Lit. mp 114 °C: ref in *g*. [q] Lit. mp 100–101 °C: K. Nakagawa, H. Onoue, and J. Sugita, *Chem. Pharm. Bull.*, 12, 1135 (1964). [r] Lit. mp 104.5 °C: R. Royer, G. Colin, P. Demerseman, S. Combrisson, and A. Gheutin, *Bull. Soc. Chim. Fr.*, 2785 (1969). [s] The reaction residue was chromatographed on an alumina column using petroleum ether (bp 60–75 °C) as eluent and the crude product was distilled under reduced pressure. [t] Lit. bp 132 °C (18 Torr): V. G. Brudz, D. A. Drapkina, V. A. Inshakova, and I. P. Plitina, *Metody Poluch. Khim. Reakt. Prep.*, 178 (1967); *Chem. Abstr.*, 71, 30387q (1969). [u] Lit. mp 86 °C: A. I. Kiprianov, I. K. Ushenko, and A. L. Gershun, *J. Gen. Chem. USSR (Engl. Transl.)*, 14, 865 (1944). [v] Lit. mp 121 °C: F. S. Babichev, L. A. Kirpianova, and T. A. Dashevskaya, *Ukr. Khim. Zh.*, 32, 706 (1966); *Chem. Abstr.*, 65, 13682*a* (1966). [w] Lit. mp 98.5–100 °C: R. E. Atkinson and P. R. H. Speakman, *J. Chem. Soc. B*, 2077 (1971).

Scheme I. Reactions of RC(=S)NHCOOEt with 1,2-Dinucleophilic Reagents



The reaction progress is followed easily by testing for evolution of H_2S with lead acetate paper. The time necessary for completion of H_2S evolution (2–48 h) depends on the basicity of the dinucleophilic reagent used, aromatic amines requiring longer reaction times. An excess of reagent and use of tetrahydrofuran (rather than ethanol) as solvent generally result in shorter reaction times. Isolation of the product is very simple, as in most cases the heterocycle is insoluble in water, and ethyl carbamate, the by-product, is soluble. Water-soluble heterocycles are isolated by conventional techniques such as selective extraction, formation of their hydrochloride salts, or column chromatography.

With very good yields in the majority of the cases studied, this reaction allows convenient preparation of several heterocyclic compounds in one step from *N*-ethoxycarbonylthioamides, which are obtainable in one step from ethoxycar-

bonyl isothiocyanate and simple aromatic or heteroaromatic compounds or alkylmagnesium halides.[1,4] It is noteworthy that in contrast to most common synthetic approaches to the same heterocyclic systems,[5] the present method circumvents the use of carboxylic acids or their derivatives as starting materials.

Experimental Section[6]

***N*-Ethoxycarbonylthioamides (1)** were prepared as previously described.[1,4]

General Procedure for Preparation of Compounds 4–9. A solution of 0.010 mol of 1 and 0.012 mol of dinucleophilic reagent in 10 ml of tetrahydrofuran (or 0.010 mol of 1 and 0.020 mol of reagent in 20 ml of ethanol) was refluxed until evolution of H_2S had stopped (2–48 h). Following removal of the solvent by distillation under reduced pressure, the residue was treated as indicated in Tables I and II.

Isolation of Ethyl Carbamate. The residue from the reaction of *N*-ethoxycarbonyl-2-pyrrolethioamide with 2-aminoethanol was treated with water and the resulting mixture was filtered. Extraction with ether of the acidified aqueous filtrate followed by evaporation of the ethereal solution (charcoal, $MgSO_4$) yielded a solid the IR and NMR spectra of which were superimposable on those of authentic ethyl carbamate.

Acknowledgments. Financial support by the Research Corporation, the Research Allocations Committee of the University of new Mexico, and the Department of Chemistry of the University of New Mexico is gratefully acknowledged.

Registry No.—1 (R = $PhCH_2$), 60705-35-3; 1 (R = MeC_6H_4), 57774-66-0; 1 (R = $MeOC_6H_4$), 57774-72-8; 1 (R = 2-pyrrolyl), 37488-43-0; 1 (R = 2-thienyl), 51774-59-5; 1 (R = Et), 59812-12-3; $H_2NCH_2CH_2NH_2$, 107-15-3; $H_2NCH_2CH_2OH$, 141-43-5; $H_2NCH_2CH_2SH$, 60-23-1; *o*-$H_2NC_6N_4NH_2$, 95-54-5; *o*-$H_2NC_6H_4OH$, 95-55-6; *o*-$H_2NC_6H_4SH$, 137-07-5.

Supplementary Material Available. NMR data for all compounds in tables (2 pages). Ordering information is given on any current masthead page.

References and Notes

(1) B. George and E. P. Papadopoulos, *J. Org. Chem.*, **41**, 3233 (1976).
(2) P. R. Atkins, S. E. J. Glue, and I. T. Kay, *J. Chem. Soc., Perkin Trans. 1*, 2644 (1973).
(3) (a) G. Forssel, *Chem. Ber.*, **24**, 1846 (1891); **25**, 2132 (1892); (b) H. Lehr and H. Erlenmeyer, *Helv. Chim. Acta*, **27**, 489 (1944).
(4) E. P. Papadopoulos, *J. Org. Chem.*, **41**, 962 (1976).
(5) R. C. Elderfield, Ed., "Heterocyclic Compounds", Vol. 5, Wiley, New York, N.Y., 1957, pp 239, 274, 377, 420, 507, 679.
(6) Melting points were determined in a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 337 spectrometer using mineral oil mulls. NMR spectra were obtained on a Varian EM 360 spectrophotometer using solutions in hexadeuteriodimethyl sulfoxide with tetramethylsilane as internal standard.

Thermolysis and Photolysis of Various *N*-Imidolyliminopyridinium Ylides

Akikazu Kakehi,* Suketaka Ito, Kenji Uchiyama, Yoshiaki Konno, and Kenji Kondo

Department of Industrial Chemistry, Faculty of Engineering, Shinshu University, Wakasato, Nagano 380, Japan

Received July 27, 1976

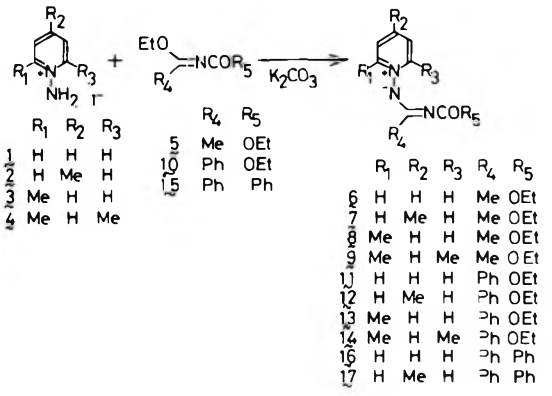
The reactions of pyridinium *N*-imines with some imidates **5**, **10**, and **15** gave the corresponding *N*-imidoyliminopyridinium ylides **6–9**, **11–14**, **16**, and **17** in very good yields. Thermolyses of these *N*-ylides **6–9** and **11–14** in refluxing xylene afforded *s*-triazolo[1,5-*a*]pyridines **18–20**, **23**, **25**, and **27**, pyrazolo[1,5-*a*]pyridines **21**, **22**, **28**, and **29**, and mesoionic compounds **24** and **26**, while thermolyses of *N*-ylides **16** and **17** and photolyses of *N*-ylides **16**, **17**, **11**, and **12** gave the corresponding 1,2,4-oxadiazoles **30** and **31** together with pyridine derivatives in considerable yields. Structural elucidation of these compounds was accomplished mainly by physical and spectral means and partially by their independent syntheses. The formation of pyrazolopyridine derivatives **21**, **22**, **28**, and **29** was confirmed to proceed via isocyanate intermediates.

Pyridinium *N*-ylide acting as an extended dipole is an intriguing molecule in heterocyclic chemistry, and we are especially interested in its reaction leading to polyazabicyclic compounds.[1-3] Recently, a novel 1,6 cyclization has been found in the photolysis of *N*-vinyliminopyridinium ylide.[4] We sought to generalize the 1,6 cyclization, but no such type of reaction could be found in other pyridinium *N*-ylides reported already by us and many investigators.[5-8] Hence, we focused our attention on synthesis of a new class of pyridinium *N*-ylides and we found the 1,6 cyclization in the case of the thermolysis of *N*-imidoyliminopyridinium ylides.[9] In this paper, we wish to report the first synthesis of some *N*-imidoyliminopyridinium ylides and their thermal and photochemical behavior involving the 1,6 cyclization.

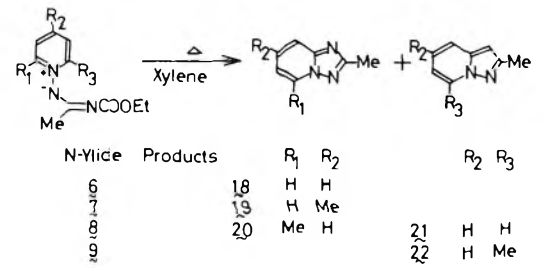
Results and Discussion

Preparation of *N*-Imidoyliminopyridinium Ylides 6–9, 11–14, 16 and 17. The title compounds, *N*-imidoyliminopyridinium ylides **6–9**, **11–14**, **16**, and **17**, were synthesized in very good yields by the reactions of 1-aminopyridinium iodides **1–4** with ethyl *N*-ethoxycarbonylacetimidate (**5**), ethyl *N*-ethoxycarbonylbenzimidate (**10**), and ethyl *N*-benzoylbenzimidate (**15**) in the presence of base (Scheme I). All of the *N*-ylides are stable, crystalline compounds and were not apt to cyclize intramolecularly at ordinary conditions. The structures assigned to these *N*-imidoyliminopyridinium ylides

Scheme I



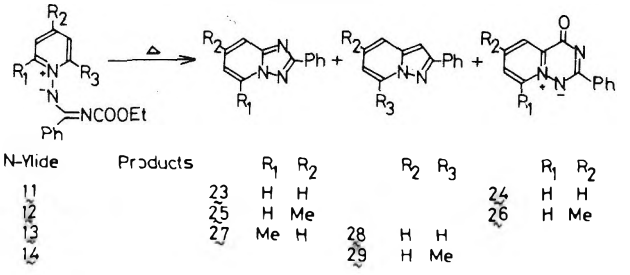
Scheme II



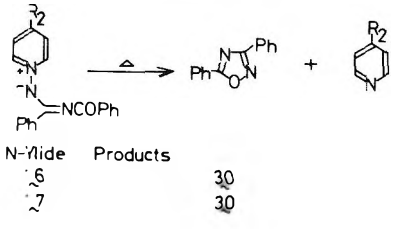
6–9, **11–14**, **16**, and **17** are consistent with the spectroscopic data. For example, they showed a characteristic carbonyl absorption at 1628–1663 cm^{-1} (**6–9** and **11–14**) or at near 1490 cm^{-1} (**16** and **17**) in the IR spectra, and, in the NMR spectra, signals due to protons on the pyridine ring appeared in the range of δ 7.3–9.0, whose values coincide well with those of other substituted *N*-iminopyridinium ylides.[5,6,9]

Thermolyses and Photolyses of *N*-Imidoyliminopyridinium Ylides. In contrast with *N*-vinyliminopyridinium ylides[5,11] and pyridinium *N*-allylides,[7,8,12] these *N*-imidoyliminopyridinium ylides **6–9**, **11–14**, **16**, and **17** did not exhibit 1,5-dipolar cyclization at room temperature at all, but they were thermolyzed in refluxing xylene. Thermolyses of *N*-ylides **6–9** gave the corresponding compounds **18** (60%), **19** (54%), **20** and **21** (total yield ca. 60%), and **22** (75%) together with considerable amounts of polymeric substances. The ratio of product **20** to **21** is 2:3, which was determined by NMR. Similarly, thermolyses of *N*-ylides **11–14** afforded the products **23** (36%) and **24** (58%), **25** (38%) and **26** (51%), **27** and **28** (product ratio **27**/**28** ⅙, total yield 81%), and **29** (87%), respectively, and those of *N*-ylides **16** and **17** gave the same compound **30** in 79 and 80% yields together with pyridine and 4-picoline.

Scheme III



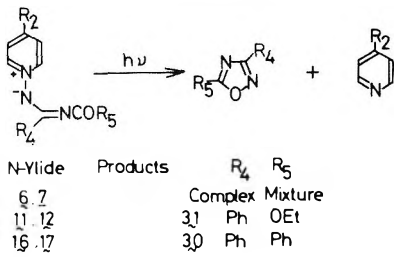
Scheme IV



On the other hand, irradiations of *N*-ylides **11** and **12** in benzene (or acetone) using a high-pressure mercury lamp afforded the same compound **31** in 58 (64) and 59% (60%) yields, together with considerable amounts of pyridine and 4-picoline (detected by TLC). Similarly, photolyses of *N*-ylides **16** and **17** in benzene gave compound **30**, quantitatively, which was the same product as that prepared by the thermolyses of the same *N*-ylides **16** and **17**. However, irradiations of *N*-ylides **6** and **7** gave only complex mixtures, and the isolation of any significant product was unsuccessful. These results are shown in Scheme V.

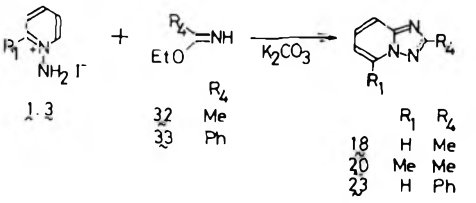
Structures of these products **18–31** were determined mainly by their physical and spectral inspections and partially by

Scheme V



comparisons with authentic samples. Compounds **18–20**, **23**, **25**, and **27** were assigned to be 2-substituted *s*-triazolo[1,5-*a*]pyridine derivatives, because no carbonyl absorption was exhibited in their IR spectra and the chemical shifts (see Table I) of the ring protons were grossly similar to those of bicyclic 10π heteroaromatics such as pyrazolo[1,5-*a*]pyridine[5,6] and indolizine.[7,8,10] Furthermore, compounds **18**, **20**, and **23** were completely in accord with the triazolopyridines prepared by the reactions of pyridinium *N*-imines with imidates **32** and **33** (Scheme VI).

Scheme VI



Structures of compounds **21**, **22**, **28**, and **29** were concluded to be 3-unsubstituted pyrazolo[1,5-*a*]pyridine derivatives from NMR and by comparison with the known pyrazolopyridine **28** reported by Bower and Ramage.[13] The NMR spectra of compounds **21**, **22**, **28**, and **29**, in particular, showed a characteristic singlet signal at δ 6.08–6.60 attributable to a methine proton at the 3 position on the pyrazolopyridine skeleton and the absence of the signal due to one methyl group on the pyridine ring derived from *N*-ylides **8**, **9**, **13**, and **14**. The melting point (107–108 °C) of compound **28** was also in accord with that (109 °C) of 2-phenylpyrazolo[1,5-*a*]pyridine.[13]

Compounds **24** and **26** were determined to be mesoionic pyrido[2,1-*f*]-*as*-triazine derivatives by the elemental and spectral analyses and by comparison with similar mesoionic pyrido[1,2-*b*]pyridazine reported recently by us.[4] For example, the NMR spectrum of compound **24** exhibited signals at δ 7.50 (3 H, m, meta, meta′, and para protons of phenyl), 7.88 (1 H, br t, J = 8.0, 7.0 Hz, 7-H), 8.13 (1 H, br t, J = 8.0, 7.5 Hz, 6-H), 8.42 (2 H, m, ortho and ortho′ protons of phenyl), 8.72 (1 H, dd, J = 7.5, 2.0 Hz, 5-H), and 8.82 (1 H, dd, J = 7.0, 1.0 Hz, 8-H), and the UV spectrum of **24** in ethanol showed two maxima at 253 (log ϵ 4.43) and 343 nm (log ϵ 4.15). The spectral pattern in the UV spectrum of compound **24** is similar to those [251 (log ϵ 4.22) and 338 nm (log ϵ 3.37)] of parent *N*-ylide **11** and those of mesoionic pyridopyridazine.[4] In particular, the enhanced extinction coefficients of product **24** in comparison with *N*-ylide **11** may be due to the increased coplanarity of the ylidic chromophore.

Compounds **30** and **31** were assigned to be 3,5-diphenyl- and 5-ethoxy-3-phenyl-1,2,4-oxadiazole by mechanistic consideration and by comparisons with authentic samples. Since the generation of pyridine derivatives in the reactions was always observed, it is clear that compounds **30** and **31** were formed by the ylidic bond fissions of the corresponding *N*-ylides **16**, **17**, **11**, and **12**. The melting points of **30** and **31** were in accord with those of samples reported in the literature.[14,15]

Mechanisms. Possible mechanisms for the formations of triazolopyridines **18–20**, **23**, **25**, and **27** and pyrazolopyridines

Table I. NMR Data of Triazolopyridines and Pyrazolopyridines

Registry no.	Compd	Solvent	C-5	C-6	C-7	C-8	C-2
768-19-4	**18**	CCl_4	8.37 d	6.73 br t	7.24 br t	7.47 dd	2.48 s
				$J_{5,6} = 7.0, J_{6,7} = 7.5, J_{7,8} = 9.0, J_{6,8} = 1.0$			
4931-22-0	**19**	CCl_4	8.19 d	6.55 dd	2.38 d	7.20 br s	2.43 s
					$J_{5,6} = 7.0, J_{6,8} = 1.5, J_{7,8} = 1.5$		
4931-28-6	**20**	CCl_4	2.65 s	6.58 dd	7.21 q	7.40 dd	2.55 s
					$J_{6,7} = 7.0, J_{7,8} = 9.0, J_{6,8} = 1.0$		
779-24-8	**23**	$CDCl_3$	8.58 dd	6.94 br t	*a*	7.75 d	7.4–7.6 and 8.2–8.5 m — m
					$J_{5,6} = J_{6,7} = 7.0, J_{7,8} = 8.0, J_{5,7} = 1.0$		
4931-23-1	**25**	$CDCl_3$	8.48 d	6.81 dd	2.46 s	*b*	7.4–7.7 and 8.2–8.4 m m
					$J_{5,6} = 7.0, J_{6,8} = 1.5$		
4931-29-7	**27**	CCl_4	2.67 s	6.53 d	7.16 q	*c*	7.2–7.5 and 8.1–8.4 m m
					$J_{6,7} = 7.0, J_{7,8} = 8.0$		

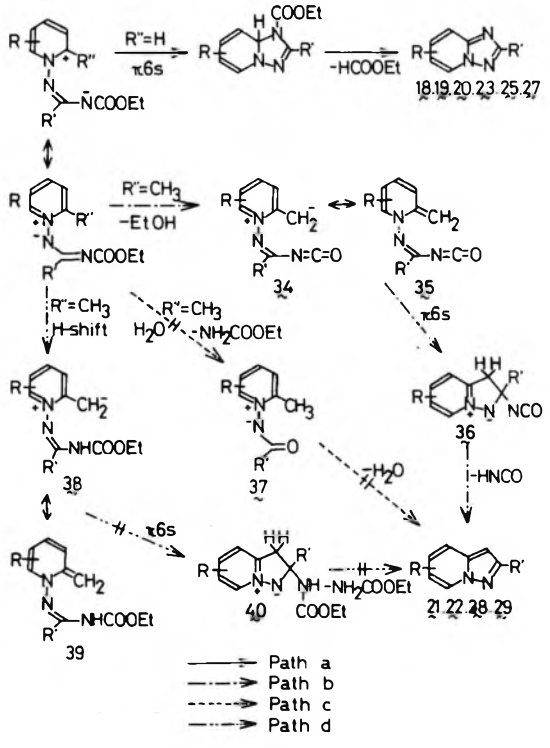
	Compd	Solvent	C-3	C-4	C-5	C-6	C-7	C-2
34760-58-2	**21**	CCl_4	6.08 s	7.23 d	6.86 br t	6.55 br t	8.22 d	2.40 s
						$J_{4,5} = 8.0, J_{5,6} = J_{6,7} = 7.0$		
60705-36-4	**22**	CCl_4	6.09 s	7.12 d	6.76 q	6.28 d	2.61 s	2.42 s
						$J_{4,5} = 8.0, J_{5,6} = 7.0$		
56983-95-0	**28**	CCl_4	6.59 s	*d*	6.87 br t	6.49 br t	8.34 d	7.0–7.5 and 7.7–8.0 m m
						$J_{4,5} = 8.0, J_{5,6} = J_{6,7} = 7.0$		
60705-37-5	**29**	CCl_4	6.60 s	*e*	6.77 q	6.33 br d	2.67 s	7.0–7.4 and 7.7–8.0 m m
						$J_{4,5} = 8.0, J_{5,6} = 7.0$		

[a] Overlapped with signals at δ 7.4–7.6. [b] Overlapped with signals at δ 7.4–7.7. [c] Overlapped with signals at δ 7.2–7.5. [d] Overlapped with signals at δ 7.0–7.5. [e] Overlapped with signals at δ 7.0–7.4.

21, **22**, **28**, and **29** are summarized in Scheme VII.

Triazolopyridines **18–20**, **23**, **25**, and **27** must be formed via 1,5-dipolar cyclizations of *N*-imidoyliminopyridinium ylides

Scheme VII



6–8 and **11–13**, followed by aromatizations of primary dihydrotriazolopyridines (path a). Such cyclizations of the corresponding 1,5-dipoles such as *N*-vinyliminopyridinium ylides[5,11] and pyridinium *N*-allylides[7,8,10,12] have been documented recently by many authors. On the other hand, there are three possible routes for the formations of pyrazolopyridines **21**, **22**, **28**, and **29**: path b, 1,5 cyclization of the isocyanate intermediate **34** or **35** formed by the elimination of 1 mol of ethanol from the corresponding *N*-ylide, followed by aromatization of the resulting 2-isocyanato-2,3-dihydropyrazolopyridine **36** with elimination of isocyanic acid; path c, hydrolysis of the *N*-ylide, followed by dehydration between the 2-methyl group and the carbonyl group in the resulting *N*-acyliminopyridinium ylide **37**; path d, 1,5 cyclization of the rearranged intermediate **38** or **39** formed by sigmatropic shift of a hydrogen on the 2-methyl group in the *N*-ylide, followed by aromatization of the resulting 2-ethoxycarbonylamino-2,3-dihydropyrazolopyridine **40** with elimination of urethan.

Analogous routes to paths c and d were proposed in the reactions of 2-picolinium *N*-phenacylides[16] and in the thermolyses of 2-picolinium *N*-allylides,[8] respectively. Paths c and d, however, can be neglected in this reaction, since no urethan could be detected from the reaction mixture by gas chromatographic examination, and dehydration of *N*-acetyliminopyridinium ylide[17] synthesized independently was unsuccessful under the reaction condition employed here. Further informative evidence was obtained by a trapping experiment, in which gaseous isocyanic acid evolved in the thermolysis of *N*-ylide **14** was introduced into ethanol and the resulting urethane was actually isolated (see Experimental Section).

Table II. Some Data of *N*-Imidoyliminopyridinium Ylides

Registry no.	*N*-Ylide[a]	Reactants: *N*-Imine	Reactants: Imidate	Yield, %	Mp, °C	ν^{KBr} (C=O), cm^{-1}
60705-38-6	**6**	**1**[b]	**5**[f]	89	138–140	1640
60705-39-7	**7**	**2**[c]	**5**	71	124–126	1660
60705-40-0	**8**	**3**[d]	**5**	91	102	1638
60705-41-1	**9**	**4**[e]	**5**	79	167–170	1645
60072-17-5	**11**	**1**	**10**[g]	74	132–133	1660
60072-18-6	**12**	**2**	**10**	88	128–130	1663
60705-42-2	**13**	**3**	**10**	78	163–165	1631
60705-43-3	**14**	**4**	**10**	67	163–164	1628
60705-44-4	**16**	**1**	**15**[h]	79	179–181	1490
60705-45-5	**17**	**2**	**15**	69	166–168	1488

[a] **6**. Anal. Calcd for $C_{10}H_{13}N_3O_2$: C, 57.96; H, 6.32; N, 20.28. Found: C, 57.86; H, 6.33; N, 20.14. **7**. Calcd for $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 18.99. Found: 59.51; H, 6.85; N, 18.73. **8**. Calcd for $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 18.99. Found: C, 59.91; H, 6.86; N, 18.83. **9**. Calcd for $C_{12}H_{17}N_3O_2$: C, 61.25; H, 7.28; N, 17.86. Found: C, 61.32; H, 7.23; N, 18.03. **11**. Calcd for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.61. Found: C, 66.99; H, 5.73; N, 15.32. λ_{max} (EtOH) 251 nm (log ϵ 4.22) and 338 (3.37). **12**. Calcd for $C_{16}H_{17}N_3O_2$: C, 67.82; H, 6.05; N, 14.83. Found: C, 68.01; H, 6.03; N, 14.72. λ_{max} (EtOH) 249 nm (log ϵ 4.24) and 330 (3.40). **13**. Calcd for $C_{16}H_{17}N_3O_2$: C, 67.82; H, 6.05; N, 14.83. Found: C, 67.73; H, 5.98; N, 14.71. **14**. Calcd for $C_{17}H_{19}N_3O_2$: C, 68.66; H, 6.44; N, 14.13. Found: C, 68.41; H, 6.45; N, 14.02. **16**. Calcd for $C_{19}H_{15}N_3O$: C, 75.73; H, 5.02; N, 13.95. Found: C, 75.68; H, 4.91; N, 14.13. **17**. Calcd for $C_{20}H_{17}N_3O$: C, 76.17; H, 5.43; N, 13.33. Found: C, 75.88; H, 5.26; N, 13.18. [b] Registry no., 6295-87-0. [c] Registry no., 7583-92-8. [d] Registry no., 7583-90-6. [e] Registry no., 36012-28-9. [f] Registry no., 31084-70-5. [g] Registry no., 33243-90-2. [h] Registry no., 19344-10-6.

Table III. NMR Data of *N*-Imidoyliminopyridinium Ylides

Compd[a]	Chemical shifts (coupling constants, Hz)
6[b]	2.38 (3 H, s, 2′-CH_3), 7.62 (2 H, br t, J = 6.0, 7.0, 3-H and 5-H), 7.92 (1 H, br t, J = 7.0, 7.0, 4-H), 8.47 (2 H, d, J = 6.0, 2-H and 6-H)
7[b]	2.35 (3 H, s, 2′-CH_3), 2.50 (3 H, s, 4-CH_3), 7.39 (2 H, d, J = 7.0, 3-H and 5-H), 8.29 (2 H, d, J = 7.0, 2-H and 6-H)
8[b]	2.41 (3 H, s, 2′-CH_3), 2.63 (3 H, s, 2-CH_3), 4.78 (1 H, br t, J = 6.0, 7.0, 5-H), 7.53 (1 H, d, J = 7.0, 3-H), 7.83 (1 H, t, J = 7.0, 7.0, 4-H), 8.30 (1 H, d, J = 6.0, 6-H)
9[b]	2.40 (3 H, s, 2′-CH_3), 2.58 (6 H, s, 2-CH_3 and 6-CH_3), 7.33 (2 H, br d, J = 7.0, 3-H and 5-H), 7.67 (1 H, t, J = 7.0, 7.0, 4-H)
11[b]	7.4–8.2 (8 H, m, 2′-Ph, 3-H, 4-H, and 5-H), 8.80 (2 H, br d, J = 7.5, 2-H and 6-H)
12[b]	2.54 (3 H, s, 4-CH_3), 7.4–7.9 (7 H, m, 2′-Ph, 3-H, and 5-H), 8.62 (2 H, d, J = 7.5, 2-H and 6-H)
13[b]	2.77 (3 H, s, 2-CH_3), 7.4–8.0 (8 H, m, 2′-Ph, 3-H, 4-H, and 5-H), 8.62 (1 H, d, J = 7.0, 6-H)
14[b]	2.74 (6 H, s, 2-CH_3 and 6-CH_3), 7.4–8.0 (8 H, m, 2′-Ph, 3-H, 4-H, and 5-H)
16	7.2–7.4 (8 H, m, Ph, 3-H, and 5-H), 7.52 (1 H, t, J = 7.5, 7.5, 4-H), 7.7–8.0 (4 H, m, pH), 8.66 (2 H, br d, J = 7.5, 2-H and 6-H)
17	2.41 (3 H, s, 4-CH_3), 7.1–7.4 (8 H, m, Ph, 3-H, and 5-H), 7.8–8.0 (4 H, m, Ph), 8.46 (2 H, d, J = 7.5, 2-H and 6-H)

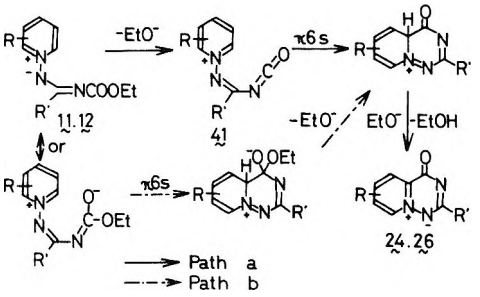
[a] These NMR spectra were measured in deuteriochloroform. [b] The ethyl signals appeared at near δ 1.00 (3 H, t, J = 7.5 Hz) and at near δ 4.00 (2 H, q, J = 7.5 Hz).

Since urethan was not decomposed under such condition, these facts strongly supported path b involving an isocyanate intermediate.

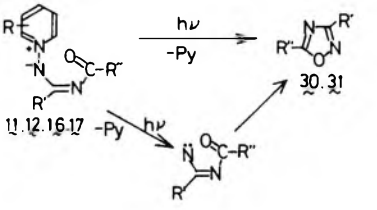
Mechanisms for the formation of mesoionic pyridotriazines **24** and **26** are similar to those given for mesoionic pyridopyridazine (Scheme VIII).[4] The facility of elimination of the ethoxide ion from the *N*-ylide in the formations of pyrazolopyridine derivatives may result in preference of path a involving isocyanate intermediate **41** rather than path b.

The formation of 1,2,4-oxaziazoles **30** and **31** resulted obviously from ylidic bond fissions of the corresponding *N*-ylides, and its possible mechanism is a concerted elimination–cyclization or its stopwise route (Scheme IX). In view of similar reaction examples of some pyridinium ylides reported by Tamura et al.,[18] the most probable route must be a concerted one.

Scheme VIII



Scheme IX



The formation of different products in the thermolyses of *N*-acetimidoyl- **6** and **7** and *N*-benzimidoyliminopyridinium ylides **11** and **12** may be caused by the difference of steric and stabilization effects between the methyl and the phenyl groups, since the introduction of a bulky substituent such as a phenyl group at the 2′ position in the *N*-ylide makes the isocyanate intermediate prefer the configuration fitted in with 1,6 cyclization and the suppression of the formation of polymeric substances in the thermolyses of the latter *N*-ylides **11** and **12** may be attributable to the stabilization effect of the phenyl group.

Experimental Section

Melting points were measured with a Yanagimoto micromelting point apparatus and are uncorrected. Microanalyses were performed on a Perkin-Elmer 240 elemental analyzer. The NMR spectra were determined with a JEOL JNM-4H-100 spectrometer in deuter-

Table IV. Some Data on the Thermolyses of *N*-Imidoyliminopyridinium Ylides

N-Ylide	Products (%)[a]	Mp, °C	ν^{KBr}, cm^{-1}	λ_{max} (EtOH), nm (log ϵ)
6	**18** (60)[21,c]	178–179[b]	1598[b]	
7	**19** (54)[d]	186–189[b]	1595[b]	
8	**20** + **21** (60)		Mixture (**20**/**21** = 2/3)	
9	**22** (75)	Oil	1639 (neat)	
11	**23** (36)[21]	135–137	1631	
	24 (58)[e]	232–234	1603 1404	253 (4.43), 343 (4.15)
12	**25** (38)	140–142	1629	
	26 (51)[f]	245 dec	1610 1388	252 (4.43), 344 (4.21)
13	**27** + **28** (81)		Mixture (**27**/**28** = 1/6)	
	(**28**)[13]	107–108	1625)	
14	**29** (87)	Oil	1630 (neat)	
16	**30** (79)[g]	106–108		
17	**30** (80)			

[a] **19**. Anal. Calcd for $C_{14}H_{12}N_6O_7$ (its picrate): C, 44.68; H, 3.21; N, 22.34. Found: C, 44.77; H, 3.19; N, 22.22. **24**. Calcd for $C_{13}H_9N_3O$: C, 69.94; H, 4.06; N, 18.83. Found: C, 69.75; H, 4.28; N, 18.62. **25**. Calcd for $C_{13}H_{11}N_3$: C, 74.62; H, 5.30; N, 20.08. Found: C, 74.84; H, 5.41; N, 19.88. **26**. Calcd for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.72; H, 4.70; N, 17.58. δ ($CDCl_3$) 2.63 (3 H, s, 6-CH_3), 7.50 (3 H, m, meta, meta′, and para protons of phenyl), 7.65 (1 H, dd, J = 7.0, 2.5 Hz, 7-H), 8.50 (3 H, m, ortho and ortho′ protons of phenyl and 5-H), and 8.70 (1 H, d, J = 7.0 Hz, 8-H). **28**. Calcd for $C_{13}H_{10}N_2$: C, 80.38; H, 5.19; N, 14.42. Found: C, 80.28; H, 5.29; N, 14.55. Compounds **22** and **29** are unstable oils and preparations of pure samples for analyses were unsuccessful. [b] Its picrate. [c] Registry no. (picrate), 7170-11-8. [d] Registry no. (picrate), 60705-46-6. [e] Registry no., 60072-19-7. [f] Registry no., 60111-74-2. [g] Registry no., 888-71-1.

iochloroform or carbon tetrachloride with tetramethylsilane as an internal standard. The chemical shifts are expressed in δ values. The IR and UV spectra were taken with a JASCO DS-301 and a Hitachi EPS-2A spectrophotometer.

Materials. 1-Aminopyridinium iodides **1**–**4** were prepared by Gösl's method[19] and *N*-acylimidates **5**, **10**, and **15** by the N-acylations of ethyl acetimidate (**32**) and ethyl benzimidate (**33**)[20] with ethyl chlorocarbonate and benzoyl chloride in ether or chloroform in the presence of potassium carbonate. Ethyl *N*-ethoxycarbonylacetimidate (**5**), colorless oil, bp 75–81 °C (14 mm). Ethyl *N*-ethoxycarbonylbenzimidate (**10**), colorless oil, bp 150–160 °C (27 mm). Ethyl *N*-benzoylbenzimidate (**15**), colorless crystals, mp 64–65 °C.

Preparations of *N*-Imidoyliminopyridinium Ylides 6–9, 11–14, 16, and 17. General Method. An equimolar mixture of 1-aminopyridinium iodide (2 mmol) and imidate (2 mmol) in ethanol (50 ml) was stirred in the presence of potassium carbonate (5 g) at room temperature for 1–2 days, and then the reaction mixture was filtered to remove insoluble inorganic substances. The filtrate was concentrated under reduced pressure and the residue was separated by column chromatography (alumina) using chloroform as an eluent. Recrystallization from chloroform–ether gave pure *N*-imidoyliminopyridinium ylide as colorless or pale yellow crystals. Some physical and spectral data of the *N*-ylides **6**–**9**, **11**–**14**, **16**, and **17** are summarized in Tables II and III.

Thermolyses of the *N*-Ylides 6–9, 11–14, 16, and 17. General Method. *N*-Ylide (1 mmol) was refluxed in xylene (50 ml) until the disappearance of the *N*-ylide was observed by its TLC (ca. 12–24 h). The reaction mixture was then concentrated under reduced pressure and the residue was separated by the usual manner.

These results and some properties are summarized in Table IV.

Photolyses of the *N*-Ylides 6, 7, 11, 12, 16, and 17. General Method. A solution of the *N*-ylide (1 or 2 mmol) in benzene (100 ml) or acetone was irradiated with a high-pressure mercury lamp (100 W) for 1–7 h. After the evaporation of the solvent, residual substances were separated by column chromatography or directly recrystallized from aqueous ethanol. However, photolyses of *N*-ylides **6** and **7** gave only unstable products; their isolations were unsuccessful. These results are shown in Table V.

Independent Syntheses of Triazolopyridines 18, 20, and 23. Triazolopyridines **18**, **20**, and **23** were synthesized in 49, 44, and 13% yields by the reactions of 1-aminopyridinium iodides **1** and **3** with ethyl acetimidate (**32**) and ethyl benzimidate (**33**) in the presence of potassium carbonate. These triazolopyridines **18**, **20**, and **23** were also prepared by the reactions of pyridinium *N*-imines with acetonitrile and benzonitrile.[21] The melting points and IR and NMR spectra of the triazolopyridines (or their picrates) **18**, **20**, and **23** were in accord with those of the products prepared by the thermolyses of the *N*-ylides **6**, **8**, and **11**.

2,5-Dimethyl-*s*-triazolo[1,5-*a*]pyridine (**20**), mp (its picrate) 175–178 °C. Anal. Calcd for $C_{14}H_{12}N_6O_7$: C, 44.68; H, 3.21; N, 22.34. Found: C, 44.58; H, 3.23; N, 22.22.

Table V. Some Data on the Photolyses of *N*-Imidoyliminopyridinium Ylides

N-Ylide	1,2,4-Oxadiazole[a]	Irradn time, h	Solvent	Yield, %
11	**31**	4	Benzene	58
	31	7	Acetone	64
12	**31**	6	Benzene	59
	31	6	Acetone	60
16	**30**	1	Acetone	100
17	**30**	1	Acetone	100

[a] 5-Ethoxy-3-phenyl-1,2,4-oxadiazole (**31**), colorless needles, mp 32–32.5 °C.[14] 3,5-Diphenyl-1,2,4-oxadiazole (**30**), colorless needles, mp 106–108 °C.[15]

Trapping Experiment with Isocyanic Acid. The apparatus consists of a 100-ml two-necked flask equipped with a gas inlet and a condenser. The exit from the condenser was connected to a trapping flask filled with 30 ml of ethanol. In order to pass isocyanic acid (bp 23.5 °C) without condensation, warm water (50–55 °C) was circulated in the condenser. A solution of *N*-ylide **14** (0.30 g, 1 mmol) in dry xylene (50 ml) was placed in the reaction flask and N_2 gas was slowly introduced. The solution was then refluxed for 1 day. Usual workup of the reaction mixture gave 7-methyl-2-phenylpyrazolo[1,5-*a*]pyridine (**29**, 0.14 g, 67%) as the only isolable product, but no urethan could be obtained. On the other hand, evaporation of ethanol in the trapping flask gave urethan (0.01 g, 11%) as white needles.

In the thermolysis of urethan using the apparatus described above, decomposition of urethan to ethanol and isocyanic acid could not be detected.

Others. In the gas chromatographic examinations of the reaction mixtures from the thermolyses of *N*-ylides **8**, **9**, **13**, and **14**, urethan could not be detected.

The thermolysis of *N*-acetylimino-2,6-lutidinium ylide[17] did not give the corresponding pyrazolopyridine **22**.

Registry No.—**20** picrate, 60705-47-7; **32**, 1000-84-6; **33**, 625-60-5; ethyl chlorocarbonate, 541-41-3; benzoyl chloride, 98-88-4; acetonitrile, 75-05-8; benzonitrile, 100-47-0.

References and Notes

(1) A. Kakehi and S. Ito, *J. Org. Chem.*, **39**, 1542 (1974).
(2) A. Kakehi, S. Ito, and T. Manabe, *J. Org. Chem.*, **40**, 544 (1975).
(3) A. Kakehi, S. Ito, T. Manabe, H. Amano, and Y. Shimaoka, *J. Org. Chem.*, **41**, 2739 (1976).
(4) A. Kakehi, S. Ito, T. Funahashi, and Y. Ota, *J. Org. Chem.*, **41**, 1570 (1976).
(5) T. Sasaki, K. Kanematsu, and A. Kakehi, *J. Org. Chem.*, **37**, 3106

(1972).
(6) T. Sasaki, K. Kanematsu, and A. Kakehi, *Tetrahedron Lett.*, 5245 (1972).
(7) Y. Tamura, Y. Sumida, and M. Ikeda, *J. Chem. Soc., Perkin Trans. 1*, 2091 (1973).
(8) Y. Tamura, Y. Sumida, S. Haruki, and M. Ikeda, *J. Chem. Soc., Perkin Trans. 1*, 575 (1975).
(9) A. Kakehi, S. Ito, K. Uchiyama, and Y. Konno, *Chem. Lett.*, 413 (1976).
(10) T. Sasaki, K. Kanematsu, A. Kakehi, and G. Ito, *J. Chem. Soc., Perkin Trans. 1*, 2089 (1973).
(11) Y. Tamura, N. Tsujimoto, Y. Sumida, and M. Ikeda, *Tetrahedron*, **28**, 21 (1972).
(12) T. Sasaki, K. Kanematsu, A. Kakehi, and G. Ito, *Tetrahedron*, **28**, 4947 (1972).
(13) J. D. Bower and G. R. Ramage, *J. Chem. Soc.*, 4506 (1957).
(14) Mp 35–36 °C: Beilstein, Vol. 27, p 607.
(15) Mp 108 °C: E. Beckmann, *Ber.*, **32**, 1589 (1899).
(16) A. E. Tschitschibabin, *Ber.*, **60**, 1607 (1927).
(17) J. Streith, J. P. Luttringer, and M. Nastasi, *J. Org. Chem.*, **36**, 2962 (1971).
(18) Y. Tamura, Y. Miki, Y. Sumida, and M. Ikeda, *J. Chem. Soc., Perkin Trans. 1*, 2580 (1973).
(19) R. Gösl and A. Meuwsen, *Org. Synth.*, **43**, 1 (1963).
(20) S. A. Glickman and A. C. Cope, *J. Am. Chem. Soc.*, **67**, 1017 (1945).
(21) T. Okamoto, M. Hirobe, Y. Tamai, and E. Yabe, *Chem. Pharm. Bull.*, **14**, 506 (1966).

Reaction of Ketenimines with an Oxaziridine and Nitrones

Nobuyuki Murai, Mitsuo Komatsu, Yoshiki Ohshiro,* and Toshio Agawa

Department of Petroleum Chemistry, Faculty of Engineering, Osaka University, Yamadakami, Suita, Osaka 565, Japan

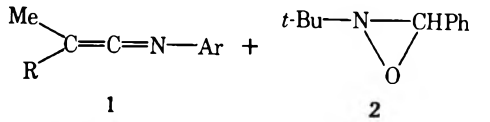
Received July 13, 1976

The reaction of the *N*-arylketenimines **1a–d** with the oxaziridine **2** gave the 1:1 adducts, 1,3-diazolidin-4-ones **3.** In the case of the diphenylketenimine **1e,** the oxindole **9** was isolated instead of **3.** No addition reaction was observed in the reaction of *N*-cyclohexylketenimines. Similar results were obtained in the reactions of **1a,d** with the nitrone **12,** but two oxindoles **9** and **13** were formed in the reaction of **1e.** A substituent effect and the difference between **2** and **12** were observed.

Synthetic application of ketenimines has been less developed than that of other heterocumulenes in the field of heterocyclic chemistry.[1]

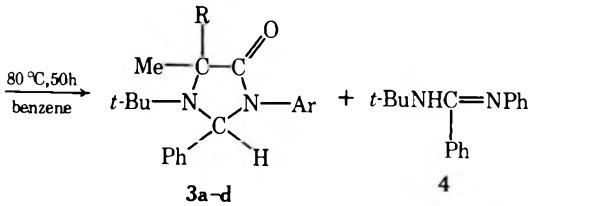
In this paper, the reactions of ketenimines with an oxaziridine and nitrones are described. We reported previously that an isocyanate, a carbodiimide, and an isothiocyanate gave 1:1 adducts in the reactions with 2-*tert*-butyl-3-phenyloxaziridine or *C*-phenyl-*N*-*tert*-butylnitrone, the isomer of the oxaziridine.[2,3] In the reaction with these isomers, on the contrary, a ketene behaved in a different manner from those of the other heterocumulenes.[2,4]

While a ketenimine has one terminal carbon atom like a ketene, the difference between their chemical behavior has been shown in many instances.[1] Most additions to a ketenimine occur on the C=C bond,[1] and Barker and his co-worker reported that *C,N*-diphenylnitrone added to diphenylketene-*N*-*p*-bromophenylimine across the C=C bond.[5] However, our present study revealed that the addition occurs on the C=N bond of ketenimines.

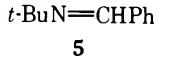


1 **2**

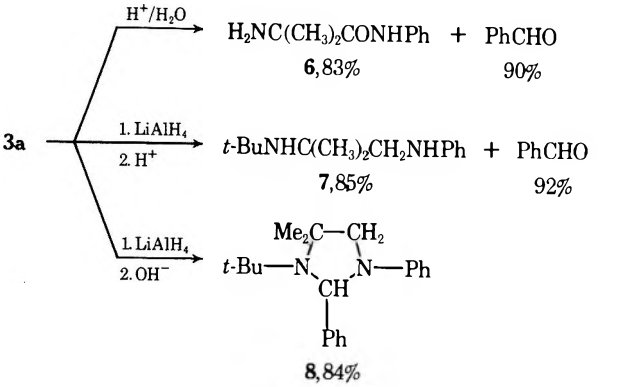
a, R = Me; Ar = Ph
b, R = Me; Ar = *p*-MeC_6H_4
c, R = Me; Ar = *p*-$MeOC_6H_4$
d, R = Ar = Ph



3a–d **4**



5



6, 83% **7**, 85% **8**, 84%

Results and Discussion

Reactions with Oxaziridine. The reaction of dimethylketene-*N*-phenylimine (**1a**) with 2-*tert*-butyl-3-phenyloxaziridine (**2**) gave the 1:1 adduct **3a,** a 1,3-diazolidine derivative, in 40% yield. The dimethylketenimines **1b** and **1c** also gave the 1:1 adducts **3b** and **3c.** In the reaction of phenylmethylketene-*N*-phenylimine (**1d**), however, N^1-*tert*-butyl-N^2-phenylbenzamidine (**4**) and *N*-*tert*-butylbenzaldimine (**5**) were isolated as major products, and the yield of the 1:1 adduct **3d** decreased to 5%.

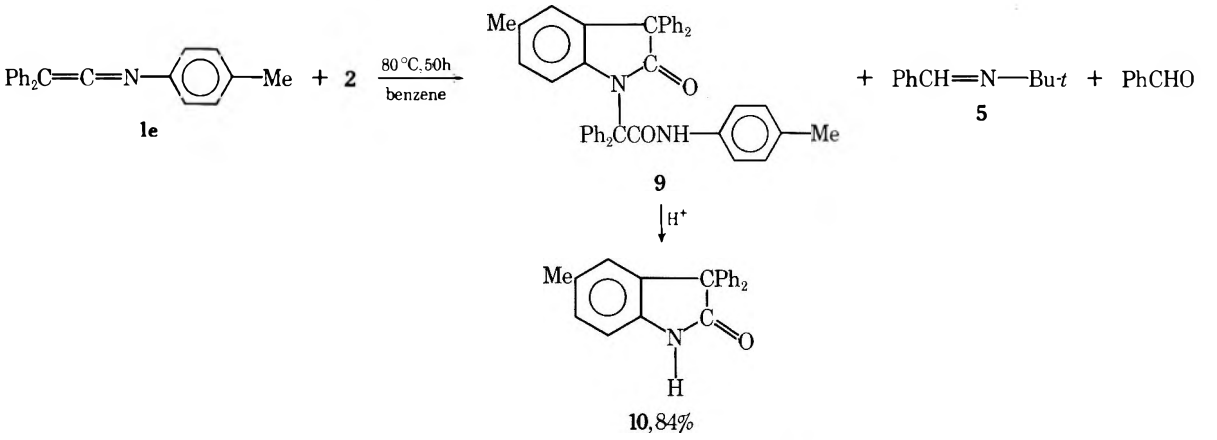
The adduct **3a** exhibited a strong infrared absorption at 1685 cm^{-1}, which was assigned to the carbonyl group. Furthermore, the following chemical evidences provided conclusive proof for the structure of **3a.** Acidic hydrolysis of **3a** gave the anilide **6** and benzaldehyde.[6] After the reaction with lithium aluminum hydride, the addition of hydrochloric acid afforded the acyclic diamine **7** and benzaldehyde, but the alkaline post-treatment gave the 1,3-diazolidine **8.**

On the other hand, diphenylketene-*N*-*p*-tolylimine (**1e**) gave no 1:1 adduct, but the oxindole **9**,[7] benzaldimine **5,** and benzaldehyde were obtained. Benzaldehyde was presumably formed from **5** by hydrolysis. The oxindole **9** was identical with an authentic sample.[8] Hydrolysis of **9** with perchloric acid gave the oxindole **10.**[9]

Table I. Reaction of Ketenimines with an Oxaziridine and Nitrones

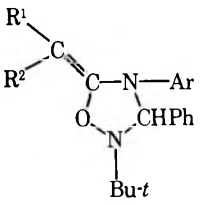
	Ketenimine $R^1R^2C{=}C{=}N{-}R^3$				Product (yield, %)						
	R^1	R^2	R^3	Reactant	3	4	5	9	13	16	PhCHO
1a	Me	Me	Ph	**2**	40						
1b	Me	Me	*p*-MeC_6H_4	**2**	42						
1c	Me	Me	*p*-$MeOC_6H_4$	**2**	60						
1d	Ph	Me	Ph	**2**	5	53	30				
1e	Ph	Ph	*p*-MeC_6H_4	**2**			25	14			45
1g	Me	Me	c-C_6H_{11}	**2**							*a*
1h	Ph	Ph	c-C_6H_{11}	**2**							*a*
1a	Me	Me	Ph	**12**	60						
1d	Ph	Me	Ph	**12**	3	42	40				
1e	Ph	Ph	*p*-MeC_6H_4	**12**			93	10	45		
1f	Ph	Ph	*p*-BrC_6H_4	**15**	33						
1a	Me	Me	Ph	**15**			13[b]			71	

[a] The oxaziridine **2** rearranged to the nitrone **12** quantitatively. [b] PhN=CHPh.



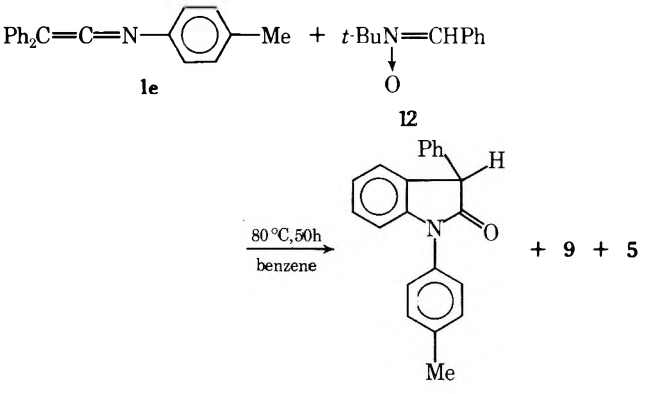
Though *N*-arylketenimines reacted with the oxaziridine **2**, no addition reaction was observed, unexpectedly, for *N*-cyclohexylketenimines. The oxaziridine **2** rearranged to the isomeric nitrone and the ketenimines were recovered quantitatively in the reactions of dimethyl- and diphenylketene-*N*-cyclohexylimines (**1g,h**). The results are summarized in Table I.

The reaction of the oxaziridine **2** can be explained by cycloaddition across the C=N bond of the cumulative system of the ketenimine **1** to form the labile cycloadduct **11**. The final adduct **3** is formed by rearrangement of the intermediate **11**, which gives the amidine **4** by decomposition[10] or the oxindole **9** by elimination of the benzaldimine **5**.

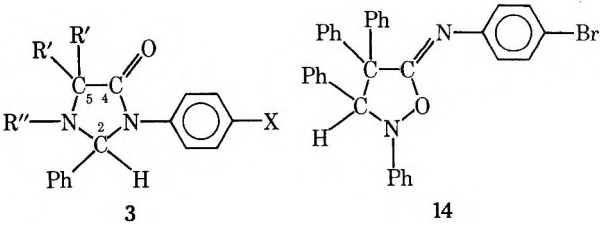


11

Reactions with Nitrones. In the reaction of the ketenimine **1a** or **1d** with *C*-phenyl-*N*-*tert*-butylnitrone (**12**), products were the same as in the case of the isomeric oxaziridine **2** (see Table I), but the reaction of **1e** with **12** gave 1-*p*-tolyl-3-phenyloxindole (**13**) in 45% yield in addition to the products obtained in the reaction of **1e** with **2**. The reaction mode of the nitrone **12** was somewhat different from that of the oxaziridine **2**. Barker had reported that the 1,2-oxazolidine **14** was formed by the addition of *C*,*N*-diphenylnitrone (**15**) across the C=C bond of diphenylketene-*N*-*p*-bromophenylimine (**1f**).[5] Nevertheless, the formation of 1,3-diazolidines **3** can be accounted for by the addition of **12** to the ketenimine



across the C=N bond followed by rearrangement. Hence, the 1,2-oxazolidine structure **14** appears doubtful. The reaction



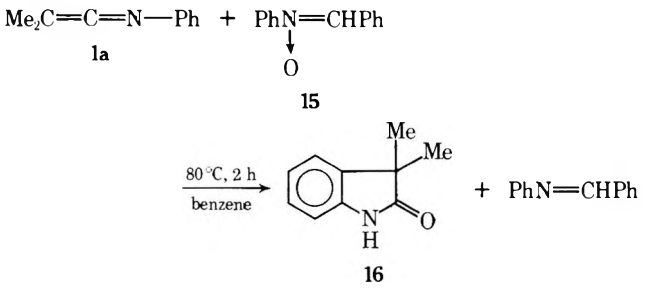
of the ketenimine **1f** and the nitrone **15** was carried out under the reported conditions,[5] and the 1:1 adduct **3f** was obtained in 33% yield. Melting point and infrared and mass spectra of **3f** agreed with the reported data. ^{13}C NMR study on the compound **3f** suggested that a 1,3-diazolidin-4-one structure is more reasonable than a 1,2-oxazolidine structure (Table II).

Table II. ^{13}C Chemical Shifts with Respect to Me_4Si ($CDCl_3$ as Solvent)

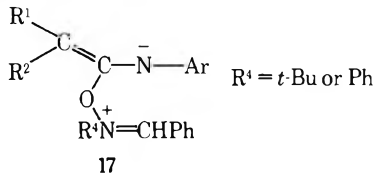
	Substituent			Chemical shift, ppm		
	R′	R″	X	C_2	C_4	C_5
3a	Me	*t*-Bu	H	77.8 (d)	174.8 (s)	64.0 (s)
3f	Ph	Ph	Br	78.2 (d)	170.8 (s)	74.8 (s)

The signal at 170.8 ppm of **3f** can be better assigned to a carbonyl carbon than to an imino or olefinic carbon.[11] The difference between the chemical shifts (C-4) of **3a** and **3f** is due to the mesomeric effect of Br. The C-2 carbons of **3a** and **3f**, whose signals can be determined easily by off-resonance technique, showed almost the same chemical shift. The downfield shift of C-2 carbons of **3** can be explained by the N–C–N linkage rather than by the C–C–N linkage.

In the reaction with *C,N*-diphenylnitrone (**15**), the ketenimine **1a** gave 3,3-dimethyloxindole (**16**) instead of a 1:1 adduct **3**. The similar reaction of **15** with bis(trifluoromethyl) ketene-*N*-phenylimine has been reported by Del'tsova and his co-workers.[12]



The difference between the oxaziridine **2** and the nitrone **12** should be taken into account for the reaction with the ketenimines. The reaction proceeds via the acyclic intermediate **17**, which gives rise to **3**, **9**, and **16** through **11** according



to their substituents. A similar intermediate to **17** has already been proposed in the reaction of a nitrone with a ketene.[13] When R^1 is a phenyl group, the oxindole **13** is formed by nucleophilic attack of the anionic nitrogen atom to the phenyl ring followed by elimination of an aldimine.

In the reaction with nitrones, the formation of the 1:1 adducts and the oxindoles is dependent on the substituents of the reactants. In this respect, chemical behavior of ketenimines resembles that of ketenes.[4] However, ketenimines showed a completely different reaction manner from that of ketenes in the reaction with oxaziridine **2**.

Experimental Section

All melting points were determined on a Yanagimoto micromelting point apparatus and were uncorrected. IR, NMR, and mass spectra were obtained on a JASCO IR-E spectrometer, JEOL LNM-3H-60 and JNM-PS-100 spectrometers, and a Hitachi RMU-6E spectrometer, respectively. The resulting benzaldehyde and benzaldimines were identified and determined by GLC using a 10% Apiezon L on Diasolid L (60–80 mesh, 4 mm × 2 m) column.

Unless noted otherwise, IR and NMR spectra were taken in Nujol mulls and in deuteriochloroform solutions, respectively. The mass spectra were obtained at 70 eV.

All reactions were carried out under nitrogen atmosphere in a 50-ml four-necked flask equipped with a reflux condenser, a dropping funnel, a thermometer, and a magnetic stirrer.

The reactions were ceased after heating to reflux for 50 h, when the characteristic absorption of the ketenimine disappeared.

Materials. Ketenimines **1** were prepared from corresponding amides according to the reported procedures.[14,15] 2-*tert*-Butyl-3-phenyloxaziridine (**2**) was prepared by oxidation of *N*-*tert*-butylbenzaldimine with perbenzoic acid.[16] *N*-*tert*-Butyl-*C*-phenylnitrone (**12**) and *C,N*-diphenylnitrone (**15**) were prepared from the oxaziridine **2**, and benzaldehyde and *N*-phenylhydroxylamine, respectively.[17,18]

Reaction of Dimethylketene-*N*-phenylimine (1a) with the Oxaziridine 2. A mixture of the ketenimine **1a** (2.9 g, 20 mmol) and the oxaziridine **2** (3.5 g, 20 mmol) in benzene (25 ml) was allowed to react at 80 °C for 50 h. The solvent was evaporated in vacuo and the residue was chromatographed (Al_2O_3, benzene–hexane) to give 2.6 g (40%) of 1-*tert*-butyl-2,3-diphenyl-5,5-dimethyl-1,3-diazolidin-4-one (**3a**). Recrystallization of **3a** from hexane yielded colorless needles: mp 93–94 °C; IR 1685 cm^{-1} (C=O); NMR δ 1.13 (s, 9, *t*-Bu), 1.58 (s, 3, Me), 1.75 (s, 3, Me), 5.79 (s, 1, CH), 6.9–7.2 (m, 10, aromatic protons); mass spectrum *m/e* 322 (M^+, calcd 322), 307 (M^+ – Me), 251 (307 – Me_2C=CH_2), 245 (M^+ – Ph), 189 (245 – Me_2C=CH_2).

Anal. Calcd for $C_{21}H_{26}N_2O$: C, 78.22; H, 8.13; N, 8.69. Found: C, 78.14; H, 8.23; N, 8.98.

Reaction of Dimethylketene-*N*-*p*-tolylimine (1b) and the Oxaziridine 2. From 3.2 g (20 mmol) of the ketenimine **1b** and 3.5 g (20 mmol) of the oxaziridine **2**, 2.9 g (42%) of 1-*tert*-butyl-2-phenyl-3-*p*-tolyl-5,5-dimethyl-1,3-diazolidin-4-one (**3b**) was obtained. The product **3b** was purified by pot distillation (100–120 °C, 1 mm) to afford colorless, viscous liquid: IR (neat) 1706 cm^{-1} (C=O); NMR δ 1.12 (s, 9, *t*-Bu), 1.58 (s, 3, Me), 1.76 (s, 3, Me), 2.53 (s, 3, Me), 5.74 (s, 1, CH), 7.0–7.3 (m, 9, aromatic protons); mass spectrum *m/e* 336 (M^+, calcd 336).

Anal. Calcd for $C_{22}H_{28}N_2O$: C, 78.53; H, 8.39; N, 8.33. Found: C, 78.27; H, 8.31; N, 8.69.

Reaction of Dimethylketene-*N*-*p*-anisylimine (1c) and the Oxaziridine 2. From 3.5 g (20 mmol) of the ketenimine **1c** and 3.5 g (20 mmol) of the oxaziridine **2**, 4.2 g (60%) of 1-*tert*-butyl-2-phenyl-3-*p*-anisyl-5,5-dimethyl-1,3-diazolidin-4-one (**3c**) was isolated and purified by pot distillation (90–120 °C, 1 mm) to give colorless solid (no attempts at recrystallization of the product were successful): mp 30–31.5 °C; IR (neat) 1698 cm^{-1} (C=O); NMR δ 1.15 (s, 9, *t*-Bu), 1.55 (s, 3, Me), 1.70 (s, 3, Me), 3.60 (s, 3, MeO), 5.68 (s, 1, CH), 6.4–6.9 (m, 4, aromatic protons), 7.0–7.2 (m, 5, aromatic protons); mass spectrum *m/e* 352 (M^+, calcd 352).

Anal. Calcd for $C_{22}H_{28}N_2O_2$: C, 74.96; H, 8.01; N, 7.95. Found: C, 74.91; H, 7.95; N, 7.87.

Reaction of Phenylmethylketene-*N*-phenylimine (1d) and the Oxaziridine 2. The reaction of the ketenimine **1d** (3.1 g, 15 mmol) and the oxaziridine **2** (2.7 g, 15 mmol) gave 0.29 g (5%) of 1-*tert*-butyl-2,3,5-triphenyl-5-methyl-1,3-diazolidin-4-one (**3d**), 2.0 g (53%) of N^1-*tert*-butyl-N^2-phenylbenzamidine (**4**), and 0.73 g (30%) of *N*-*tert*-butylbenzaldimine (**5**). Recrystallization of the amidine **4** from benzene–hexane yielded colorless needles: mp 131–133 °C; IR 3360 (NH), 1610 cm^{-1} (C=N); NMR δ 1.53 (s, 9, *t*-Bu), 4.3–4.5 (broad, 1, NH), 6.5–7.2 (m, 10, aromatic protons); mass spectrum *m/e* 252 (M^+, calcd 252), 196 (M^+ – Me_2C=CH_2), 180 (Ph=CPh)$^+$.

Anal. Calcd for $C_{17}H_{20}N_2$: C, 80.91; H, 7.99; N, 11.10. Found: C, 81.33; H, 7.77; N, 11.15.

The diazolidine **3d** was recrystallized from benzene–hexane to afford colorless needles: mp 154–156 °C; IR 1680 cm^{-1} (C=O); NMR δ 0.91 (s, 9, *t*-Bu), 2.25 (s, 3, Me), 5.77 (s, 1, CH), 6.9–7.2 (m, 15, aromatic protons); mass spectrum *m/e* 384 (M^+, calcd 384), 251 (*t*-BuNCPh=NPh)$^+$.

Anal. Calcd for $C_{26}H_{28}N_2O$: C, 81.21; H, 7.34; N, 7.29. Found: C, 81.40; H, 7.27; N, 7.56.

Hydrolysis of the Diazolidine 3a. To a solution of 0.5 g (1.4 mmol) of **3a** in 20 ml of ethanol, 3 ml of 2 N HCl was added. The mixture was heated to reflux for 5 h, and then extracted (ether) to give 0.1 g (90%) of benzaldehyde. The inorganic layer was neutralized (NaOH) and extracted (ether). The ethereal extract was concentrated in vacuo to give 0.25 g (83%) of 2-amino-2-methylpropananilide (**6**), which was recrystallized (benzene–hexane) to afford colorless needles: mp 58.5–60.0 °C; IR 3280 (NH), 1670 cm^{-1} (C=O); NMR δ 1.43 (s, 6, 2 Me), 1.61 (s, 2, NH_2), 6.9–7.6 (m, 5, aromatic protons), 9.8–10.0 (broad, 1, NH); mass spectrum *m/e* 178 (M^+, calcd 178).

Anal. Calcd for $C_{10}H_{14}N_2O$: C, 67.38; H, 7.92; N, 15.72. Found: C, 67.34; H, 8.00; N, 15.54.

Reduction of 3a with $LiAlH_4$. A. To a suspension of 100 mg of $LiAlH_4$ in 30 ml of ether, 0.50 g (1.4 mmol) of **3a** in 10 ml of ether was added dropwise with cooling. The mixture was stirred for 1 h at room

temperature and then heated to reflux for 2 h. The mixture was treated with 1 N HCl and was extracted (ether) to give 0.12 g (92%) of benzaldehyde. The inorganic layer was neutralized (NaOH) and extracted (ether). Evaporation of ether yielded 0.31 g (85%) of *N*-(2-*tert*-butylamino-2-methylpropyl)aniline (7), which was purified by sublimation to afford colorless needles: mp 54–55 °C; IR 3350 cm^{-1} (NH); NMR δ 0.7–0.9 (broad, 1, NH), 1.17 (s, 9, *t*-Bu), 1.25 (s, 6, 2 Me), 2.83 (d, 2, J = 4 Hz, CH_2), 4.5–4.7 (broad, 1, NH) 6.5–7.3 (m, 5, aromatic protons); mass spectrum m/e 220 (M^+, calcd 220).

Anal. Calcd for $C_{14}H_{24}N_2$: C, 76.31; H, 10.98; N, 12.71. Found: C, 76.59; H, 11.29; N, 12.62.

B. After the reduction under the same conditions, the mixture was treated with 2 N NaOH and was extracted (ether) to give 0.41 g (84%) of 1,2-diphenyl-3-*tert*-butyl-4,4-dimethyl-1,3-diazolidine (8). The product 8 was purified by pot distillation (100 °C, 1 mm) to give colorless, viscous liquid: IR (neat) no characteristic absorption; NMR δ 1.13 (s, 9, *t*-Bu), 1.15 (s, 3, Me), 1.27 (s, 3, Me), 3.15 (d, 1, J = 9.0 Hz, CHH), 3.45 (d, 1, J = 9.0 Hz, CHH), 5.80 (s, 1, CHPh), 6.5–7.5 (m, 10, aromatic protons); mass spectrum m/e 308 (M^+, calcd 308).

Anal. Calcd for $C_{21}H_{28}N_2$: C, 81.77; H, 9.15; N, 9.08. Found: C, 81.71; H, 9.39; N, 9.16.

Reaction of Diphenylketene-*N*-*p*-tolylimine (1e) and the Oxaziridine 2. The same treatment of 4.2 g (15 mmol) of the ketenimine **1e** and 2.7 g (15 mmol) of the oxaziridine **2** afforded 0.95 g (45%) of benzaldehyde, 0.45 g (25%) of **5**, and 0.62 g (14%) of 1-(*p*-tolylcarbamoyldiphenylmethyl)-3,3-diphenyl-5-methyloxindole (**9**). The crystallization of the oxindole **9** from benzene–hexane gave colorless granules, mp 245–246 °C (lit.[8] 249–251 °C), which showed no depression by mixing with an authentic sample. The spectral data agreed well with those of the authentic sample.

Hydrolysis of the Oxindole 9. The oxindole **9** (0.45 g) was refluxed in 20 ml of ethanol containing 2 ml of 40% $HClO_4$ for 25 h. Removal of the solvent yielded 5-methyl-3,3-diphenyloxindole (**10**, 3.9 g, 84%).[9] Recrystallization of **10** from ethanol gave colorless needles, whose melting point and spectral data agreed with those of an authentic sample.[8]

Reactions of the Ketenimines 1g,h with the Oxaziridine 2. After the same treatment of 2.5 g (17 mmol) of dimethylketene-*N*-cyclohexylimine **1g** and 3.0 g (17 mmol) of the oxaziridine **2**, no change in the IR spectrum of the reaction mixture was observed. The additional heating to reflux for 22 h did not affect the reaction. The reaction mixture was chromatographed (Al_2O_3, benzene–hexane) to give 2.76 g (92%) of *N*-*tert*-butyl-*C*-phenylnitrone (**12**) and 2.45 g (86%) of *N*-cyclohexyl-2-methylpropionamide. The amide was recrystallized (benzene–hexane) to give colorless needles, mp 121–122 °C, which showed no depression by mixing with an authentic sample prepared from isobutanoyl chloride and cyclohexylamine.

The same result was obtained from the reaction of diphenylketene-*N*-cyclohexylimine (**1h**) with the oxaziridine **2**. From 4.1 g (15 mmol) of **1h** and 2.6 g (15 mmol) of **2**, 2.2 g (87%) of the nitrone **12** and 3.4 g (88%) of *N*-cyclohexyldiphenylacetamide were obtained.

Reaction of the Ketenimine 1a with *N*-*tert*-Butyl-*C*-phenylnitrone (12). The reaction of 1.45 g (10 mmol) of **1a** with 1.77 g (10 mmol) of **12** gave 1.93 g (60%) of the diazolidine **3a**.

Reaction of the Ketenimine 1d with the Nitrone 12. The reaction of 3.1 g (15 mmol) of **1d** with 2.7 g (15 mmol) of **12** gave 0.17 g (3%) of the diazolidine **3d**, 1.58 g (42%) of **4**, and 1.1 g (40%) of **5**.

Reaction of the Ketenimine 1e and the Nitrone 12. From the reaction mixture of 2.83 g (10 mmol) of the ketenimine **1e** and 1.77 g (10 mmol) of the nitrone **12**, 1.49 g (93%) of **5** was obtained by distillation (42–45 °C, 5 mm). The residue was chromatographed (Al_2O_3, benzene) to give 0.30 g (10%) of the oxindole **9** and 1.34 g (45%) of 1-*p*-tolyl-3-phenyloxindole (**13**). The oxindole **13** was recrystallized (benzene–hexane) to afford colorless needles: mp 168–170 °C; IR 1725 cm^{-1} (C=O); NMR δ 2.39 (s, 3, Me), 4.72 (s, 1, CH), 6.7–7.2 (m, 13, aromatic protons); mass spectrum m/e 299 (M^+, calcd 299), 270 (M^+ – CHO), 194 ($PhC{=}NC_6H_4Me)^+$.

Anal. Calcd for $C_{21}H_{17}NO$: C, 84.25; H, 5.72; N, 4.68. Found: C, 84.41; H, 5.74; N, 4.68.

Reaction of Diphenylketene-*N*-*p*-bromophenylimine (1f) and *C*,*N*-Diphenylnitrone (15). A mixture of 1.74 g (5 mmol) of the ketenimine **1f** and 0.98 g (5 mmol) of the nitrone **15** in ether was heated to reflux for 20 h. Collection of the precipitate afforded 0.89 g (33%) of 1,2,5,5-tetraphenyl-3-*p*-bromophenyl-1,3-diazolidin-4-one (**3f**), which was recrystallized from ethanol to give colorless needles: mp 214–216 °C; IR 1685 cm^{-1} (C=O); NMR δ 6.5–7.5 (m, aromatic protons and CH); mass spectrum m/e 546 and 544 (M^+), 469 and 467 (M^+ – Ph), 347 (M^+ – p-$BrC_6H_4N{=}C{=}O$), 257 ($Ph_2C{=}NPh)^+$, 180 ($PhC{=}NPh)^+$.

Anal. Calcd for $C_{33}H_{25}N_2OBr$: C, 72.66; H, 4.62; N, 5.14. Found: C, 72.47; H, 4.47; N, 5.18.

Acidic hydrolysis of **3f** with $HClO_4$ or HBr in refluxing ethanol was not successful and the diazolidine **3f** was recovered.

Reaction of the Ketenimine 1a and the Nitrone 15. To a solution of 2.9 g (20 mmol) of the ketenimine **1a** in benzene, 3.9 g (20 mmol) of the nitrone **15** (in benzene) was added dropwise at 80 °C, and the mixture was kept refluxing for 2 h. From the reaction mixture, 0.5 g (13%) of *N*-phenylbenzaldimine was distilled away (100 °C, 2 mm). The residue was chromatographed (Al_2O_3, benzene–ethanol) to give 2.1 g (71%) of 3,3-dimethyloxindole **16**, which was recrystallized (benzene–hexane) to give colorless plates: mp 151–152 °C; IR 3120 (NH), 1705 (C=O), and 1660 cm^{-1}; NMR δ 1.42 (s, 6, 2 Me), 6.8–7.2 (m, 4, aromatic protons), 9.7–9.9 (broad, 1, NH); mass spectrum m/e 161 (M^+, calcd 161), 146 (M^+ – Me), 132 (M^+ – CHO), 128 (146 – H_2O).

Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.22; H, 6.63; N, 8.75.

Acknowledgment. The authors are indebted to Professor M. W. Barker of Mississippi State University for his suggestion for the structure of **9**.

Registry No.—**1a**, 14016-34-3; **1b**, 18779-86-7; **1c**, 14016-32-1; **1d**, 32907-79-2; **1e**, 5110-45-2; **1f**, 29376-76-9; **1g**, 14251-68-4; **1h**, 24932-57-8; **2**, 7731-34-2; **3a**, 60687-68-5; **3b**, 60687-69-6; **3c**, 60687-70-9; **3d**, 60687-71-0; **3f**, 60687-72-1; **4**, 50484-26-9; **6**, 20049-03-0; **7**, 60687-73-2; **8**, 60687-74-3; **9**, 6834-59-9; **12**, 3376-24-7; **13**, 60687-75-4; **15**, 1137-96-8; **16**, 19155-24-9.

References and Notes

(1) G. R. Krow, *Angew. Chem., Int. Ed. Engl.*, **10**, 435 (1971).
(2) M. Komatsu, Y. Ohshiro, H. Hotta, and T. Agawa, *J. Org. Chem.*, **39**, 948 (1974).
(3) M. Komatsu, Y. Ohshiro, K. Yasuda, S. Ichijima, and T. Agawa, *J. Org. Chem.*, **39**, 957 (1974).
(4) D. St. C. Blanck, R. F. Crozier, and V. C. Davis, *Synthesis*, 205 (1975).
(5) M. W. Barker and J. H. Gardner, *J. Heterocycl. Chem.*, **5**, 881 (1968).
(6) Such a type of de-*tert*-butylation under acidic condition has been reported [C. Ainsworth and N. R. Easton, *J. Org. Chem.*, **27**, 4118 (1962); Y. Ohshiro, M. Komatsu, Y. Yamamoto, K. Takaki, and T. Agawa, *Chem. Lett.* 383 (1974); G. Simig and K. Lempert, *Tetrahedron*, **31**, 983 (1975)].
(7) Our first proposition of the piperadine structure for 9 [Y. Ohshiro, N. Murai, M. Komatsu, and T. Agawa, Abstracts, 5th International Congress of Heterocyclic Chemistry, Ljubljana, Yugoslavia, July 1975, p 385] was excluded by ^{13}C NMR study [165.5 and 184.0 ppm (C=O); 71.9 and 83.3 ppm (Ph_2C)]. The oxindole 9 was isolated by Barker in the reaction of an amine oxide and a ketenimine (M. W. Barker, 1975, personal communication).
(8) (a) J. C. Sheehan and J. W. Frankenfeld, *J. Am. Chem. Soc.*, **83**, 4729 (1961); (b) J. C. Sheehan and H. Beeson, *J. Org. Chem.*, **31**, 1637 (1961).
(9) It has already been reported that 1 mol of 9 gives 2 mol of **10** upon acidic treatment (ref 8).
(10) Similar rearrangement and decomposition were observed in the reaction of diphenylcarbodiimide with the nitrone **12** (ref 2).
(11) (a) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972; (b) L. F. Johnson and W. C. Jankowski, "Carbon-13 NMR Spectra", Wiley-Interscience, New York, N.Y., 1972.
(12) D. P. Del'tsova, N. P. Gambaryan, and I. L. Knunyants, *Dokl. Akad. Nauk SSSR*, **206**, 620 (1972); *Chem. Abstr.*, **78**, 15959 (1973).
(13) R. N. Pratt, D. P. Stokes, G. A. Taylor, and P. C. Brookes, *J. Chem. Soc.*, 2086 (1968).
(14) C. L. Stevens and J. C. French, *J. Am. Chem. Soc.*, **76**, 4398 (1954).
(15) C. L. Stevens and G. H. Singhal, *J. Org. Chem.*, **29**, 34 (1964).
(16) R. G. Pews, *J. Org. Chem.*, **32**, 1628 (1967).
(17) W. D. Emmons, *J. Am. Chem. Soc.*, **79**, 5739 (1957).
(18) I. Brünig, R. Grashey, H. Hauck, R. Huisgen, and H. Seidl, *Org. Synth.*, **46**, 127 (1966).

Reactions of Azines with Electron-Deficient Alkynes. Formation of 1,5-Dihydropyrazolo[1,2-*a*]pyrazoles, α,β-Unsaturated Azines, and *N*-Allyl- and *N*-Propenylpyrazoles

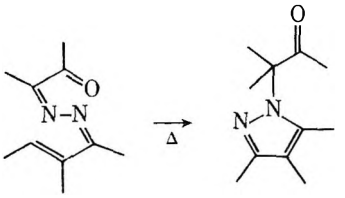
Steven Evans,[1a] Richard C. Gearhart, Lloyd J. Guggenberger,[1b] and Edward E. Schweizer*

Department of Chemistry, University of Delaware, Newark, Delaware 19711, and Contribution No. 2470 from the Central Research Department, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898

Received August 20, 1976

The reactions of simple acyclic azines with dimethyl acetylenedicarboxylate or methyl propiolate have been shown to yield either α,β-unsaturated azines or *N*-allyl- and/or *N*-propenylpyrazoles depending on the nature of the azine. The intermediacy of 1,5-dihydropyrazolo[1,2-*a*]pyrazoles has been demonstrated and the stereochemistry of the reaction probed. An x-ray crystallographic structure determination on one of the *N*-allylpyrazoles is also reported.

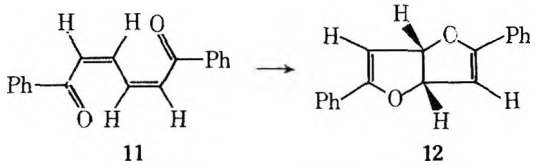
The thermolysis of α,β-unsaturated azines is a simple and efficient route to the pyrazole ring system. For example, azines (**1**) derived from α-diketone monohydrazones and α,β-unsaturated carbonyl compounds readily rearrange[2] on heating to α-pyrazolyl ketones (**2**). Similarly, cinnamaldehyde azine



1 **2**

(**3a**) yields[3] *N-cis*-propenylpyrazole (**5a**) on pyrolysis. These reactions are quite general, requiring only that one of the substituents on the terminal double bond of the azine be a proton. The proposed[4] mechanism for the conversion of **3a** to **5a** involves formation of azomethine imine **4a** followed by intramolecular hydrogen transfer (path A, Scheme I).

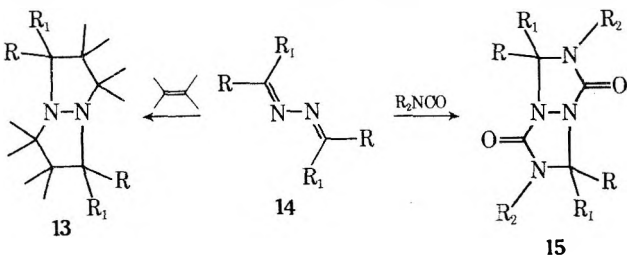
Maier's report[5] of the ring closure of 1,4-dibenzoylbutadiene (**11**) to furano[3,2-*b*]furan **12** suggests an alternative mecha-



11 **12**

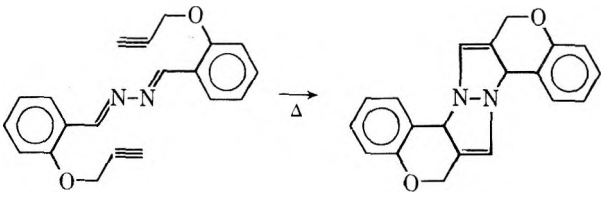
nistic possibility for the **3a** → **5a** conversion involving bicyclic heterocycle **7a** (path B, Scheme I). A synthesis of examples of **7** and investigation of their thermal behavior would offer a test, in part, of this hypothesis. When none of the substituents in the 1 and 5 positions is a proton, reversion to **3** would be expected (either directly or via **4**), while if at least one proton is in the 1 or 5 position, **5** and/or **6** may result as well.

The 1,5-dihydropyrazolo[1,2-*a*]pyrazoles **7** were unknown at the beginning of this investigation. However, simple ald- and ketazines (**14**) are known to react with olefins[6] and isocyanates[7,8] to yield related perhydro systems **13** and **15**, re-



13 **14** **15**

spectively. We reasoned that this "criss-cross"[7] cycloaddition could be extended to alkynes as a synthetic approach to **7**. During the course of this study, several reports appeared in the literature which confirmed, to some extent, our thinking. Hexafluoroacetone azine **10a** reacts at room temperature with phenylacetylene (**9a**) or acetylene (**9b**) to yield[9] dihydropyrazolopyrazoles **7b** and **7c**, respectively. At higher temperatures[10] or upon thermolysis or photolysis[9] of **7b** or **7c**, unsaturated azines **3b** or **3c** result. Recently, Suschitsky et al. re-



16 **17**

ported[11] that dihydropyrazolopyrazole **17** results from rearrangement of the azine of salicylaldehyde propargyl ether (**16**) in refluxing diethylaniline. We wish to report the results of our investigations into the reactions of azines with electron-deficient alkynes.

Results and Discussion

Benzophenone azine (**10b**) reacts slowly with dimethyl acetylenedicarboxylate (**9c**) to form a single product, isolated in 82% yield as a bright yellow solid. Analytical data indicate the formation of 2:1 (alkyne:azine) adduct. The ^{13}C and ^{1}H NMR spectra show only two distinct carbomethoxy groups and the lack of any saturated carbons (other than the ester methyl carbons). This indicates a fully unsaturated, symmetrical structure which is consistent with the product being the acyclic azine **3d**, resulting from rearrangement of intermediate **7d** analogously to the **7b/c** → **3b/c** conversion.

Reaction of benzaldehyde (**10c**) or benzaldehyde–benzophenone (**10d**) azines with **9c** under similar conditions yields colorless, crystalline 2:1 adducts in approximately 80% isolated yield. The ^{13}C NMR spectra of both products distinctly show four nonequivalent carbomethoxy groups and a single, nonester methyl saturated carbon at about 60 ppm. In the proton spectrum of the **10c**–**9c** product, two one-proton singlets (at δ 5.88 and 7.93 ppm) are observed for the nonaromatic/methyl hydrogens. The single proton of this type in the **10d**–**9c** adduct resonates at 5.49 ppm. Of the possible products for this reaction, dihydropyrazolopyrazoles **7e/f**, azines **3e/f**, and *N*-propenylpyrazoles **5e/f** are clearly inconsistent with these spectral data. The *N*-allylpyrazoles **6e/f** are consistent with the data but since a wide variety of compounds containing the C–N double bond form dihydropyridines when allowed to

Table I. Selected ^{1}H NMR Parameters for *N*-Allyl- (6) and *N*-Propenyl- (5) pyrazoles

Compd	R_2[a]	R_8	R_4	R_3	R_5
6e	7.93[b]	5.88	c	c	c
6f	C_6H_5	5.49	c	c	c
6g	7.99	6.08	c	c	c
6i	6.24	5.35	c	6.65	7.96
	d, J = 16.0	d, J = 6.5		dd, J = 16.0, 6.5	
6j	7.92 (7.95)	4.85, 2 H		c	7.92 (7.95)
6k	C_6H_5	5.41	c		7.97
		d, J = 10.0			
6l	C_6H_5	4.78, 2 H		c	7.92
5i	3.26, 2 H		c	d	8.07
	d, J = 7.5				
5j	4.34, 2 H		7.61	c	8.04
5l	C_6H_5		7.59	c	7.91

[a] Numbering refers to Scheme I. [b] One proton singlets, parts per million (δ) vs. Me_4Si except as noted. [c] CO_2CH_3, δ 3.4–3.85 ppm. [d] Obscured by aromatic region.

Table II. Pertinent ^{13}C NMR Parameters for *N*-Allyl- (6) and *N*-Propenyl- (5) pyrazoles

Compd	C-4[a]	C-6	C-8	CO_2CH_3	CO_2CH_3
6e	114.4[b]	58.6	c	51.7, 52.2, 52.5, 52.8	162.4, 162.9, 166.5, 167.9
6f	114.0	63.0	c	51.8, 52.0 (2), 53.2	162.1, 163.1, 168.0, 168.7
6i	112.7	63.1	c	51.1, 52.4	163.0 (2)
6j	d	46.4	c	51.0, 52.2	163.2, 166.8
6k	112.3	60.0	c	51.0, 53.0	163.1, 169.1
6l	112.5	51.7	c	51.0, 51.7	163.4, 169.0
5i	112.7	c	34.2	51.1, 53.0	163.0, 168.3
5j	115.8	c	31.8	51.4, 52.2	162.7, 167.9
5l	113.6	c	46.9	51.3, 51.7	162.6, 167.2

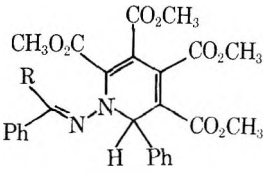
[a] Numbering as in Scheme I. [b] Parts per million (δ) vs. Me_4Si. [c] Not assigned. [d] Obscured by baseline noise.

Table III. Selected Interplanar Angles[a] for 6f

Plane 1[b]	Plane 2	Angle, deg
N2–C1–C2–C25	C1–C25–O1–O2	2.2
C1–C2–C3–C27	C2–C27–O3–O4	65.5
C4–C5–C6–C29	C5–C29–O5–O6	44.0
N1–C3–C2–C19	C3–C19–C20–C24	67.5
C5–C6–C7–C13	C6–C7–C8–C12	53.7
C5–C6–C7–C13	C6–C13–C14–C18	40.8

[a] Angle between the normals to the calculated planes. [b] Labels refer to Figure 1 (text).

react with **9c**,[12] we were forced to consider structures **18a** and **18b** as likely candidates for these products. Although consistent with the NMR data, we rule out these structures since most dihydropyridines are colored to some extent[13] and we are unable to detect benzaldehyde or benzophenone upon acid hydrolysis. We thus assign the structure of the products resulting from the reaction of azines **10c** and **10d** with alkyne **9c** as the *N*-allylpyrazoles, **6e** and **6f**. Pertinent ^{1}H and ^{13}C NMR parameters are listed in Tables I and II, respectively.



18a, R = H
b, R = Ph

We have confirmed this assignment by x-ray crystallography. The ORTEP[14] perspective drawing of **6f** based on the x-ray analysis is shown in Figure 1 and clearly shows the pyrazole ring (N1–N2–C1–C2–C3) with its substituents. Table III lists selected angles between calculated planes containing the indicated atoms which reflect the orientations of the phenyl and carbomethoxy groups. It is interesting to note that the phenyl ring in the 5 position of the pyrazole ring (i.e., C19 → C24) is tilted approximately 67.5° from the plane of the

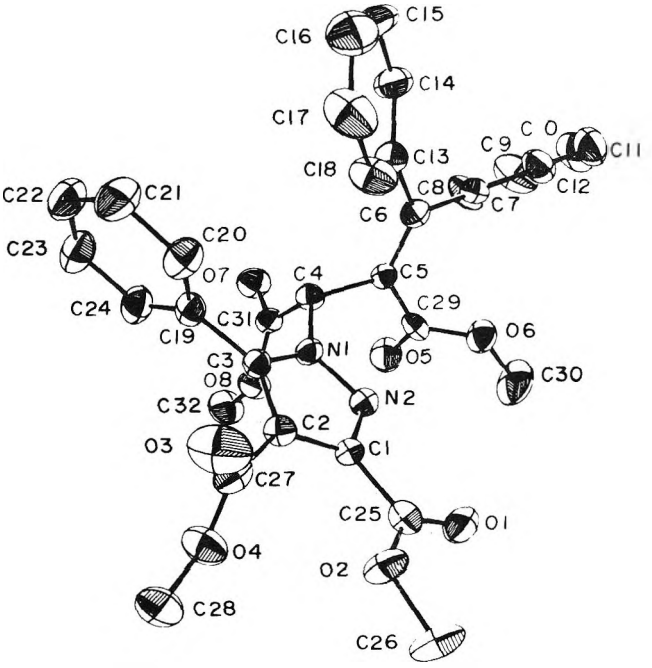
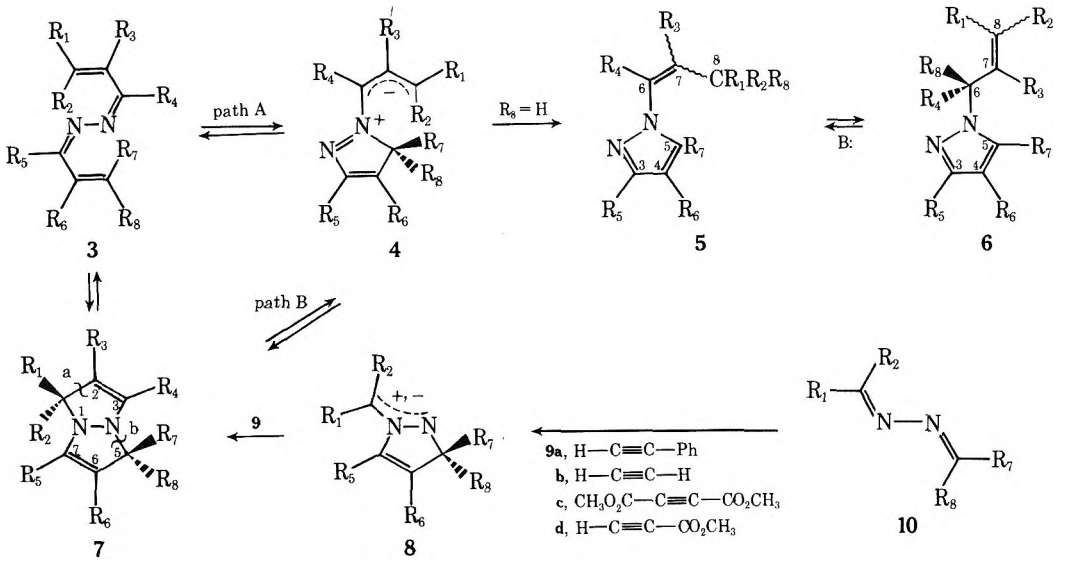


Figure 1. ORTEP perspective drawing of **6f** with thermal ellipsoids scaled to 50% probability (hydrogens not shown).

Scheme I



Compd	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
10a	CF_3	CF_3					CF_3	CF_3
b	Ph	Ph					Ph	Ph
c	Ph	H					Ph	H
d	Ph	Ph					Ph	H
e	3,4-dimethoxyphenyl	H					3,4-dimethoxyphenyl	H
3–8a	Ph	H	H	H	H	H	Ph	H
b	CF_3	CF_3	H	Ph	Ph	H	CF_3	CF_3
c	CF_3	CF_3	H	H	H	H	CF_3	CF_3
d	Ph	Ph	CO_2CH_3	CO_2CH_3	CO_2CH_3	CO_2CH_3	Ph	Ph
e	Ph	H	CO_2CH_3	CO_2CH_3	CO_2CH_3	CO_2CH_3	Ph	H
f	Ph	Ph	CO_2CH_3	CO_2CH_3	CO_2CH_3	CO_2CH_3	Ph	H
g	3,4-dimethoxyphenyl	H	CO_2CH_3	CO_2CH_3	CO_2CH_3	CO_2CH_3	3,4-dimethoxyphenyl	H
h	CF_3	CF_3	H	CO_2CH_3	H	CO_2CH_3	CF_3	CF_3
i	Ph	H	H	CO_2CH_3	H	CO_2CH_3	Ph	H
j	Ph	H	CO_2CH_3	H	H	CO_2CH_3	Ph	H
k	Ph	Ph	H	CO_2CH_3	H	CO_2CH_3	Ph	H
l	Ph	Ph	CO_2CH_3	H	H	CO_2CH_3	Ph	H

heterocyclic ring. Acoplanarity of the 5-phenyl and pyrazole rings has been cited as a reason for the different ^1H[15] and ^{13}C[16] NMR spectra of 3- and 5-phenylpyrazoles. All bond lengths and angles in **6f** are within expected ranges.[17] Owing to the obvious spectral similarities of **6f** and **6e**, it is assumed that the structural assignment of the latter is also correct.

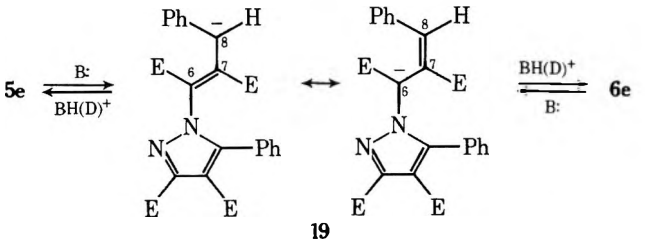
The structures of the products isolated thus far (**3d, 6e,** and **6f**) imply the intermediacy of dihydropyrazolopyrazoles **7d–f**, but we cannot detect them. Presumably they rearrange to the observed products as fast as or faster than they are formed. Criss-cross cycloaddition has been shown[18] to be a two-step reaction involving initial formation of azomethine imines 8 (Scheme I). We reasoned that introducing electron-donating groups into the aromatic rings of **10c** would facilitate the formation of 8. Since the 1,3-dipolar cycloaddition of 8 with a second mole of acetylene should be relatively fast, we hoped to be able to detect or isolate **7** using a more electron-rich azine.

In fact, 3,4-dimethoxybenzaldehyde azine **10e** reacts slowly at room temperature with **9c** to form the expected *N*-allylpyrazole **6g** and a second 2:1 adduct in approximately a 1:2 ratio. ^{13}C NMR spectroscopy of the second product shows the presence of only two nonequivalent carbomethoxy groups and a single saturated carbon (other than ester methyl and ring methoxy carbons) resonating at 67.5 ppm. A two-proton singlet at δ 5.64 ppm characterizes the proton spectrum. Based on this spectral data and the facile thermal (1 h, 100 °C) and photochemical transformation into **6g**, we assign the structure of this second product as the dihydropyrazolopyrazole **7g**.

Azomethine imine **4** is presumably an intermediate in the transformation of **7** (or **3**) to **5** and/or **6**. However, when **7g** is thermolyzed in CH_3OD, essentially no deuterium is found at C-8 in **6g** formed. The same lack of deuterium incorporation is observed in the rearrangement of **3a** to **5a** in benzyl alcohol-*O*-*d*. In addition, **6g** is formed exclusively when **7g** is heated in the presence of excess maleic anhydride or phenyl isocyanate. These results imply that if **4g** is being generated, intramolecular hydrogen transfer is occurring much faster than either external protonation (deuteration) or reaction with dipolarophiles. Further work on the nature of the **7** to **5/6** transformation is warranted and currently underway in these laboratories.

None of the *N*-propenyl isomers **5e–g** could be detected even though they are presumably precursors for the observed products since hydrogen transfer in the **3a** → **4a** → **5a** conversion is proposed[4] to be intramolecular and to C-8 exclusively. Assuming this is true, the conversion of **5** to **6** most likely involves an allyl carbanion such as **19** (Scheme II). Any of a number of nitrogen bases present in the reaction mixture could act as the requisite base catalyst. The relative rates of

Scheme II

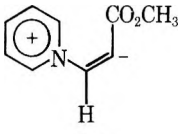


19

E = CO_2CH_3

H/D exchange at carbons 6 and 8 in **6e** support this view as well as the preference for the *N*-allyl isomer in this system. Hydrogen is completely exchanged for deuterium at C-6 within 15 min when a $CDCl_3$ solution of **6e** is exposed to D_2O/triethylamine. It takes 8 days to effect 80% deuterium incorporation at C-8. Thus, **19** is readily formed but greatly prefers deuteration (protonation) at C-6. If **5e** is formed deprotonation/reprotonation will lead rapidly to **6e.** Allyl–propenylpyrazole interconversion has been directly observed in a related system (see below).

The use of symmetrical alkyne **9c** clouds the stereochemistry of these reactions. Examination of the literature reveals that symmetrically substituted tetra- or dihydropyrazolopyrazoles result from the reaction of azines with unsymmetrical olefins[6] and alkynes,[9] respectively. The rationale for this stereochemistry is that the initial reaction between the azine and dienophile to form an azomethine imine (e.g., 8) should proceed to bond the relatively electron-rich azine nitrogen to the more electrophilic dienophile carbon. Analogous behavior is observed with imines (e.g., pyridine) which react with electron-deficient alkynes via 1,4 dipoles such as **20.**[19] Sym-



20

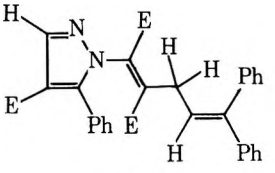
metrical pyrazolopyrazoles will result if the 1,3-dipolar cycloaddition of the azomethine imine thus formed with a second mole of dienophile proceeds as if nitrogen is the electron-rich end of the dipole. This is the normal mode of azomethine imine cycloaddition but steric and electronic factors may alter the direction of addition.[20]

The recent report[21] that the unsymmetrical dihydropyrazolopyrazole **7h** is the major product of the reaction between hexafluoroacetone azine (**10a**) and methyl propiolate (**9d**) indicated that the stereochemical course of these reactions described above is not inviolate and prompted us to investigate the reactions of azines **10c** and **10d** with unsymmetrical alkyne **9d.** Four major products result from the reaction of **10c** with **9d** in refluxing toluene. In addition to unreacted **10c** (10%), we have identified *N*-allylpyrazoles **6i** (32%) and **6j** (10%) along with their *N*-propenyl isomers **5i** (37%) and **5j** (8%) as the products of this reaction based on analyses of their NMR spectra. We expected, based on our earlier results, that the products would be substituted pyrazoles, and this is confirmed in all cases by the presence in the ^{13}C NMR of a peak at about 114 ppm assignable to C-4 of the pyrazole ring (Table II). In a series of 4-unsubstituted pyrazoles, C-4 is found[16] to resonate at 105–107 ppm. Replacement of the proton by a carbomethoxy group should result in a 5–10-ppm deshielding.[22] In addition, a peak at δ 7.9–8.1 ppm in the ^1H NMR indicates that the pyrazole ring is unsubstituted in the 3 position (R_5, Table I).

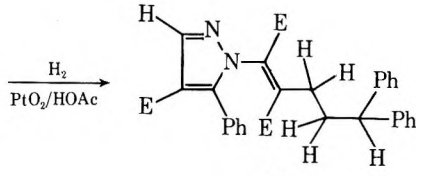
The remaining peaks in the ^1H NMR define the structure of the three carbon pyrazole side chains. For **6i** the expected AXY pattern is readily discernible and the magnitude of the coupling between the olefinic protons (16 Hz) indicates a trans double bond. The C-8 methylene in **5i** is a doublet and the carbon chemical shift of C-8 agrees quite well with the value of 33.3 ppm which we observe for the analogous carbon in **5a.** As a final proof, **5i** and **6i** are interconverted simply by heating. Similarly the ^1H and ^{13}C NMR data (Tables I and II) for **5j**[23] and **6j** are consistent with the proposed structures. The difference in chemical shift for the C-8 methylene protons in **5i** and **5j** may reflect a difference in conformation about the double bond (see discussion below).

The substituent patterns in these products bespeak their origin. Thus, the major route apparently involves unsymmetrical intermediate **7i,** which yields **5i** and **6i** by ring opening at a (Scheme I) followed by proton transfer and equilibration. Minor products **5j** and **6j** arise by similar processes from symmetrical dihydropyrazolopyrazole **7j.** Assuming that azomethine imine **8i/j** is a common intermediate, the product ratio (**5i** + **6i**)/(**5j** + **6j**) of 3.8 reflects an apparent kinetic preference for **8i/j** to react with methyl propiolate as if the carbon is the negative end of the dipole. Interestingly, no products resulting from ring cleavage of **7i** at b can be detected. This may reflect the dual resonance stabilization afforded the carbanionic portion of **4i** by the carbomethoxy and phenyl substituents which is lacking in the analogous dipole resulting from ring opening of **7i** at b.

Finally, we have investigated the reaction of azine **10d** with **9d.** Reaction in refluxing toluene for an extended period of time (22 days) yields a mixture containing unreacted **10d** (7%) and *N*-allylpyrazoles **6k** (26%) and **6l** (18%) as determined by quantitative NMR analysis. In addition, column chromatography allows the isolation of *N*-propenylpyrazole **5l** (26%) and a small amount (~5%) of a 3:1 adduct, identified as the *N*-pentadienylpyrazole **21.**



21

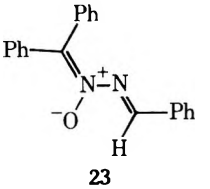


22

E = CO_2CH_3

Once again, peaks at 112–113 ppm in the ^{13}C and 7.95–8.05 ppm in the ^1H NMR for all products, including **21,** indicate a 3-unsubstituted pyrazole nucleus. The remaining NMR parameters collected in Tables I and II support the structural assignments.

Since azine **10d** is unsymmetrical, discrimination between N-1 and N-2 in the formation of **8** is possible. In reactions with peracids **10d** has been shown[24] to form azine oxide **23** exclu-



23

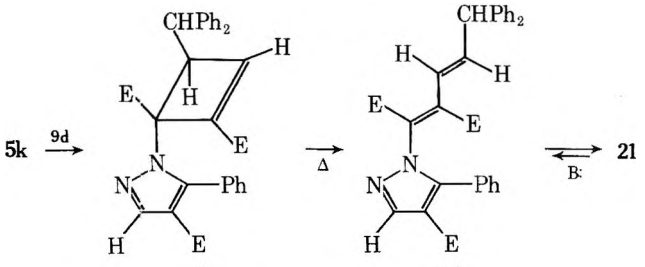
sively. This reflects the greater ability of the benzhydrilidene carbon to stabilize charge buildup. The products of the **10d**–**9d** reaction (**5l, 6k, 6l,** and **21**) can all be derived from common

intermediate **8k/l** in which the exocyclic benzhydrilidene carbon shares the charge. Reaction of **8k/l** with a second mole of **9d** as if the nitrogen bears the excess electron density yields symmetrical intermediate **7l,** the precursor for **5l** and **6l.** Reaction of **8k/l** in the opposite manner yields **6k** via unsymmetrical dihydropyrazolopyrazole **7k.** The (**5l** + **6l**)/(**6k**) ratio of 1.7 reflects the apparent kinetic preference for **8k/l** to react with **9d** as if the nitrogen is the more electron-rich center in the 1,3 dipole.

Our assignment of structure **21** to the 3:1 adduct is based in part on analysis of the spectral data. Three distinct carbomethoxy groups are readily apparent in both the ^{13}C and ^{1}H NMR spectra, and elemental analysis confirms that the product is a 3:1 adduct. In addition, the ^{13}C spectrum shows a single saturated carbon at 33.9 ppm while a one-proton triplet (δ 5.69 ppm) and a two-proton doublet (δ 2.76 ppm) characterize the ^{1}H spectrum. The best fit for this data is pentadienyl pyrazole **21.** Hydrogenation affords a dihydro derivative whose NMR and mass spectra are consistent with **22.**

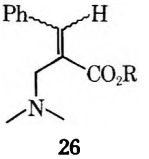
A mechanistic scheme which accounts for the formation of **21** requires that **5k** react as an enamine[25] with a third mole of **9d** to form cyclobutenyl pyrazole **24** (Scheme III), although

Scheme III



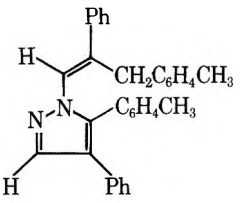
it has been stated,[26] without explanation, that vinyl pyrazoles do not behave as enamines. Thermal ring opening of the cyclobutene ring to **24** followed by double bond migration would yield **21.** However neither **6k** (which would yield **5k** by double bond migration), **5a,** nor a **5i/6i** mixture reacted with excess **9d** to yield products analogous to **21.** This mechanism must therefore remain a tentative proposal at this time.

We have delayed our discussion on the configuration of the double bonds in the various products since, with the exception of **6i,** we are unable to unambiguously define the stereochemistry. However, reasonable assignments may be made utilizing model compounds and empirical additivity relationships which have been developed[27] for predicting olefinic chemical shifts in a wide variety of alkenes. In addition, Trofimenko[26] has extended this concept to vinyl pyrazoles. Using the relationship $\delta = 5.25 + Z_{gem} + Z_{trans} + Z_{cis}$ and literature[27] Z values, chemical shifts of 7.7 and 7.0 ppm are predicted for the E and Z isomers of the α-(dialkylaminomethyl)cinnamate **26** as a model for **6e, 6g,** and **6j.** The observed (Table I) values of 7.9–8.0 are much closer to the calculated shift for **26-***E* and we assign this stereochemistry to these products.



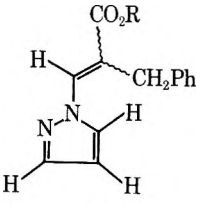
26

In attempting to assign the stereochemistry of the double bond in the *N*-propenylpyrazoles **5i, 5j,** and **5l,** several model compounds are available for comparison. The benzyl methylene protons in **5a** and **27**[4] resonate at δ 3.91 and 4.33 ppm, respectively, which is very close to the value observed for the analogous protons in **5j** (4.34 ppm). Since **5a** and **27** are known[3,4] to have the pyrazole and benzyl groups cis, we assign



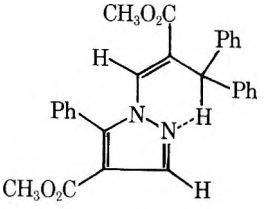
27

E stereochemistry to **5j.** In addition, the observed chemical shift for the C-6 proton of 7.61 in **5j** is closer to the value calculated for **28-***E* (7.8) than for **28-***Z* (7.2). The benzyl methylene protons in **5i** resonate at considerably higher field (more shielded) than those in either **27** or **5a.** Methyl groups trans to the pyrazole ring in *N*-propenylpyrazoles are known[26] to appear at higher field than when cis. Such a "trans" configuration in **5i** might also be favored on steric grounds. Thus we feel fairly confident in assigning *E* stereochemistry to the double bond in **5i.**



28

The remaining product of unknown stereochemistry is *N*-propenylpyrazole **5l.** The chemical shift of the vinyl proton in this product (7.59) is similar to that observed for **5j** and suggests similar stereochemistry. However, the C-8 proton resonates at significantly lower field than expected (chemical shifts of 6.0–6.3 ppm have been reported[28] for protons in similar environments). An intramolecular interaction between the C-8 proton and the pyrazole nitrogen as shown below may



5l

be involved. Such an interaction resembles the "carbinyl hydrogen bonding" invoked[29] to explain larger than expected acylation chemical shifts and Eu(fod)$_3$ gradients in certain acylated alcohols.

Conclusion

We have demonstrated that the reaction of azines with electron-deficient alkynes is a general route to 1,5-dihydropyrazolo[1,2-*a*]pyrazoles (**7**) and their rearrangement products, either acyclic azines (**3**) or N-substituted pyrazoles (**5** and/or **6**) depending on the availability of a proton at C-1 or 5 of **7.** In addition, we have probed the stereochemistry of this reaction in some detail. The nature of the products formed in these reactions and preliminary experiments on the nature of the **7** → **5/6** transformation are consistent with the proposal that **7a** is involved in the rearrangement of **3a** to **5a** but do not constitute proof of this hypothesis. Nonetheless, the reactions of aldazines and alkynes provide a simple and efficient route

to pyrazoles which would be difficult to prepare by standard routes.

Experimental Section

General. Azines used in this investigation were prepared by standard procedures. Dimethyl acetylenedicarboxylate (**9c**, Aldrich) and methyl propiolate[30] (**9d**) were distilled and stored in a desiccator prior to use. Reaction solvents were dried by standard methods and glassware was baked for a minimum of 4 h at 110–120 °C. A dry nitrogen atmosphere was maintained in all reactions. ^{1}H NMR spectra were obtained on either a Varian A-60A or Perkin-Elmer R-12b while a Bruker HFX-90 spectrometer equipped for Fourier transform pulsed NMR with a Nicolet 1085 data system operating at 22.63 MHz was used to collect the ^{13}C data. Mass spectra were recorded using a Du Pont CEC21-110D instrument. Chemical shifts are reported as parts per million (δ) vs. Me_4Si as an internal standard in $CDCl_3$ as solvent. Melting points obtained with a Hoover-Thomas apparatus are uncorrected. Elemental analyses were performed by Micro-Analysis Inc., Wilmington, Del.

X-Ray Crystallography for $C_{32}H_{28}N_2O_8$ (6f). Crystals were received as colorless, prismatic crystals showing clear triclinic morphology. The crystal chosen for study was approximately 0.40 × 0.16 × 0.13 mm in dimension and was mounted with the longest direction corresponding to the ϕ axis. This direction coincides with the crystal c^* axis.

The data were collected using Zr-filtered Mo Kα radiation (λ = 0.7107 Å) out to a maximum of 40° in 2θ. Each peak was scanned at a rate of 2.5°/min over a range of 2° plus the K_{α_1}–K_{α_2} dispersion. Backgrounds of 10-s duration were taken at each limit of the scan. A total of 2702 reflections were measured of which 160 were classified as unobserved. Reflection standard deviations were calculated based upon counting statistics. Structure factors with $F_o < 1.5\sigma(F_o)$ were given zero weight in the refinement. No crystal decomposition was detected and no correction for absorption was deemed necessary.

Precision lattice constants were obtained by least-squares refinement of eight carefully centered reflections. The pertinent cell parameters are as follows: space group $P\bar{1}$, a = 11.587 (21), b = 11.626 (6), c = 11.420 (8) Å, $\cos\alpha = -0.1485$ (4), $\cos\beta = -0.2975$ (14), $\cos\gamma = 0.0550$ (14), $Z = 2$, $\rho_{calcd} = 1.31$ g/cm^3, $\mu = 1.023$ cm^{-1}. Numbers in parentheses refer to standard deviations.

The structure was resolved by direct method tangent refinement techniques using the ORTEP program to search for a possible molecule from peaks observed in several trial e maps. One trial model incorporated all but one peak as possible atoms.

Subsequent cycles of difference Fourier maps and least-squares refinement[31] proved the model correct, located the additional nonhydrogen atom, and showed $P\bar{1}$ rather than $P1$ to be the correct space group. Anisotropic temperature factors were then introduced and hydrogen positions calculated by placing them at expected bond distances from the nonhydrogen atoms.

Cycles of refinement were continued, resulting in a final $R = 0.054$ and $R_w = 0.065$ where $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ and $R_w = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{1/2}$.

Seven strong reflections with low 2θ values and $F_\epsilon < F_c$ were given negligible weight in the refinement owing to likely extinction problems.

The scattering factors used were for the neutral atoms and the function $\Sigma w(|F_o| - |F_c|)^2$ was minimized in the refinement. A final difference Fourier map showed no electron density greater than 0.5 e/Å^3.

Preparation of Methyl 2-Oxo-3-carbomethoxy-4,4-diphenylbut-3-enoate Azine (3d). A solution of 2.12 g (15 mmol) of alkyne **9c** and 1.81 g (5 mmol) of azine **10b** was heated at reflux in dry acetonitrile for 40 days. TLC (silica gel, CH_2Cl_2) showed incomplete reaction. On cooling, the product (**3d**) and unreacted **10b** cocrystallized from the reaction mixture. After chilling at 0–5 °C for 2 h the solid was filtered, yielding 2.31 g of a yellow powder. Fractional crystallization from ethanol yielded 1.60 g (82% based on recovered azine) of **3d** as a yellow solid, mp 194–196 °C. Recrystallization from ethanol yielded an analytical sample: mp 195–197 °C; ^{1}H NMR δ 3.26, 3.54 (s, 6 H each, $-CO_2CH_3$), 7.00–7.40 (m, 20 H, aromatic); ^{13}C NMR 52.1, 52.4 ($-CO_2CH_3$), 156.9 (C=N), 162.4, 166.2 ppm ($-CO_2CH_3$). Anal. Calcd. for $C_{38}H_{32}N_2O_8$: C, 70.80; H, 5.00. Found: C, 70.55; H, 5.05.

Preparation of Methyl 2-(3,4-Dicarbomethoxy-5-phenylpyrazolyl)-3-carbomethoxy-4-phenylbut-3-enoate (6e). A solution of 5.2 g (0.025 mol) of azine **10c** and 10.5 g (0.074 mol) of **9c** in 40 ml of dry acetonitrile was heated at reflux for 60 h. The solvent was removed in vacuo and the residual amber oil dissolved in 40 ml of methanol. Crystallization was initiated by cooling in an ice–salt bath while scratching the vessel walls with a glass rod. Chilling at 0 °C for several hours, filtration, and vacuum drying yielded 9.7 g (79%) of **6e** as a white solid, mp 71–74 °C. Crystallization from methanol afforded an analytical sample: mp 80–81 °C; ^{1}H NMR δ 3.45, 3.56, 3.77, 3.81 (s, 3 H each, $-CO_2CH_3$), 5.88 (s, 1 H, C-6 H), 7.14 (br s, 10 H, aromatic), 7.93 (s, 1 H, C-8 H). Anal. Calcd for $C_{26}H_{24}N_2O_8$: C, 63.42; H, 4.90. Found: C, 63.57; H, 4.84.

Preparation of Methyl 2-(3,4-Dicarbomethoxy-5-phenylpyrazolyl)-3-carbomethoxy-4,4-diphenylbut-3-enoate (6f). A solution of 1.42 g (0.005 mol) of azine **10d** and 2.12 g (0.015 mol) of **9c** in 20 ml of dry acetonitrile was heated at reflux for 146 h. Workup as above afforded 2.38 g (84%) of **6f** as a white solid, mp 145–148 °C. Recrystallization from ethanol afforded an analytical sample: mp 149–151 °C; ^{1}H NMR δ 3.48, 3.56, 3.65, 3.76 (s, 3 H each, $-CO_2CH_3$), 5.49 (s, 1 H, C-6 H), 7.10 (br s, 15 H, aromatic). Anal. Calcd for $C_{32}H_{28}N_2O_8$: C, 67.60; H, 4.96. Found: C, 67.70; H, 4.95.

Preparation of Methyl 2-[3,4-Dicarbomethoxy-5-(3,4-dimethoxyphenyl)pyrazolyl]-3-carbomethoxy-4-(3,4-dimethoxyphenyl)but-3-enoate (6g). A solution of 1.84 g (0.005 mol) of azine **10e** and 1.5 g (0.0106 mol) of **9c** in 20 ml of dry acetonitrile was heated at reflux for 20 h. Workup as above yielded 2.11 g (69%) of **6g** as a pale yellow solid, mp 87–93 °C, essentially pure by NMR. Repeated crystallization from methanol afforded a colorless analytical sample: mp 131–132 °C; ^{1}H NMR δ [3.30 (s, 6 H), 3.63 (s, 3 H), 3.76 (br s, 6 H), 3.85 (br s, 12 H), all $C_6H_3(OCH_3)_2$ or $-CO_2CH_3$], 6.08 (s, 1 H, C-6 H), 6.59–7.58 (m, 6 H, aromatic), 7.99 (s, 1 H, C-8 H). Calcd for $C_{30}H_{32}N_2O_{12}$: C, 58.82; H, 5.26. Found: C, 58.50; H, 5.27.

Preparation of 1,5-Bis(3,4-dimethoxyphenyl)-2,3,6,7-tetrakis(carbomethoxy)-1,5-dihydropyrazolo[1,2-*a*]pyrazole (7g). A slurry of 1.00 g (3.05 mmol) of azine **10e** in 2.13 g (15.0 mmol) of **9c** and 2 ml of dry $CHCl_3$ was stirred in the dark at ambient temperatures for 10 days. The chloroform was removed in vacuo at less than 35 °C. Methanol was added and the resulting slurry was chilled and filtered, yielding 0.17 g (17%) of unreacted **10e**. Removal of methanol in vacuo (<35°) followed by column chromatography (silica gel, 0.5% MeOH in CH_2Cl_2) afforded in order of elution (a) unreacted **9c**; (b) 0.90 g (48%) of **7g** as an amorphous, amber solid; (c) 0.42 g (22%) of **6g**. Attempts at further purification of **7g** failed owing to the lability of the product. ^{1}H NMR δ [3.48 (br s, 6 H), 3.75 (brs, 12 H), 3.86 (brs s, 6 H), all $C_6H_3(OCH_3)_2$ or $-CO_2CH_3$], 5.64 (s, 2 H, C-1 H, C-5 H), 6.55–7.53 (m, 6 H, aromatic).

Thermal Rearrangement of 7g. $CDCl_3$ Solvent. A solution of **7g** (200 mg) in 0.5 ml of $CDCl_3$ in a sealed 5-mm NMR tube was heated in a thermostated oil bath at 65 °C. At intervals, the sample tube was cooled in ice and its NMR spectrum recorded. From this, the half-life for the conversion of **7g** to **6g** was estimated to be 2.5 h at this temperature. Only peaks corresponding to **6g** were detected.

Methanol Solvent. A solution of 100 mg of **7g** in 3 ml of MeOH was heated in a capped pyrolysis tube at 100 °C for 1.5 h. A ^{1}H NMR spectrum of the crude product after removal of solvent showed only **6g**.

Methanol-*O-d* Solvent. A solution of 100 mg of **7g** in 3 ml of MeOD (99.5% D) was heated at 100 °C for 1.5 h as above. The NMR spectrum of the crude product showed 0.95 H at C-8 (~5% D incorporation).

In the Presence of Maleic Anhydride. A solution of 100 mg (0.163 mmol) of **7g** and 100 mg (1.02 mmol) of maleic anhydride in 0.5 ml of dry CH_3CN was heated for 1.25 h at 100 °C as above. The NMR spectrum of the crude product showed only **6g** and maleic anhydride.

In the Presence of Phenyl Isocyanate. A mixture of 80 mg (0.13 mmol) of **7g** and 0.22 g (1.85 mmol) of PhNCO (freshly distilled) was heated for 1.5 h at ~100 °C as above. The crude product was partitioned between ether and 5% HCl. The layers were separated, and the organic phase washed with 5% HCl and H_2O, dried (Na_2SO_4), and evaporated in vacuo. The ^{1}H NMR showed the presence of **6g** only.

Photolysis of 7g. A solution of 20 mg of **7g** in 2 ml of benzene in a Pyrex test tube was irradiated with a 140-W Hanovia mercury lamp at 20 °C. The conversion of **7g** to **6g** was conveniently monitored by TLC (0.5% MeOH in CH_2Cl_2, silica gel) and was complete after 12 h.

Reaction of 10c with Methyl Propiolate (9d). A solution of 1.04 g (5 mmol) of azine **10c** and 1.05 g (12.5 mmol) of **9d** in 15 ml of dry toluene was heated at reflux for 97 h. Solvent and excess **9d** were removed in vacuo (40 °C, 0.5 mm) to yield 1.88 g (theory 1.88) of a thick, golden oil. Quantitative NMR analysis indicated the presence of 0.47 mmol (10%) of **10c**, 1.58 mmol (32%) of **6i**, 1.85 mmol (37%) of **5i**, 0.41 mmol (8%) of **5j**, and 0.52 mmol (10%) of **6j**. The crude product was

then chromatographed (silica gel, 0.5% MeOH in CH_2Cl_2 as eluent) to yield the following, in order of elution. (a) **10c,** identical by NMR with authentic **10c.** (b) **5j,** white solid, mp 108.5–110 °C (MeOH); ^1H NMR δ 3.55, 3.64 (s, 3 H each, $-CO_2CH_3$), 4.34 (s, 2 H, C-8 H_2), 6.93–7.54 (m, 10 H aromatic), 7.61 (s, 1 H, C-6 H), 8.04 (s, 1 H, C-3 H). Anal. Calcd for $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36. Found: C, 69.98, 5.45. (c) **5i + 6i,** pale yellow oil. We were unable to completely separate these isomers but fractions enriched in one or the other allowed complete assignment of spectral data. ^1H NMR δ 3.26 (d, J = 7.5 Hz, 2 H, **5i,** C-8 H_2), 3.52, 3.57, 3.64 (3 s, total 6 h, **5i + 6i,** $-CO_2CH_3$), 5.35 (d, J = 6.5 Hz, 1 H, **6i,** C-6 H), 6.24 (d, J = 16.0 Hz, 1 H, **6i,** C-8 H), 6.65 (dd, J = 6.5, 16.0 Hz, 1 H, **6i,** C-7 H), 6.90–7.50 (m, 11 H, **5i + 6i,** aromatic and **5i,** C-7 H), 7.96 (s, 1 H, **6i,** C-3 H), 8.07 (s, 1 H, **5i,** C-3 H). A fraction containing isomers **5i, 6i,** and **6j** in approximate ratio of 2:1:0.5 was prepared for analysis by short-path, bulb-to-bulb distillation at 180 °C (0.05 mm). Anal. Calcd for $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36. Found: C, 69.92; H, 5.23. (d) **6j,** brown oil contaminated with **5i, 6i,** and some dark, tarry material. Bulb-to-bulb distillation yielded a pale yellow oil containing mostly **6j** with some **5i** and **6i.** ^1H NMR δ 3.62, 3.71 (s, 3 H each, $-CO_2CH_3$), 4.85 (s, 2 H, C-6 H_2), 6.93–7.64 (m, 10 H, aromatic), 7.92, 7.95 (s, 1 H each, C-3 H, C-8 H).

Thermal Equilibration of 5i and 6i. A mixture of **5i** and **6i** (**6i/5i** = 2.4) was heated at reflux in acetonitrile for 48 h. The solvent was removed in vacuo and an NMR analysis showed the **6i/5i** ratio to be 0.8.

Reaction of 10d with Methyl Propiolate (9d). A solution of 1.42 g (5 mmol) of azine **10d** and 1.25 g (1.5 mmol) of **9d** in 15 ml of dry toluene was heated at reflux for 22 days. The solvent and excess **9d** were removed in vacuo (40 °C, 0.5 mm) to yield 2.33 g (theory 2.26) of a yellow, amorphous solid. Quantitative NMR analysis indicated the presence of 0.34 mmol (7%) of **10d,** 1.31 mmol (26%) of **6k,** and 0.91 mmol (18%) of **61.** The crude product was then chromatographed (silica gel, 0.5% MeOH in CH_2Cl_2 as eluent) to yield the following, in order of elution.

(a) **10d,** identical by NMR with authentic **10d.**

(b) **5l.** 0.59 g (1.30 mmol, 26%); white solid, mp 122.5–123.5 °C (MeOH); ^1H NMR δ 3.38, 3.60 (s, 3 H each, CO_2CH_3), 6.93 (s, 1 H, C-8 H), 6.95–7.50 (m, 15 H, aromatic), 7.59 (s, 1 H, C-6 H), 7.96 (s, 1 H, C-3 H). Anal. Calcd for $C_{28}H_{24}N_2O_4$: C, 74.32; H, 5.34. Found: C, 74.50; H, 5.36.

(c) **6k.** White solid, mp 142–143 °C (MeOH); ^1H NMR δ 3.55, 3.59 (s, 3 H each, CO_2CH_3), 5.41 (d, J = 10.0 Hz, C-6 H), 6.60 (d, J = 10.0 Hz, C-7 H), 7.10 (br s, 10 H, aromatic), 7.97 (s, 1 H, C-3 H). Anal. Calcd for $C_{28}H_{24}N_2O_4$: C, 74.32; H, 5.34. Found: C, 74.52; H, 5.35.

(d) **6l.** White solid, mp 111.5–112.5 °C (MeOH); ^1H NMR δ 3.25, 3.54 (s, 3 H each, CO_2CH_3), 4.78 (s, 2 H, C-6 H_2), 6.78–7.56 (m, 15 H, aromatic), 7.92 (s, 1 H, C-3 H). Anal. Calcd for $C_{28}H_{24}N_2O_4$: C 74.32; H, 5.34. Found: C, 74.11; H, 5.21.

(e) **21.** 100 mg (0.19 mmol, 4%); white solid, mp 162.5–163.5 °C (MeOH); ^1H NMR δ 2.76 (d, J = 7.5 Hz, 2 H, C-8 H_2), 3.22, 3.40, 3.57 (s, 3 H each, CO_2CH_3), 5.69 (t, J = 7.5 Hz, 1 H, C-9 H), 6.53–7.23 (m, 15 H, aromatic), 7.72 (s, 1 H, C-3 H). ^{13}C NMR 33.9 (C-8), 51.0, 51.7, 51.8 (CO_2CH_3), 112.5 (C-4), 162.9, 169.0, 169.7 (CO_2CH_3). Anal. Calcd for $C_{32}H_{28}N_2O_6$: C, 71.63; H, 5.26. Found: C, 71.57; H, 5.18.

Hydrogenation of 21. A solution of 150 mg of **21** in 10 ml of glacial acetic acid and 3 ml of methylene chloride was hydrogenated at 5–10 psi H_2 for 21 h over 10 mg of PtO_2. The catalyst was removed by filtration and the solvents removed in vacuo. The residue was dissolved in 20 ml of ether, extracted with 2 × 5 ml of 5% NaOH and 1 × 5 ml of H_2O, the organic phase dried (Na_2SO_4), and the ether removed in vacuo to yield 0.14 g (93%) of **22** as an off-white solid. Crystallization from CH_2Cl_2–heptane yielded a colorless analytical sample: mp 197–198 °C; ^1H NMR δ 1.99–2.99 (br m, 4 H, C-8 H_2, C-9 H_2), 3.34, (s, 6 H, $-CO_2CH_3$), 3.58 (s, 3 H, $-CO_2CH_3$), 5.05 (m, 1 H, C-10 H), 6.33–7.73 (m, 15 H, aromatic), 7.90 (s, 1 H, C-3 H). ^{13}C NMR 29.6, 30.7 (C-8, C-9), 51.1, 51.5 (br) (CO_2CH_3), 58.8 (C-10). Mass spectum *m/e* 538 (M^+). Anal. Calcd for $C_{32}H_{30}N_2O_6$: C, 71.36; H, 5.61. Found: C, 71.22; H, 5.70.

Acknowledgments. Generous financial support for one of us (S.E.) by the National Science Foundation is gratefully acknowledged. In addition, we would like to thank Drs. D. L. Dalrymple and J. A. Moore for many helpful discussions.

Registry No.—**3d,** 60896-16-4; **5i,** 60896-17-5; **5j,** 60896-18-6; **5l,** 60896-19-7; **6e,** 60896-20-0; **6f,** 60896-21-1; **6g,** 60896-22-2; **6i,** 60896-23-3; **6j,** 60896-24-4; **6k,** 60896-25-5; **6l,** 60896-26-6; **7g,** 60896-27-7; **9c,** 762-42-5; **9d,** 922-67-8; **10b,** 983-79-9; **10c,** 588-68-1; **10d,** 13118-38-2; **10e,** 17745-86-7; **21,** 60896-28-8; **22,** 60934-68-1.

Supplementary Material Available. Tables of positional and thermal parameters for the structure of **6f** (4 pages). Ordering information is given on any current masthead page.

References and Notes

(1) (a) National Science Foundation Graduate Feliow, 1974–1976. (b) E. I. du Pont de Nemours and Co.
(2) E. E. Schweizer, C. S. Kim, C. S. Labaw, and W. P. Murray, *J. Chem. Soc., Chem. Commun.*, 7 (1973); S. Evans, A. B. Russiello, and E. E. Schweizer, manuscript in preparation.
(3) R. L. Stern and J. G. Krause, *J. Org. Chem.*, **33,** 213 (1968).
(4) R. L. Stern and J. G. Krause, *J. Heterocycl. Chem.*, **5,** 263 (1968).
(5) G. Maier and M. Wiessler, *Tetrahedron Lett.*, 4987 (1969).
(6) T. Wagner-Jauregg, L. Zirngibl, A. Demolis, H. Guenther, and S. W. Tam, *Helv. Chim. Acta*, **52,** 1672 (1969), and references cited therein; S. E. Armstrong and A. E. Tipping, *J. Chem. Soc., Perkin Trans. 1,* 1411 (1975), and references cited therein.
(7) J. R. Bailey and N. H. Moore, *J. Am. Chem. Soc.*, **39,** 279 (1917); J. R. Bailey and A. T. McPherson, *ibid.*, **39,** 1322 (1917).
(8) O. Tsuge and S. Kanemasa, *Bull. Chem. Soc. Jpn.*, **45,** 3591 (1972); R. E. Walrond and H. Suschitzky, *J. Chem. Soc., Chem. Commun.*, 570 (1973).
(9) K. Burger, H. Schickaneder, and W. Thenn, *Tetrahedron Lett.*, 1125 (1975).
(10) A. E. Tipping and T. P. Forshaw, *J. Chem. Soc. C,* 2404 (1971).
(11) S. S. Mathur and H. Suschitsky, *J. Chem. Soc., Perkin Trans. 1,* 2479, (1975).
(12) R. Huisgen and K. Herbig, *Justus Liebigs Ann. Chem.*, **688,** 98 (1975); R. M. Acheson and G. A. Taylor, *J. Chem. Soc.*, 1961 (1960); D. H. Aue and D. Thomas, *J. Org. Chem.*, **40,** 2361 (1975).
(13) U. Eisner and J. Kuthan, *Chem. Rev.*, **72,** 1 (1972).
(14) "Oak Ridge Thermal-Ellipsoid Program", Dr. Carroll K. Johnson, Oak Ridge National Laboratory, ORNL-3794, 1971.
(15) L. G. Tensmeyer and C. Ainsworth, *J. Org. Chem.*, **31,** 1878 (1966).
(16) J. Elguero, C. Marzin, and J. D. Roberts, *J. Org. Chem.*, **39,** 357 (1974).
(17) "International Tables for X-Ray Crystallography", Vol. III, Kynoch Press, Birmingham, England, 1968.
(18) K. Burger, W. Thenn, R. Rauh, H. Schickaneder, and A. Gieren, *Chem. Ber.*, **108,** 1460 (1976), and references cited therein.
(19) A. Crabtree, A. W. Johnson, and J. C. Tebby, *J. Chem. Soc.*, 3497 (1961).
(20) R. Huisgen, *Angew. Chem.*, **75,** 604 (1963).
(21) K. Burger, H. Schickaneder, and M. Pinzel, *Chem. Ztg.*, **100,** 90 (1976).
(22) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972, p 63.
(23) See H. K. Reimlinger, M. A. Priren, and R. Merenyi, *Chem. Ber.*, **103,** 3252 (1970), for a ^1H NMR of a related system.
(24) W. M. Williams and W. R. Dolbier, *J. Org. Chem.*, **34,** 155 (1969).
(25) K. C. Brannock, R. D. Burpitt, V. W. Goodlett, and J. G. Thweatt, *J. Org. Chem.*, **29,** 818 (1964).
(26) S. Trofimenko, *J. Org. Chem.*, 35, 3459 (1970).
(27) U. E. Matter, C. Pascual, E. Pretsch, A. Pross, W. Simon, and S. Sternhell, *Tetrahedron*, **25,** 691 (1969).
(28) ^1H NMR spectra 8347, 8349, 8724 and 8351, "Sadtler Standard Spectra", Sadtler Research Laboratories, Philadelphia, Pa.
(29) W. H. Pirkle and J. R. Hauske, *J. Org. Chem.*, **41,** 801 (1976).
(30) E. H. Ingold, *J. Chem. Soc.*, 127, 1203 (1925).
(31) Structural refinements were done using the "X-ray '70" package of programs of J. M. Stewart, F. A. Kundell, and J. C. Baldwin, University of Maryland.

Synthetic Scope of the Triethyloxonium Ion Catalyzed Homologation of Ketones with Diazoacetic Esters[1a]

William L. Mock*[1b] and Marvis E. Hartman

Department of Chemistry, Carnegie-Mellon University, Pittsburgh, Pennsylvania 15213

Received April 20, 1976

Numerous examples of homologation of ketones to β-keto esters with ethyl diazoacetate catalyzed by triethyloxonium fluoroborate are described. Practical considerations concerning this general technique are treated in detail. With unsymmetrical ketones (RCOR′) a preponderance of insertion into the least highly substituted C(O)–C bond is consistently observed. It is feasible to separate the isomeric products by partial, selective hydrolysis and decarboxylation. Analogous expansion reactions were observed with diazoacetonitrile, 2,2,2-trifluorodiazoethane, dimethyl diazomethylphosphonate, and *tert*-butyl diazoacetate. Intramolecular homologation was seen with a diazo ketone. Certain of the same reactions may be catalyzed by antimony pentachloride at −78 °C; the advantages which accrue with this reagent are discussed, and a summary evaluation of the homologation technique is presented.

The homologation of aliphatic and aromatic ketones by one carbon atom is a frequently encountered synthetic objective. The most direct technique is the insertion of a methylene unit from diazomethane (eq 1).[2a–c] This reaction has

$$R_2CO + CH_2N_2 \longrightarrow RCOCH_2R \left(+ R_2C\overset{O}{\underset{CH_2}{<}} + RCH_2COCH_2R \text{ etc.} \right) \quad (1)$$

severe experimental limitations, the most serious of which are oxirane formation and multiple homologation (which usually cannot be avoided). Various alternative sequences[2] have been developed to partially overcome these drawbacks; however, all leave something to be desired in terms of requiring multiple steps which impose limits upon the presence of other functionality (not to mention diminution in yield).

A reaction which overcomes many of these restrictions is the triethyloxonium ion catalyzed insertion of a carbalkoxymethylene group from an alkyl diazoacetate into a carbonyl–alkyl or –aryl bond (eq 2).[3] This transformation proceeds se-

$$R_2CO + N_2CHCO_2R' \xrightarrow[CH_2Cl_2,\ 0\ °C]{(C_2H_5)_3O^+} RCOCHR(CO_2R') + N_2 \quad (2)$$

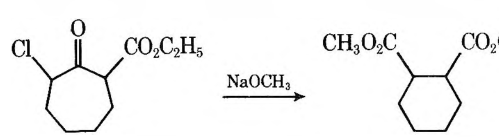
lectively in high yield under mild conditions, results in a useful β-keto ester product, and is compatible with numerous other functional groups. We here summarize the findings of an extensive investigation[1a] into the scope of this novel reaction. In an accompanying article we consider mechanistic information such as is necessary for intelligent application of this homologation technique.[4]

Results

General. Ethyl diazoacetate by itself is insufficiently nucleophilic to attack carbonyl groups. However, under the influence of base[5] or Lewis acid catalysis,[6] products arising from addition to the diazo carbon may be obtained. In the latter case the most efficacious reagents are triethyloxonium fluoroborate and antimony pentachloride (the latter in certain circumstances, as considered subsequently). A generally smooth reaction results when ethyl diazoacetate is dropped into a methylene chloride solution of triethyloxonium fluoroborate and a ketone at 0–25 °C. The progress of the reaction may usually be estimated by the rate of nitrogen evolution, by the disappearance of the color of the ethyl diazoacetate, by TLC analysis (product β-keto esters usually stain intensely blue with alcoholic ferric chloride spray), or by GLC or other conventional technique. Generally the reaction takes 2–5 h (occasionally longer). Standard workup is particularly simple; an excess of aqueous sodium bicarbonate solution is added to the reaction mixture which is then agitated until the catalyst has been consumed. Separation and evaporation of the methylene chloride phase provides a product contaminated only with minor amounts of by-products (see Experimental Section).

Typical Expansions. Table I contains a list of illustrative examples. Only a few of the entries will be commented upon. In the case of unsymmetrical ketones, two β-keto esters are possible, and in general both are produced. In order to determine the product ratio in such instances, it was necessary to hydrolyze and decarboxylate, whence the relative proportions of decarboxylated ketones could be determined by GLC analysis (last column in Table I). As a general pattern it will be noted that the least substituted residue on the carbonyl appears to migrate preferentially in the case of the aliphatic ketones, although an aryl ring does compete relatively effectively in those cases examined. A considerable effort was put into discerning the factors which control the product ratio in such diversely substituted ketones, in order to render the synthetic method more selective. These studies form the body of an accompanying article on the mechanism of this homologation,[4] and will not be further commented upon here.

Of synthetic significance is the apparent insensitivity of this reaction to steric congestion. Yields do not suffer severely with less hindrance than that provided by pinacolone (Table I, entry 5), isobutyrophenone (entry 10), or adamantanone (entry 17). In these cases unreacted ketone was also recovered; the reactions could likely have been forced to higher conversion. The method was attempted on an unsaturated ketone (entry 7) with disappointing results. Since unreacted mesityl oxide was not recovered, a better yield might require substantially modified conditions. Likewise in the case of cyclopentanone, complex by-products consumed the bulk of the reactant (aldol condensations?). No attempt to improve this homologation was made, since carbethoxycyclohexanones are generally available by other means. The method apparently works well for the expansion of cyclobutanones.[7] The case of 2-chlorocyclohexanone (entry 16) deserves comment; the apparently exclusive product was 7-chlorocarbethoxycycloheptanone. With base a clean Favorskii rearrangement of this material was induced (eq 3).[8a] The net transformation (cy-



(3)

clohexanone → dicarbalkoxycyclohexane) is unique. It is noteworthy that reaction of chlorocyclohexanone with diazomethane yielded predominantly an oxirane.[8b]

Hydrolysis and Decarboxylation. In many synthetic applications a decarbethoxylated homologated ketone will be

Table I. Homologation of Typical Ketones

Registry no.	Reactant (RCOR')[a]	Reaction time, h	Product keto ester(s), total yield, %	Decarbethoxylation, ratio (RCH_2COR':$RCOCH_2R'$)[b]
67-64-1	1. CH_3COCH_3	6[c,e]	78	
96-22-0	2. $CH_3CH_2COCH_2CH_3$	6[c,e]	86	
78-93-3	3. $CH_3COCH_2CH_3$	2[d,e]	89	50:50
565-69-5	4. $CH_3CH_2COCH(CH_3)_2$	13[d,f]	54	66:34
75-97-8	5. $CH_3COC(CH_3)_3$	17[d,f]	10[g]	95:5
103-79-7	6. $CH_3COCH_2C_6H_5$	5[d,f]	96	62:38
141-79-7	7. $CH_3COCH{=}C(CH_3)_2$	5[d,e]	10[g]	2:98[h]
98-86-2	8. $CH_3COC_6H_5$	3[d,f]	78	10:90
495-40-9	9. $CH_3CH_2CH_2COC_6H_5$	20[d,f]	89	43:57
611-70-1	10. $(CH_3)_2CHCOC_6H_5$	17[d,f]	26	69:31
120-92-3	11. $(CH_2)_4CO$ (cyclopentanone)	4[c,e]	38	
108-94-1	12. $(CH_2)_5CO$ (cyclohexanone)	3[c,e]	90	
502-42-1	13. $(CH_2)_6CO$ (cycloheptanone)	4.5[c,e]	81	
502-49-8	14. $(CH_2)_7CO$ (cyclooctanone)	6[d,f]	85	
583-60-8	15. $CH_2COCHCH_3$ $\lfloor(CH_2)_3\rfloor$	4[d,e]	96	85:15
822-87-7	16. $CH_2COCHCl$ $\lfloor(CH_2)_3\rfloor$	4[d,f]	74	98:2[i]
700-58-3	17. $C_9H_{14}CO$ (adamantanone)	4[d,f]	63[j]	

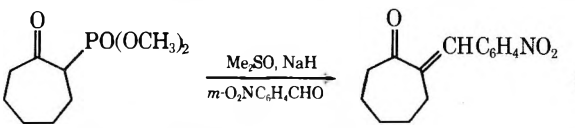
[a] Conditions: $C_2H_5O_2CCHN_2$, 1.7 equiv in each case. [b] Determined by GLC, R, R' as in first column. [c] $(C_2H_5)_3O^+BF_4^-$, 1.7 equiv. [d] $(C_2H_5)_3O^+BF_4^-$, 3.0 equiv. [e] Temperature 0 °C. [f] Temperature 24 °C. [g] Plus several unidentified components. [h] Only $RCOCH_2R'$ detected, $CH_3COCH_2CH{=}C(CH_3)_2$ and $CH_3COCH{=}CHCH(CH_3)_2$, 4:1. [i] Only RCH_2COR' detected by base treatment; see text. [j] Incomplete conversion, product (oil) separated by column chromatography.

desired. This may generally be achieved by hot aqueous acid treatment of the keto esters. However, in our work we have adopted an alternative procedure. The keto ester is simply heated in (neutral) distilled water for several hours in a sealed tube at 230 °C.[9] Our finding is that this technique gives consistently higher yields of cleaner product, apparently since acid-catalyzed side reactions (e.g., aldol) are thereby suppressed. A practical qualification on the latter statement is that the homologated material must be totally free of acid-forming impurities (i.e., methylene chloride); however, simple distillation suffices for this purpose.

We have made further observations which suggest a technique for overcoming the major practical limitation of this homologation technique, namely, its nonexclusive regioselectivity. As may be seen from Table I, unsymmetrical ketones characteristically yield both conceivable products of expansion. Considerable experimental work has failed to yield a reaction modification which will completely avoid this problem[4] (which is common to all homologations). Furthermore, conventional simple purification techniques (distillation, chromatography) are usually inadequate for separation of the isomeric keto ester products, and such statement also applies to the mixture of ketones produced by decarbethoxylation. However, it was discovered in several instances that if the hydrolysis–decarboxylation were carried out at ca. 185 °C instead of 230 °C, selective reaction of one of the keto ester isomers may ensue. For example, the product mixture obtained from *p-tert*-butylacetophenone yielded at 230 °C an 89:11 mixture of arylacetone and butylpropiophenone.[4] However, at 185 °C pure 1-(*p-tert*-butylphenyl)acetone was isolated by distillation of the hydrolysate. An extensive examination of this phenomenon was not undertaken, since it might be expected that the optimum temperature and duration of hydrolysis would have to be determined on an individual basis for each substance. In summary, while neither the keto esters nor the homologated ketones may be readily separated into pure isomers, the difference in physical properties between the keto esters and *one* of the product homologated ketones (produced by an intrinsic rate differential in hydrolysis) renders separation easy. In this regard our two-step methylene insertion method is superior to a single-step diazomethane expansion.

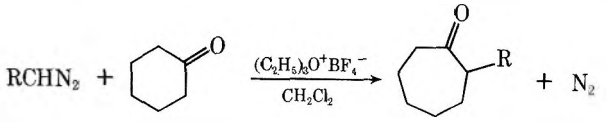
Diazo Variations. In exploring the scope of this new homologation technique, we attempted the expansion of cyclohexanone with several analogues of ethyl diazoacetate. The experiments are summarized in Table II, and discussed individually below. In general, yields have not been optimized.

Diazoacetonitrile[10] substitutes satisfactorily for ethyl diazoacetate, providing 2-cyanocycloheptanone. With trifluorodiazoethane[11] an expanded product was obtained in good yield, which is noteworthy for the ease with which the trifluoromethyl group may be removed. Mild basic hydrolysis (85 °C, 48 h) afforded cycloheptanone directly. A sequence of HF eliminations followed by hydrations is most plausible; however, no deliberate decarboxylation step was experimentally necessary (possibly, cleavage of an intermediate fluoroformyl derivative occurs). The third entry in Table II, dimethyl diazomethylphosphonate,[12] provides a valuable type of homologated intermediate for subsequent synthetic transformations. Treatment of the product keto phosphonate with base (sodium methylsulfinylmethide in dimethyl sulfoxide) followed by *m*-nitrobenzaldehyde yielded the Wadsworth–Emmons product (eq 4). Of utmost significance for the synthesis of complex substances is the successful result with *tert*-butyl diazoacetate[13] (fourth entry in Table II). The keto ester product, which is especially susceptible to mild decarbalkoxylation, may be obtained without appreciable ester interchange involving the triethyloxonium salt. The final entry



(4)

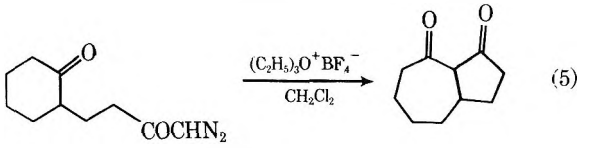
Table II. Homologations with Diverse Diazomethane Derivatives Catalyzed by Triethyloxonium Fluoroborate



Registry no.	Substituent (R)[a]	Catalyst [equiv $(C_2H_5)_3O^+BF_4^-$]	Reaction time, h	Yield, %
13138-21-1	CN	1.7	3[b]	58
371-67-5	CF_3	3.0	2[b]	~85
28447-24-7	$PO(OCH_3)_2$	4.0[c]	5[d]	65
35059-50-8	$CO_2C(CH_3)_3$	3.0	2.5[b]	46[e]
2684-62-0	$COCH_3$	1.7	3[b]	0

[a] With 1.7–2.5 equiv of substituted diazomethane (quantity not optimized). [b] Temperature 0 °C. [c] Trimethyloxonium fluoroborate (triethyloxonium salt gives phosphate ester exchange). [d] Temperature 24 °C. [e] After decarbalkoxylation ($CH_3C_6H_4SO_3H$, C_6H_6, 80 °C).

in Table II indicates failure in an attempted homologation with a diazo ketone. However, such a successful reaction conducted *intramolecularly* uniquely combines ring expansion with annelation to provide another potentially useful type of synthetic intermediate (eq 5).[3] Characterization of this

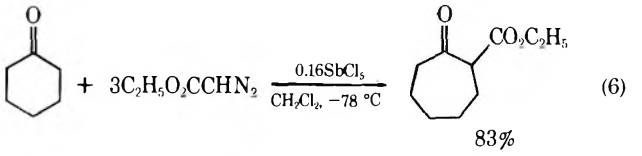


(5)

reaction has been reported;[3] details are in the Experimental Section.

Catalyst Variations. While triethyloxonium fluoroborate is a particularly convenient and efficacious catalyst for the ketone–diazo ester reaction, it is by no means the only Lewis acid which will induce homologation. In conjunction with mechanistic studies we have used trimethyl- and tripropyloxonium fluoroborates.[4] Yields were essentially identical; the trimethyloxonium salt is inferior for solubility reasons and the tripropyloxonium ion is less easily prepared. Boron trifluoride etherate had been shown to catalyze homologation prior to our investigation;[6c] in our experience it gives inferior results.

We have discovered one new catalyst which usefully complements the oxonium salt. Antimony pentachloride induces reaction between ketones and ethyl diazoacetate at −78 °C, a temperature at which the other catalysts are ineffective (eq 6). A coordination complex ($R_2CO{\cdot}SbCl_5$) may actually be



(6)

isolated.[14] As in the other cases, reaction workup is especially easy. Aqueous sodium bicarbonate treatment precipitates the catalyst as a fine, white solid which is removed by filtration. Yields are typically 70–80%. Regioselectivity appears to be slightly greater than in the case of the oxonium ion induced reactions. For example, 2-methylcyclohexanone with $SbCl_5$ yields ultimately a 94:6 mixture of cycloheptanones (2-CH_3:3-CH_3) whereas with $(C_2H_5)_3O^+$ the ratio was 85:15 (Table I). In several other cases examined (see Experimental Section) there was a 7–35% improvement in selectivity with $SbCl_5$. This may be a consequence merely of the lower temperature of reaction, although alternative explanations cannot be excluded.[4]

The antimony catalyst also succeeded in homologation with *tert*-butyl diazoacetate, with a similar improvement in regioselectivity in the case of acetophenone. Furthermore, $SbCl_5$ gave a clean insertion product with acetone and 2,2,2-trichloroethyl diazoacetate (eq 7). In this reaction triethyloxonium fluoroborate was ineffective, yielding a considerably contaminated product. Deesterification of the trichloroethyl carboxylate may be achieved reductively (Zn, HOAc), allowing conversion to an expanded ketone under mild, minimally acidic conditions.[15a] These keto esters have a direct use in regiospecific aldol synthesis.[15b] One further generalization may be made; in the case of hindered ketones somewhat better overall yields were obtained with $(C_2H_5)_3O^+$ BF_4^- than with $SbCl_5$.[1a]

$$CH_3COCH_3 + N_2CHCO_2CH_2CCl_3 \xrightarrow[-N_2]{SbCl_5} CH_3COCH(CH_3)CO_2CH_2CCl_3 \quad (7)$$

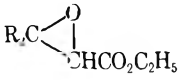
Discussion

The purpose of this article has been to survey the scope of this new homologation technique. Several unique advantages of this reaction may be listed. (1) Foremost is the uniformly high yields (Table I) under simple, standard conditions. An accompanying article provides numerous other examples with arylalkyl and cyclic ketones.[4] (2) Compared to diazomethane expansions and related techniques,[2] our method is far superior with regard to product purity as well as yield. The latter reactions frequently result in complex mixtures containing epoxides and products of multiple expansions. In the diazoacetate homologation these by-products are negligible or totally absent. (3) The keto ester product represents a highly useful type of synthetic intermediate. It may be readily alkylated, etc., prior to hydrolysis and decarboxylation. Although discrimination between possible expansion products in the case of unsymmetrically substituted ketones is less than complete, selective hydrolysis and decarboxylation of the keto esters offers a way to secure homogeneous products. (4) The rate of reaction depends upon the environment of the target carbonyl group in a way which suggests that selectivity would be expected for diketones. (5) The reaction may usefully be run from −14 to 40 °C in methylene chloride. With $SbCl_5$ as catalyst, expansion rapidly goes to completion at −78 °C. Velocity of reaction is directly dependent upon the concentration of triethyloxonium fluoroborate;[4] a 1.5–3 molar excess is recommended routinely. However, a catalytic amount of $SbCl_5$ suffices. (6) Finally, a variety of substituted diazomethanes enter into this reaction (Table II). The diversely functionalized ketones so produced suggest numerous subsequent synthetic uses (see also eq 5). In all cases homologation does not proceed beyond the introduction of one residue. The assortment of substituents which can be accommodated on the diazo species suggests that polyfunctionalized ketones would be acceptable substrates. In unpublished studies we have found this to be so; various esters, lactones, ketals, cyclopropanes, etc., survive homologation unscathed.

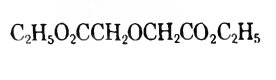
Experimental Section

Only a few illustrative examples of homologations will be recorded.[1a] Reagent grade methylene chloride was used without purification. Ethyl diazoacetate[16] was redistilled at reduced pressure (*caution*: explosion hazard). It may be stored under refrigeration. Triethyloxonium fluoroborate[17] may be prepared and stored under dry ether at room temperature; it is quite stable under these conditions. Just prior to use, ether was removed from the salt on a glass filter, and it was evacuated (20 mm) for 15 min at 25 °C. Triethyloxonium fluoroborate was routinely weighed and transferred in the ambient laboratory; however, the hygroscopic nature of the salt requires prompt manipulations and the avoidance of extreme humidity. Glassware was routinely dried at 150 °C, then assembled and allowed to cool in a stream of dry nitrogen. An inert atmosphere was maintained throughout our reactions. This was for the purpose of exclusion of moisture; there is no evidence that oxygen is deleterious. Quantitative analyses of product ratios were determined (in duplicate or triplicate) by cutting and weighing of Xerographic copies of GLC traces; we estimate the error limit as ±2%. Spectroscopic analyses were made on common commercial instrumentation; elemental analyses were by Galbraith Laboratories, Inc. Melting points (capillary) and boiling points are uncorrected.

Reaction Technique. Most of our reaction optimization work was done with cyclohexanone. An experimental procedure has been given[3] (see following typical procedure). Two types of by-products may occur in this homologation, which the experimenter should be prepared to recognize. Although usually undetected in most diazo ester expan-



I



2

sions, the glycidic ester from the reactant ketone (e.g., 1) may be found (<5% from cyclohexanone).[18] Such a structure may usually be recognized by an NMR singlet at δ 3.2, corresponding to the newly introduced oxirane proton. The other common contaminant of the product is diethyl diglycolate (2), which is thought to arise from diazoacetic ester, possibly during workup. These easily removable substances ought not to interfere with many subsequent applications of keto ester products, which should be usable with minimal purification.

Additional practical observations, which may prove critical with unreactive ketones, are as follows. It was found that slightly better yields were obtained if the diazoacetate were added gradually to the reaction mixture of ketone plus catalyst, rather than all at once. On the other hand, inordinate delay between exposure of ketone to triethyloxonium fluoroborate and commencement of diazo ester addition is to be avoided; ketone may be consumed in self-condensations of the aldol type.[19] Coloration of the reaction mixture due to diazoacetate and continuous nitrogen evolution should be noted until completion of the homologation (which may conveniently be estimated by cessation of outgassing). It is practical to initiate the reaction at 0 °C, and to allow the temperature of the reaction mixture to come to 25 °C should homologation prove sluggish. The aqueous sodium bicarbonate workup (destruction of triethyloxonium fluoroborate) is critical. Agitation of the two-phase reaction mixture should be vigorously maintained until well after the cessation of carbon dioxide evolution; no catalyst must be carried into a subsequent distillation. It has been our experience (and that of others) that β-keto esters tend to decompose on attempted GLC analysis.

Methylcycloheptanones. A solution of 2.8 g (0.025 mol) of 2-methylcyclohexanone in 100 ml of methylene chloride was cooled to 0 °C in a dry flask protected with a drying tube under a nitrogen atmosphere. To the magnetically stirred solution, 15 g (0.079 mol) of triethyloxonium fluoroborate was added, followed by the dropwise addition of 5.2 g (0.046 mol) of ethyl diazoacetate. The reaction mixture was stirred for 4 h at 0 °C, during which time nitrogen was evolved, before the reaction was quenched with 150 ml of saturated aqueous sodium bicarbonate solution, and allowed to warm to room temperature. After stirring vigorously for about 0.5 h, the methylene chloride layer was separated from the aqueous layer (should be ca. pH 8), which was washed twice with 25 ml of methylene chloride. The combined methylene chloride extract was dried over anhydrous magnesium sulfate, solvent was removed, and the residue was distilled at reduced pressure. Distillation gave 4.7 g (96%) of keto ester product, bp 73–78 °C (0.4 mm). The product was not characterized, but 1.0 g (0.0050 mol) was hydrolyzed and decarboxylated by heating it with 5 ml of distilled water in a sealed tube for 2.5 h at 230 °C. The tube was allowed to cool before it was opened and the heterogeneous mixture was extracted three times with 5 ml of methylene chloride. The combined methylene chloride extract was dried over anhydrous magnesium sulfate, solvent was removed, and the residue was distilled at reduced pressure. Distillation gave 0.55 g (87%) of ketonic product, bp 88–90 °C (30 mm). GLC analysis showed two peaks which were collected and identified by NMR as 85% of 2-methylcycloheptanone [NMR (CCl_4) δ 1.0 (d, 3, J = 7 Hz), ca. 1.6 (m, 8), and ca. 2.3 ppm (m, 3)] and 15% of 3-methylcycloheptanone [NMR (CCl_4) 1.0 (d, 3, J = 7 Hz), ca. 1.7 (m, 7), and ca. 2.3 ppm (m, 4)], respectively. The two compounds were distinguished by the fact that 2-methylcycloheptanone showed an NMR methyl group doublet which slowly collapsed to a singlet in trifluoroacetic acid and deuterium oxide, whereas the corresponding doublet from 3-methylcycloheptanone did not coalesce upon deuterium exchange.

The above procedure was also used to expand 2-methylcyclohexanone at room temperature instead of at 0 °C as reported above. The keto ester product (72%) was hydrolyzed and decarboxylated as described. The same products were obtained (ratio 82:18).

2-Carbethoxycyclononanone. The homologation of cyclooctanone, which is a rather unreactive ketone, is here included as an example of a preparative reaction under forcing conditions. A solution of 32 g (0.25 mol) of cyclooctanone in 500 ml of methylene chloride was cooled to 5–10 °C in an ice–water bath under dry nitrogen. With continuous stirring 150 g (0.79 mol) of triethyloxonium fluoroborate was dissolved, and promptly (to minimize aldol condensation)[19] the rapid dropwise addition of 52 g (0.46 mol) of ethyl diazoacetate was commenced. Addition was regulated such that the solution temperature was maintained in the range 15–25 °C, and took 10–60 min, depending on the efficiency of cooling and other factors. Stirring was continued for an additional 3 h (nitrogen evolution). The contents of the flask were then added cautiously to a solution of 200 g of sodium bicarbonate and 2 l. of water in a 4-l. beaker. Magnetic stirring was slowly initiated and finally a state of vigorous agitation was maintained for 2 or 3 h (until well after the cessation of CO_2 evolution). Phases were separated and the aqueous layer (pH ca. 8) was washed with additional CH_2Cl_2. Solvent was removed from the organic extracts (rotary evaporator) and the residue was distilled through a 30-cm Vigreux column to yield 37.4–40.4 g (69–75%) of 2-carbethoxycyclononanone, bp 89–95 °C (0.2 mm). Anal. ($C_{12}H_{20}O_3$) C, H. This material was further characterized spectroscopically and by decarbethoxylation to yield solely cyclononanone (GLC analysis).

2-Carbethoxy-7-chlorocycloheptanone and Subsequent Transformation. 2-Chlorocyclohexanone (3.3 g) was homologated in the usual way (preceding and Table I). The crude product was purified by column chromatography on 80 g of silicic acid ($CHCl_3$ eluent) to give 4 g (74%) of a single, apparently homogeneous product, 2-carbethoxy-7-chlorocycloheptanone: NMR (CCl_4) δ 1.2 (t, 3, J = 7 Hz), ca. 1.8 (m, 8), ca. 3.7 (m, 1), 4.1 (q, 2, J = 7 Hz), and ca. 4.3 ppm (m, 1). Dehydrohalogenation of this material with base yielded no trace of carbethoxycycloheptenone, as should have been expected from 2-carbethoxy-3-chlorocycloheptanone. Instead, Favorskii rearrangement occurred. The chloro keto ester was refluxed in a 1.7 M solution of sodium methoxide in methanol for 8 h. Neutralization and workup yielded 1,2-dicarbomethoxycyclohexane: NMR (CCl_4) δ ca. 1.3 (m, 8), ca. 2.6 (m, 2), and 3.6 ppm (s, 6); MS calcd m/e 200.1050, obsd 200.1049. Saponification yielded *trans*-1,2-cyclohexanedicarboxylic acid, mp 222–224 °C.[20]

Other Ketones. Products of additional homologations included in Table I are listed below. All keto esters were characterized spectroscopically and/or by decarbethoxylation to readily identifiable ketones. Where feasible, comparison was made with authentic materials. The important experimental parameters are in Table I; the procedure follows that in the previous examples. (1) Ethyl 2-methylacetylacetate, bp 90–95 °C (35 mm), glycidic ester specifically absent from product (compare Tai and Warnhoff[6c]). (2) Ethyl 2-ethylpropionylacetate, bp 78–83 °C (3 mm). (3) Products from 2-butanone: keto ester mixture, bp 99–120 °C (31 mm), yielding a 50:50 mixture of 2- and 3-pentanone upon total hydrolysis. (4) Products from 2-methyl-3-pentanone:keto ester mixture, bp 71–100 °C (1 mm), yielding a 66:34 mixture of 2-methyl-3-hexanone and 5-methyl-3-hexanone upon total hydrolysis.[21] (5) Products from 3,3-dimethyl-2-butanone: keto ester mixture (grossly contaminated), bp 55–110 °C (0.1 mm), yielding a 95:5 mixture of 2,2-dimethyl-3-pentanone and 4,4-dimethyl-2-pentanone (by comparison with authentic materials, mixture also containing several unidentified components). (6) Products from phenylacetone:keto ester mixture, bp 114–126 °C (0.5 mm), yielding a 62:38 mixture of 1-phenyl-2-butanone and 4-phenyl-2-butanone. (7) Products from 4-methyl-3-penten-2-one:keto ester mixture (contaminated), bp 66–90 °C (0.4 mm), yielding an 80:20 mixture of 5-methyl-4-hexen-2-one and 5-methyl-3-hexen-2-one (also

contaminated with unhomologated ketone and other materials but free of 5-methyl-4-hexen-3-one). A semicarbazone was obtained from the homologated ketones, mp 149–151 °C. (8) Products from acetophenone:keto ester mixture, bp 88–98 °C (0.2 mm), yielding a 90:10 mixture of phenylacetone and propiophenone upon total hydrolysis. (9) Products from butyrophenone:keto ester mixture, bp 97–120 °C (0.4 mm), yielding a 57:43 mixture of 1-phenyl-2-pentanone and 1-phenyl-1-pentanone upon total hydrolysis. (10) Products from isobutyrophenone:keto ester mixture (incomplete conversion), bp 96–115 °C (0.2 mm), yielding a 69:31 mixture of 1-phenyl-3-methyl-1-butanone and 1-phenyl-3-methyl-2-butanone upon total hydrolysis. (11) 2-Carbethoxycyclohexanone, bp 99–109 °C (4.5 mm); phenylhydrazine derivative (pyrazolone), mp 180–182 °C.[6c] (12) 2-Carbethoxycycloheptanone[3], bp 80–82 °C (0.5 mm, note: incorrect previous[3] pressure recording), phenylhydrazine derivative (pyrazolone) mp 211–212 °C.[6c] (13) 2-Carbethoxycyclooctanone, bp 80–89 °C (0.6 mm); phenylhydrazine derivative (pyrazolone), mp 174–175 °C. (14–16) See preceding. (17) 3-Carbethoxy-2-oxotricyclo[4.3.1.1^{4,8}]undecane, oil (chromatographically purified, silicic acid–chloroform), yielding (upon decarbethoxylation) homoadamantanone, mp 268–270 °C.[22]

2-Cyanocycloheptanone. Diazoacetonitrile[10] was obtained from the diazotization of aminoacetonitrile hydrochloride according to the procedure used for the preparation of ethyl diazoacetate.[16] *Caution:* because of an explosion hazard,[10] diazoacetonitrile was not isolated from the methylene chloride solvent used in the diazotization, but, after partial removal of solvent, the concentration of diazoacetonitrile in methylene chloride was determined from the integral of the NMR spectrum.

A solution of 2.5 g (0.025 mol) of cyclohexanone in 100 ml of methylene chloride was cooled to 0 °C in a dry flask protected with a drying tube under a nitrogen atmosphere. To the magnetically stirred solution, 9 g (0.046 mol) of triethyloxonium fluoroborate was added, followed by the dropwise addition of 3.1 g (0.046 mol) of diazoacetonitrile in methylene chloride. The reaction mixture was stirred for 3 h at 0 °C, during which time nitrogen was evolved, before the reaction was quenched with 150 ml of saturated aqueous sodium bicarbonate solution. After stirring for about 0.5 h at room temperature, the reaction mixture was worked up in the usual manner. Distillation gave 2.0 g (58%) of 2-cyanocycloheptanone: bp 103–107 °C (0.1 mm); IR (neat) λ 4.40 and 5.80 μ; NMR (neat) δ ca. 1.7 (m, 8), ca. 2.6 (m, 2), and ca. 3.9 ppm (m, 1); MS calcd *m/e* 137.0841, obsd 137.0851. A semicarbazone derivative was obtained, mp 155–158 °C.[23]

2-(Trifluoromethyl)cycloheptanone. A solution of 1.2 g (0.012 mol) of cyclohexanone in 50 ml of methylene chloride was cooled to 0 °C in a dry flask protected with a drying tube, under a nitrogen atmosphere. To the magnetically stirred solution, 7 g (0.037 mol) of triethyloxonium fluoroborate was added, followed by the addition of ca. 3 g (0.03 mol) of 2,2,2-trifluorodiazoethane[11] in 7 ml of methylene chloride. The reaction mixture was stirred for 2 h at 0 °C, during which time nitrogen was evolved, before the reaction was quenched with 150 ml of saturated aqueous sodium bicarbonate solution. After stirring for about 0.5 h at room temperature, the reaction mixture was worked up in the usual manner. Distillation gave 2.2 g of impure 2-(trifluoromethyl)cycloheptanone, bp 85–105 °C (45–50 mm), after preparative GLC (net yield 85%): IR (neat) λ 5.80 μ; NMR (CCl_4) δ ca. 1.8 (m, 8), ca. 2.6 (m, 2), and ca. 3.2 ppm (m, 1). Anal. ($C_8H_{11}F_3O$) C, H.

A mixture of ca. 1 g of 2-(trifluoromethyl)cycloheptanone and 20 ml of aqueous 20% potassium hydroxide was heated at 80–90 °C for 48 h, during which time the reaction mixture appeared to become homogeneous. The basic mixture was cooled and extracted three times with 5 ml of ether. The basic aqueous layer was acidified with hydrochloric acid and again extracted three times with 5 ml of ether. Essentially nothing was obtained from the acidic extract; however, a good yield of cycloheptanone was obtained directly from the basic extract. The 2,4-dinitrophenylhydrazone of the product was obtained (yellow needles), mp 147–148 °C (no mixture melting point depression with authentic DNP derivative of cycloheptanone).

2-Carbo-*tert*-butoxycycloheptanone. A solution of 2.5 g (0.025 mol) of cyclohexanone in 100 ml of methylene chloride was cooled to 0 °C in a dry flask protected with a drying tube under a nitrogen atmosphere. To the magnetically stirred solution, 15 g (0.079 mol) of triethyloxonium fluoroborate was added, followed by the dropwise addition of 7.1 g (0.50 mol) of *tert*-butyl diazoacetate.[13] The reaction mixture was stirred for 2.5 h at 0 °C, during which time nitrogen was evolved, before the reaction was quenched with 150 ml of saturated aqueous sodium bicarbonate solution. After stirring for about 0.5 h at room temperature, the reaction mixture was worked up in the usual manner. The crude product after solvent removal was chromatographed on 100 g of silicic acid. Elution with chloroform gave a single major fraction which consisted of 6.2 g of a ferric chloride positive material. While the NMR spectrum showed the required resonances for *tert*-butyl 2-oxocycloheptanecarboxylate, it also showed several unexplained signals, indicating contamination. Therefore, the product was directly refluxed in 50 ml of benzene containing 0.5 g of *p*-toluenesulfonic acid. After 14 h, the reaction mixture still gave a positive ferric chloride test. Regardless, the mixture was cooled and washed with 20 ml of distilled water and then with 20 ml of saturated sodium bicarbonate solution. Benzene was removed and the residue was distilled at reduced pressure. Distillation gave 1.3 g (46%, based on cyclohexanone) of cycloheptanone, bp 80–83 °C (30 mm), as the sole volatile product. It might be noted that superior yields have been obtained with other ketones.[4]

***O,O*-Dimethyl 2-Oxocycloheptylphosphonate.** A solution of 1.2 g (0.012 mol) of cyclohexanone in 50 ml of methylene chloride was cooled to 0 °C in a dry flask protected with a drying tube, under a nitrogen atmosphere. To the magnetically stirred solution 7 g (0.047 mol) of trimethyloxonium fluoroborate was added. The ice bath was removed and 4.5 g (0.030 mol) of dimethyl diazomethylphosphonate[12] was dropped into the reaction mixture as it warmed to room temperature. The heterogeneous mixture was stirred for 5 h, during which time nitrogen was evolved, before the reaction was quenched with 150 ml of saturated aqueous sodium bicarbonate solution. After stirring for about 0.5 h, the reaction mixture was worked up in the usual manner. Distillation gave 0.5 g of an unidentified product mixture, bp 53–80 °C (0.3 mm), followed by 1.7 g (65%) of *O,O*-dimethyl 2-oxocycloheptylphosphonate, bp 80–140 °C (0.3 mm). Pure material was obtained by chromatography of the distillation fraction on 40 g of silicic acid with chloroform–methanol (99:1) elution: IR (neat) λ 5.88, 8.0, 9.5, and 9.7 μ; NMR (CCl_4) δ ca. 1.7 (m, 8), ca. 2.8 (m, 3), and 3.7 ppm (d, 6, J = 11 Hz). Anal. ($C_9H_{17}O_4P$) C, H.

Using the above conditions, cyclohexanone was also expanded with dimethyl diazophosphonate using triethyloxonium fluoroborate instead of trimethyloxonium fluoroborate as the catalyst. The reaction product was similarly purified to give the corresponding mixed methyl and ethyl phosphonates, adequate for further synthetic transformation.

To a solution of 200 mg of *O,O*-dimethyl 2-oxocycloheptylphosphonate in 20 ml of dimethyl sulfoxide (Me_2SO) was added 2 ml of 0.65 N sodium methylsulfinylmethide in Me_2SO. After 15 min, 150 mg of *m*-nitrobenzaldehyde was added to the solution. The reaction mixture was heated for 20 h at 55–60 °C before it was cooled and diluted with distilled water. The mixture (pH 7) was then extracted three times with 5 ml of ether. The combined ether extract was dried over anhydrous magnesium sulfate, solvent was removed, and the residue was chromatographed on 5 g of silicic acid. Elution with chloroform gave a single fraction which was identified as 2-(*m*-nitrobenzylidene)cycloheptanone: IR (neat) λ 5.92 and 6.20 μ; NMR ($CDCl_3$) δ 1.9 (m, 6), 2.8 (m, 4), and ca. 7.8 ppm (m, 5); MS calcd *m/e* 245.1052, obsd 245.1058. The product was obtained as an oil in good yield. A 2,4-dinitrophenylhydrazone was obtained as orange needles, mp 192–194 °C.

1-Diazo-4-(2-oxocyclohexyl)-2-butanone. A solution of 5.1 g (0.03 mol) of (2-oxocyclohexyl)propionic acid[24] and 3.1 g (0.03 mol) of triethylamine in 100 ml of ether was cooled to −5 °C in an ice–salt bath. To the magnetically stirred solution, 3.3 g (0.03 mol) of ethyl chloroformate was slowly added dropwise such that the temperature of the reaction mixture remained below 0 °C. After 3 h, triethylammonium chloride was removed by filtration and the filtrate was concentrated to ca. 25 ml under reduced pressure. The ethereal solution of the anhydride was slowly added to a solution of 0.064 mol of diazomethane in 200 ml of dry ether at 0 °C. After 5 h at 0 °C, excess diazomethane and solvent were removed to give the crude diazo ketone as an oil. The product crystallized at −80 °C from ether–petroleum ether to give 2.5 g (50%) of 1-diazo-4-(2-oxocyclohexyl)-2-butanone (yellow needles): mp 33–36 °C; IR (neat) λ 4.75, 5.88, and 6.12 μ; NMR ($CHCl_3$) δ ca. 1.8 (m, 8), ca. 2.2 (m, 5), and 5.2 ppm (s, 1).

Bicyclo[5.3.0]decane-2,10-dione. A solution of 0.5 g (2.6 mmol) of the diazo ketone in 100 ml of methylene chloride was cooled to 0 °C in a dry flask protected with a drying tube under a nitrogen atmosphere. To the magnetically stirred solution, 0.5 g (2.6 mmol) of triethyloxonium fluoroborate was added. The reaction mixture was stirred for 0.5 h, during which time nitrogen was evolved, before the reaction was quenched with 50 ml of saturated aqueous sodium bicarbonate solution. The mixture was allowed to warm to room temperature (0.5 h) before the methylene chloride layer was separated from the aqueous layer. The methylene chloride extract was dried over anhydrous magnesium sulfate and solvent was removed to give bicyclo[5.3.0]decane-2,10-dione. The crude product revealed by GLC

analysis a single substance which was collected for characterization: mp 23–25 °C; IR ($CHCl_3$) λ 6.07 and 6.25 μ; NMR ($CDCl_3$) δ ca. 1.2 (m, 8), ca. 2.4 (m, 5), and ca. 13.6 ppm (broad, 1, enolic OH). Anal. ($C_{10}H_{14}O_2$) C, H. A 2,4-dinitrophenylhydrazine derivative was obtained (yellow-orange plates), mp 191–192 °C.

Structure Proof for Bicyclo[5.3.0]decane-2,10-dione. In order to establish the presence of the β-diketone function in the above product, it was alkylated with methyl iodide. The enolate was prepared in benzene from 0.40 g (2.5 mmol) of the diketone and 0.07 g (3.0 mmol) of sodium hydride. After 1 h, an excess of methyl iodide was added to the mixture and stirring was continued for 24 h. Workup consisted of washing the reaction mixture with 10% hydrochloric acid. Removal of solvent gave 1-methylbicyclo[5.3.0]decane-2,10-dione, which was collected by preparative GLC: IR ($CHCl_3$) λ 5.72 and 5.91 μ; NMR ($CDCl_3$) δ 1.3 (s, 3), ca. 1.8 (m, 9), and ca. 2.4 ppm (m, 5). Anal. ($C_{11}H_{16}O_2$) C, H.

Cleavage of 1.2 g (0.007 mol) of bicyclo[5.3.0]decane-2,10-dione was effected by refluxing the diketone with 10 g of barium hydroxide in 50 ml of water for 20 h. Neutralization of the reaction mixture with carbon dioxide and acidification with 10% sulfuric acid gave, after extraction with chloroform and removal of solvent, 1.0 g (77%) of (3-oxocycloheptyl)propionic acid. Wolff–Kishner reduction of 1 g (0.005 mol) of the keto acid with 1 g of potassium hydroxide and 1 ml of hydrazine hydrate in 30 ml of diethylene glycol, according to the Huang-Minlon procedure,[25] gave 0.68 g (74%) of nearly pure cycloheptylpropionic acid: IR (neat) λ 5.85 μ; NMR ($CHCl_3$) δ ca. 1.5 (m, 15), ca. 2.2 (m, 2), and 9.1 ppm (s, 1). GLC analysis of the product showed a very minor amount of cyclopentylvaleric acid (the other possible acid from cleavage of the diketone), by comparison with authentic samples of the acids. The amide derivative of the major acid was obtained (colorless needles), mp 81.5–82.5 °C (no mixture melting point depression with authentic material).

Authentic cyclopentylvaleric acid was prepared according to the procedure given by Herz.[26a] The authentic isomeric cycloheptylpropionic acid was obtained in the following manner. The reaction between the morpholine enamine of cycloheptanone[26b] and methyl acrylate gave methyl (2-oxocycloheptyl)propionate in 75% yield after workup and distillation. Hydrolysis of the ester with sodium hydroxide gave (2-oxocycloheptyl)propionic acid. Reduction of 4 g (0.022 mol) of the acid by the Huang-Minlon procedure gave 3.2 g (87%) of cycloheptylpropionic acid, from which the amide was obtained, mp 84–85 °C.

Homologations Catalyzed with Antimony Pentachloride. A. Cyclohexanone. A solution of 2.5 g (0.025 mol) of cyclohexanone in 80 ml of methylene chloride was cooled to −78 °C in a dry flask, protected with a drying tube, under a nitrogen atmosphere. To the magnetically stirred solution, 3.7 g (0.012 mol) of antimony pentachloride was added, followed by the dropwise addition of 5.2 g (0.046 mol) of ethyl diazoacetate. The reaction mixture was stirred for 1 h at −78 °C, during which time nitrogen was evolved, before the cold bath was removed and the reaction mixture was allowed to warm to room temperature. After ca. 15 min of warming, the reaction was quenched with 150 ml of saturated aqueous sodium bicarbonate solution and stirred for about 0.5 h. During the workup, the antimony pentachloride precipitated as an inorganic complex that was removed from the aqueous layer, which phase was washed twice with 25 ml of additional methylene chloride. The combined methylene chloride extract was dried over anhydrous magnesium sulfate, solvent was removed, and the residue was distilled at reduced pressure. Distillation gave 3.6 g (77%) of 2-carbethoxycycloheptanone, bp 81–92 °C (0.6 mm). The spectral properties of the product were identical with those previously described; however, GLC analysis indicated that the product was somewhat less contaminated with trace components than in the case of triethyloxonium fluoroborate catalysis.

B. Other Ketones. (1) 2-Methylcyclohexanone was homologated by the above procedure to give a keto ester mixture (72%), bp 74–85 °C (0.5 mm), yielding a 94:6 mixture of 2- and 3-methylcycloheptanones on total hydrolysis. (2) *trans*-2-Isopropyl-5-methylcyclohexanone gave a keto ester mixture (63%), bp 92–97 °C (0.3 mm), yielding a 94:6 mixture of 2-isopropyl-5-methyl- and 3-isopropyl-6-methylcycloheptanone on total hydrolysis. (3) *cis*-2-Isopropyl-5-methylcyclohexanone gave a keto ester mixture (27%), bp 110–125 °C (0.4 mm), contaminated with lower boiling unreacted ketone and ethyl glycolate, yielding a 74:26 mixture of 2-isopropyl-5-methyl- and 3-isopropyl-6-methylcycloheptanone on total hydrolysis. (4) Bicyclo[2.2.1]heptan-2-one (norcamphor) gave a keto ester mixture (79%), bp 79–86 °C (0.3 mm), yielding a 86:14 mixture of bicyclo[3.2.1]octan-2-one and bicyclo[3.2.1]octan-3-one on total hydrolysis. (5) Phenylacetone gave a keto ester mixture (89%), bp 92–106 °C (0.3 mm), yielding a 77:23 mixture of 1-phenyl- and 4-phenyl-2-butanone on total hydrolysis. Product ratios (and identities) for the preceding substituted cyclohexanones may be compared with the results of triethyloxonium ion catalyzed homologations reported in the accompanying article.[4]

C. Acetophenone Complex. Acetophenone was homologated after first isolating the antimony pentachloride–acetophenone complex, which was then treated with ethyl diazoacetate. A solution of 6 g (0.05 mol) of acetophenone in 150 ml of carbon tetrachloride was cooled to 0 °C. To the magnetically stirred solution, 15 g (0.05 mol) of $SbCl_5$ was cautiously added. The complex immediately crystallized from solution. The ice bath was removed and the reaction mixture was allowed to warm to room temperature. The mixture was filtered under dry nitrogen and washed with carbon tetrachloride to give the complex in nearly quantitative yield. A few grams were recrystallized from methylene chloride–carbon tetrachloride to give colorless needles of $C_6H_5COCH_3{\cdot}SbCl_5$: mp 134 °C dec (lit. 138 °C dec[14]); NMR ($CDCl_3$) δ 3.2 (s, 3) and ca. 7.8 ppm (m, 5). The complex was slightly soluble in chloroform, moderately soluble in methylene chloride, and quite soluble in liquid sulfur dioxide.

The hygroscopic complex as prepared above was added to 150 ml of methylene chloride in a dry flask, protected with a drying tube, under a nitrogen atmosphere. The partially soluble mixture was cooled to −78 °C and 9.9 g (0.087 mol) of ethyl diazoacetate was added dropwise. The reaction mixture was magnetically stirred for 1.5 h at −78 °C, during which time nitrogen was evolved and the reaction solution became homogeneous, whereupon the cold bath was removed and the mixture was allowed to warm to room temperature. After 0.5 h, the reaction was quenched with 200 ml of saturated sodium bicarbonate solution. The mixture was stirred for about 0.5 h before the precipitated antimony pentachloride complex was removed by suction filtration. The methylene chloride layer was separated from the aqueous layer, which was washed twice with 25 ml of methylene chloride. Solvent was removed from the combined methylene chloride extract. The crude product was hydrolyzed and decarboxylated by heating it with 75 ml of 10% sulfuric acid on a steam bath. After 40 h the reaction mixture was extracted with ether, which was worked up in the usual manner. Distillation gave 3.5 g (52%, from acetophenone) of ketonic product, bp 52–62 °C (0.8 mm), shown to be a mixture of some unreacted acetophenone and phenylacetone by GLC analysis. Significantly, propiophenone was specifically absent (<2%).

D. Homologation of Acetophenone with *tert*-Butyl Diazoacetate. A solution of 3.0 g (0.025 mol) of acetophenone in 100 ml of methylene chloride was cooled to −78 °C in a dry flask, protected with a drying tube, under a nitrogen atmosphere. To the magnetically stirred solution, 4.0 g (0.020 mol) of antimony pentachloride was added, followed by the dropwise addition of 7.1 g (0.050 mol) of *tert*-butyl diazoacetate.[13] The reaction mixture was stirred for 1.5 h at −78 °C, during which time nitrogen was evolved, before the cold bath was removed and the reaction mixture was allowed to warm to room temperature. After briefly warming, the reaction was quenched with 150 ml of saturated aqueous sodium bicarbonate solution, which treatment was followed by the usual workup. The crude product was chromatographed on 100 g of neutral silicic acid and eluted with chloroform. Obtained was 3.5 g of a ca. 1:1 mixture of phenylacetone and *tert*-butyl 2-phenylacetylacetate, plus a small amount of acetophenone, followed by ca. 1.0 g of mixture of unidentified components. The major product mixture was further decarbalkoxylated by heating it in 50 ml of benzene containing 0.2 g of *p*-toluenesulfonic acid for 16 h. After the usual workup and distillation, GLC analysis revealed only phenylacetone and acetophenone (85:15); propiophenone was again absent. Significantly, attempts to catalyze the reaction between acetophenone and *tert*-butyl diazoacetate with triethyloxonium fluoroborate gave a complex mixture of unidentified products.

E. 2,2,2-Trichloroethyl 2-Methylacetylacetate. A solution of 10.6 g (0.043 mol) of 2,2,2-trichloroethyl glycinate hydrochloride[27] in 50 ml of methylene chloride and 50 ml of distilled water was cooled to 0 °C, at which point some of the glycinate hydrochloride precipitated. To the mixture was added 4 g of sodium nitrite in 10 ml of distilled water, followed by 10 ml of 10% sulfuric acid. The temperature of the reaction mixture rose briefly to 10 °C. After 0.5 h, the methylene chloride layer was separated from the aqueous layer. The golden methylene chloride extract was washed with a saturated sodium bicarbonate solution and was dried over anhydrous sodium sulfate. Solvent was removed, and the residue was distilled at reduced pressure, yielding 5.3 g (56%) of 2,2,2-trichloroethyl diazoacetate: bp 53–55 °C (0.2 mm); IR (neat) λ 4.70 and 5.84 μ; NMR (CCl_4) δ 4.7 (s, 2) and 4.9 ppm (s, 1).

A solution of 0.3 g (5.2 mmol) of acetone in 25 ml of methylene chloride was cooled to −78 °C in a dry flask, protected with a drying tube, under a nitrogen atmosphere. To the magnetically stirred solution 1.0 g (3.3 mmol) of antimony pentachloride was added, followed

by the dropwise addition of 2.5 g (0.011 mol) of 2,2,2-trichloroethyl diazoacetate. The reaction mixture was stirred for 1 h at −78 °C, during which time nitrogen was evolved, before the cold bath was removed and the reaction mixture was allowed to warm to room temperature. After warming for 0.5 h, the reaction was quenched with 75 ml of saturated aqueous sodium bicarbonate solution. The mixture was stirred for about 0.5 h before the antimony complex was removed by suction filtration. The methylene chloride layer was separated and the aqueous layer was washed twice with 10 ml of methylene chloride. The combined methylene chloride extract was dried over anhydrous magnesium sulfate, solvent was removed, and the crude product was analyzed by GLC. Two peaks were collected and identified. The first was 2,2,2-trichloroethyl hydroxyacetate. The second product was identified as 2,2,2-trichloroethyl 2-methylacetylacetate: IR (CCl_4) λ 5.68 and 5.80 μ; NMR (CCl_4) δ 1.4 (d, 3, J = 7 Hz), 2.3 (s, 3), 3.6 (q, 1, J = 7 Hz), and 4.8 ppm (s, 2). Anal. ($C_7H_9Cl_3O_3$) C, H.

Attempts to catalyze the reaction between acetone and 2,2,2-trichloroethyl diazoacetate with triethyloxonium fluoroborate failed to give any of the desired product. The products obtained were difficult to separate and were not identified.

Acknowledgment. This work was partially funded through the National Science Foundation. Particular thanks are given to the PPG Industries for financial support (to M.E.H.), and to the A. P. Sloan Foundation for a fellowship (to W.L.M.).

Registry No.—Triethyloxonium fluoroborate, 368-39-8; 2-methylcycloheptanone, 932-56-9; 3-methylcycloheptanone, 933-17-5; 2-carbethoxycyclononanone, 4017-57-6; 2-carbethoxy-7-chlorocycloheptanone, 60719-11-1; 1,2-dicarbomethoxycyclohexane, 4336-20-3; 2-carbethoxycyclooctanone phenylhydrazone, 60719-12-2; 2-cyanocycloheptanone, 7391-45-9; 2-(trifluoromethyl)cycloheptanone, 60719-13-3; cycloheptanone 2,4-DNP, 3349-73-3; dimethyl diazomethylphosphonate, 27491-70-9; *O,O*-dimethyl 2-oxocycloheptylphosphonate, 60719-14-4; *m*-nitrobenzaldehyde, 99-61-6; 2-(*m*-nitrobenzylidene)cycloheptanone, 60719-15-5; 2-(*m*-nitrobenzylidene)cycloheptanone 2,4-DNP, 60719-16-6; (2-oxocyclohexyl) propionic acid, 2275-26-5; 1-diazo-4-(2-oxocyclohexyl)-2-butanone, 60719-17-7; bicyclo[5.3.0]decane-2,10-dione, 60719-18-8; bicyclo[5.3.0]decane-2,10-dione di(2,4-DNP), 60719-19-9; 1-methylbicyclo[5.3.0]decane-2,10-dione, 60719-20-2; (3-oxocycloheptyl)propionic acid, 60719-21-3; cycloheptylpropionic acid, 4448-78-6; cycloheptylpropionamide, 60719-22-4; cycloheptanone morpholine enamine, 60719-23-5; methyl (2-oxocycloheptyl)propionate, 10407-26-8; acetophenone $SbCl_5$, 25538-03-8; 2,2,2-trichloroethyl glycinate HCl, 21646-95-7; 2,2,2-trichloroethyl diazoacetate, 60719-24-6; 2,2,2-trichloroethyl 2-methylacetylacetate, 60719-25-7.

References and Notes

(1) (a) Taken from the Ph.D. Thesis of M. E. Hartman, Carnegie-Mellon University, 1972; *Diss. Abstr. Int. B*, **33**, 3553 (1973). (b) Address inquiries to Department of Chemistry, University of Illinois at Chicago Circle, Box 4348, Chicago, Ill. 60680.
(2) (a) C. D. Gutsche, *Org. React.*, **8**, 364 (1954); (b) C. D. Gutsche and D. Redmore, "Carbocyclic Ring Expansion Reactions", Academic Press, New York, N.Y., 1968; (c) G. W. Cowell and A. Ledwith, *Q. Rev., Chem. Soc.*, **24**, 119 (1970); (d) J. E. McMurry and A. P. Coppolino, *J. Org. Chem.*, **38**, 2821 (1973).
(3) W. L. Mock and M. E. Hartman, *J. Am. Chem. Soc.*, **92**, 5767 (1970).
(4) W. L. Mock and M. E. Hartman, *J. Org. Chem.*, following paper in this issue.
(5) E. Wenkert and C. A. McPherson, *J. Am. Chem. Soc.*, **94**, 8084 (1972); U. Schöllkopf, B. Bánhidai, H. Frasnelli, R. Meyer, and H. Beckhaus, *Justus Liebigs Ann. Chem.*, 1767 (1974).
(6) (a) E. Müller and M. Bauer, *Justus Liebigs Ann. Chem.*, **654**, 92 (1962); (b) B. Eistert, F. Haupter, and K. Schank, *ibid.*, **665**, 55 (1963); (c) W. T. Tai and E. W. Warnhoff, *Can. J. Chem.*, **42**, 1333 (1964); (d) H. J. Liu and S. P. Majumdar, *Synth. Commun.*, **5**, 125 (1975); (e) H. J. Liu, *J. Org. Chem.*, **40**, 2252 (1975).
(7) D. Fărcaşiu, P. v. R. Schleyer, and D. B. Ledlie, *J. Org. Chem.*, **38**, 3455 (1973); see also H. J. Liu and T. Ogino, *Tetrahedron Lett.*, 4937 (1973).
(8) (a) Precedent: unpublished results of E. E. van Tamelen and J. E. Brenner (Ph.D. Thesis of J.E.B., University of Wisconsin, 1958), cited by A. S. Kende, *Org. React.*, **11**, 272 (1960). (b) Reference 2b, footnote 271a, p 88.
(9) A. T. Nielsen and W. R. Carpenter, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 288.
(10) J. Hooz and S. Linke, *J. Am. Chem. Soc.*, **90**, 6891 (1968); S. H. Harper and K. C. Sleep, *J. Sci. Food Agric.*, **6**, 116 (1955); T. Curtius, *Chem. Ber.*, **31**, 2489 (1898).
(11) H. Gilman and R. G. Jones, *J. Am. Chem. Soc.*, **65**, 1458 (1943); R. Fields and R. N. Haszeldine, *J. Chem. Soc.*, 1881 (1964).
(12) D. Seyferth, R. S. Marmor, and P. Hilbert, *J. Org. Chem.*, **36**, 1379 (1971).
(13) M. Regitz, J. Hocker, and A. Liedhegener, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 179.
(14) F. Klages, H. Träger, and E. Mühlbauer, *Chem. Ber.*, **92**, 1819 (1959); F. Klages and E. Zange, *ibid.*, **92**, 1828 (1959), F. Klages, J. E. Gordon, and H. A. Jung, *ibid.*, **98**, 3748 (1965); G. Olofsson, *Acta Chem. Scand.*, **22**, 377 (1968); I. Lindqvist and M. Zackrisson, *ibid.*, **14**, 453 (1960).
(15) (a) T. B. Windholz and D. B. R. Johnston, *Tetrahedron Lett.*, 2555 (1967); R. B. Woodward, K. Heusler, J. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan, and H. Vorbrüggen, *J. Am. Chem. Soc.*, **88**, 852 (1966). (b) T. Mukaiyama, T. Sato, S. Suzuki, T. Inoue, and H. Nakamura, *Chem. Lett.*, 95 (1976).
(16) N. E. Searle, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 424. Commercial material is suitable after purification.
(17) H. Meerwein, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 1080. Although trialkyloxonium salts are commercially available, the preparation of material suitable for this application is exceptionally easy.
(18) This may be excluded as a reaction intermediate.
(19) We thank Drs. H. O. House, W. C. McDaniel, and W. C. Liang for contributions in establishing this conclusion.
(20) G. E. Ficken, H. France, and R. P. Linstead, *J. Chem. Soc.*, 3730 (1954).
(21) Acknowledgment is given to Mr. W. Brant (Gulf Research and Development Co., Harmarville, Pa.) for the difficult GLC analysis of this ketone product ratio.
(22) J. E. Nordlander, F. Y.-H. Wu, S. P. Jindal, and J. B. Hamilton, *J. Am. Chem. Soc.*, **91**, 3962 (1969); P. v. R. Schleyer, E. Funke, and S. H. Liggero, *ibid.*, **91**, 3965 (1969).
(23) C. Iwanoff, *Chem. Ber.*, **87**, 1600 (1954).
(24) H. O. House, H. Babad, R. B. Toothill, and A. W. Noltes, *J. Org. Chem.*, **27**, 4141 (1962).
(25) H.-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).
(26) (a) W. Herz, *J. Org. Chem.*, **22**, 630 (1953); (b) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).
(27) E. S. Granatek and A. P. Granatek (Bristol-Meyers Co.), South African Patent 67 07 666; *Chem. Abstr.*, **70**, 68740 (1969).

Mechanism of the Triethyloxonium Ion Catalyzed Homologation of Ketones with Diazoacetic Esters[1a]

William L. Mock*[1b] and Marvis E. Hartman

Department of Chemistry, Carnegie-Mellon University, Pittsburgh, Pennsylvania 15213

Received April 20, 1976

In the homologation of cyclohexanone with ethyl diazoacetate catalyzed by triethyloxonium fluoroborate, the rate-determining step is O-alkylation of ketone by trialkyloxonium salt, as evidenced by an approximately linear dependency of rate on oxonium ion concentration, and by no systematic dependency upon diazoacetate concentration. The intermediate carboxonium ion has been independently prepared and shown to be kinetically and regiodirectively competent. The relative proportions of aryl and methyl migration in a series of substituted acetophenones was nearly invariant. From this the absence of a significant regiodirective inductive effect is inferred. Neither variation in steric demand in the 2 position of substituted cyclohexanones nor change in alkyl residue size in the catalyst could be experimentally directly implicated in determining regioselectivity. There is an apparent dependency on the size of the diazo reagent, with increasing bulk conferring specificity on the homologation product. Evidence is presented that the syn–anti ratio of the initially formed carboxonium ions influences the ultimate product distributions. It is concluded that the observed regioselectivity is in fact under conformational control, with a number of (partially offsetting) steric factors consistently combining to result in an only slightly varying pattern of limited steric discrimination.

The scope of the exceedingly useful conversion of ketones to β-keto esters with ethyl diazoacetate and triethyloxonium fluoroborate has been described.[2,3] In the present article we consider the mechanism of this reaction. While we are chiefly interested in the reaction as a synthetic tool, knowledge of its intermediate steps is a prerequisite to intelligent application. These are here elucidated by kinetic studies and by the testing of potential intermediates. We have focused particularly on the factors controlling the direction of insertion in the case of unsymmetrical ketones (eq 1), for which a peculiar pattern of

$$\mathrm{RCOR' + C_2H_5O_2CCHN_2} \xrightarrow{(C_2H_5)_3O^+BF_4^-} \mathrm{RCH(CO_2C_2H_5)COR' + RCO(CO_2C_2H_5)CHR'} \quad (1)$$

regioselectivity has been observed. The utility of the reaction would be greatly increased if it could be directed exclusively to the formation of one product or the other. This article does not describe attainment of the latter goal; however, the numerous homologations which are given allow reasonable predictions of product distributions on empirical grounds, as well as a theoretical model within the framework of conformational analysis for interpretation of the results.

Similar studies have been carried out by other authors on diazomethane expansions.[4] The mechanistic insight herein provided has applicability for these homologations and for related amino alcohol deaminations, as is briefly considered later.

Results

Rate-Determining Step. Semiquantitative kinetic studies of the reaction were carried out in order to determine the concentration dependency of the critical reactants. Rates were determined spectrophotometrically by measuring the accumulation of β-keto ester (as its $FeCl_3$ chelate, 583 nm) from cyclohexanone. The reaction proved to be approximately linearly dependent upon the concentration of catalyst triethyloxonium fluoroborate (over a 2.5-fold range). However, reaction velocity was *independent* (or perhaps even slightly inversely dependent) upon the concentration of ethyl diazoacetate. It follows that the rate-determining step involves reaction only between ketone and triethyloxonium salt, most probably by the scheme given in eq 2.

Intermediacy of Carboxonium Ion. The implication of eq 2 is that the ketone reactant undergoes O-alkylation by

$$\mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}R + (C_2H_5)_3O^+ \xrightarrow{slow} R{-}\overset{OC_2H_5}{\overset{|}{C^+}}{-}R + (C_2H_5)_2O}$$

$$\xrightarrow[fast]{C_2H_5O_2CCHN_2} \left(\mathrm{R_2C(CO_2C_2H_5)CHN_2^+} \rightarrow \mathrm{RC^+(CO_2C_2H_5)CHR} + N_2 \right)$$

$$\xrightarrow[fast]{(C_2H_5)_2O} \mathrm{RC(=O)CH(CO_2C_2H_5)R} + (C_2H_5)_3O^+ \quad (2)$$

triethyloxonium fluoroborate to yield a carboxonium ion (alkoxycarbenium ion) in the rate-determining step. In fact this is an endothermic transformation with most ketones (contrary to literature inferences);[5] our NMR examination of reaction mixtures containing ordinary aliphatic ketones reveals insignificant transfer of ethyl residue from tertiary oxonium ion to carbonyl at equilibrium. This is in accord with a reasonable extrapolation from heats of protonation of ethers and ketones.[6] (It is for this reason that such massive amounts of catalyst are prescribed.)

However, acetophenone may be alkylated with the more potent reagent, *O,O'*-diethylformate hexachloroantimonate, to give the corresponding carboxonium salt, isolable as a crystalline solid (eq 3).[7] This material reacted very rapidly

$$\mathrm{C_6H_5COCH_3 + HC^+(OC_2H_5)_2\ SbCl_6^-} \rightarrow \mathrm{C_6H_5C^+(CH_3)OC_2H_5\ SbCl_6^- + HCO_2C_2H_5} \quad (3)$$

with ethyl diazoacetate to give, after hydrolysis–decarboxylation, a low yield of phenylacetone and propiophenone. The yield was substantially increased in the presence of diethyl ether, from which we hypothesize the necessity of an alkyl residue acceptor in the ultimate step of the homologation (eq 2). Significantly, even in the absence of ether, the product ratio (phenylacetone:propiophenone) was the *same* as in the standard homologation. Hence, independent evidence (regiodirective and kinetic[8]) is consistent with the formulation of the mechanism in eq 2.

It is a reasonable a priori anticipation that the intermediates **1** or **2** might accumulate (eq 4), explaining the lack of further

$$\underset{\mathbf{1}}{\mathrm{RC^+(OC_2H_5)CHRCO_2C_2H_5}} \overset{-H^+}{\underset{?}{\rightleftharpoons}} \underset{\mathbf{2}}{\mathrm{RC(OC_2H_5)=CRCO_2C_2H_5}} \quad (4)$$

Table I. Homologation of Aryl Methyl Ketones

$ArCOCH_3 + 1.7C_2H_5O_2CCHN_2 \xrightarrow[CH_2Cl_2,\ 3h,\ 24\ °C]{3.0(C_2H_5)_3O^+BF_4^-} ArCH(CO_2C_2H_5)COCH_3 + ArCOCH(CO_2C_2H_5)CH_3$

Registry no.	Aryl substituent ($XC_6H_4COCH_3$)	Product keto esters total yield, %	Decarbethoxylation, ratio ($ArCH_2COCH_3$: $ArCOCH_2CH_3$)[a]
100-06-1	1. *p*-C_2H_5O	55[b]	>98:2
943-27-1	2. *p*-*t*-C_4H_9	77	90:10
122-00-9	3. *p*-CH_3	62	90:10
92-91-1	4. *p*-C_6H_5	79	90:10
98-86-2	5. H	78	90:10
99-91-2	6. *p*-Cl	68	90:10
99-90-1	7. *p*-Br	70[c]	89:11
2142-63-4	8. *m*-Br	82	90:10
1443-80-7	9. *p*-CN	80	84:16
121-89-1	10. *m*-NO_2	74	85:15
100-19-6	11. *p*-NO_2	81	81:19

[a] Ratio average of NMR and (where feasible) GLC determination after complete hydrolysis and decarboxylation. [b] Incomplete conversion (30% recovery of ethoxyacetophenone). [c] Incomplete conversion (15% recovery of bromoacetophenone).

homologation, etc. However this appears not to be the case. Precipitation of all oxonium salts in the reaction mixture (before workup) with CCl_4 yields only pure $(C_2H_5)_3O^+BF_4^-$ in nearly quantitative recovery (NMR analysis). Likewise, no evidence has ever been obtained for the presence of enol ethers (2) in the reaction mixture;[9] they should certainly survive the sodium bicarbonate workup conditions. Our supposition is that 1 undergoes prompt dealkylation (ethyl transfer to ether or another ketone) and the product is thereby protected (by the inductive effect of the carbethoxy group) from further homologation.

Arylalkyl Ketones. A conventional Hammett treatment was applied to a series of substituted acetophenones in order to evaluate the electronic effect on "migratory aptitudes" in unsymmetrical ketones. The results are summarized in Table I. It will be observed that there is indeed only a very slight substituent effect, with consistently 80–90% insertion into the carbonyl–aryl bond. In order to calculate a ρ value, the assumption was made that the rate of insertion into the carbonyl–methyl bond was constant; i.e., that the facility with which methyl migrates is independent of the nature of the aryl substituent. While evidence to support this hypothesis is lacking, it does allow a quantitative comparison of the rate of migration of the various aryl groups. In Figure 1 is plotted log k_{Ar}/k_{Me} vs. σ.[10] Upon the assumption that k_{Me} is invariant, this yields a ρ of −0.30 (root mean square error 0.066). However, this computation excludes *p*-ethoxyacetophenone, for which only a single product was detected (Table I). Since the point for the latter substance would fall well off Figure 1, a different mechanism (rate-determining step) perhaps applies. We regard the small ρ value recorded as a null result. The systematic errors embodied in the experimental design are sufficient to account for the deviation from $\rho = 0$. In any event, one should not lose sight of the fact that methyl migration in fact competes effectively with aryl participation in the product-determining step. We tentatively conclude that some other factor(s) than an inductive effect largely determines the position of insertion.

Analysis of Steric Factors. Since the preceding evidence failed to reveal a substantial inductive effect within the product-determining step, attention was directed to a systematic variation of steric factors. It was hoped that a limited

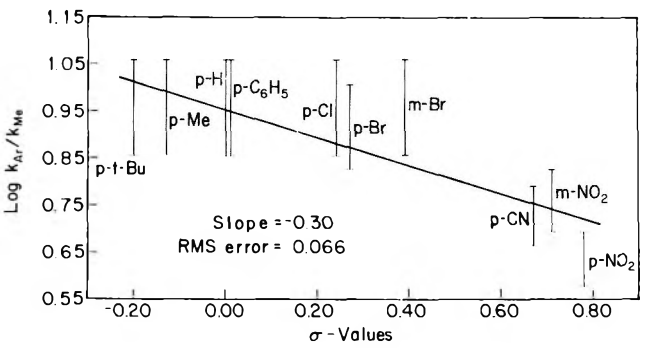


Figure 1. Log k_{Ar}/k_{Me} vs. σ for a series of substituted acetophenones.

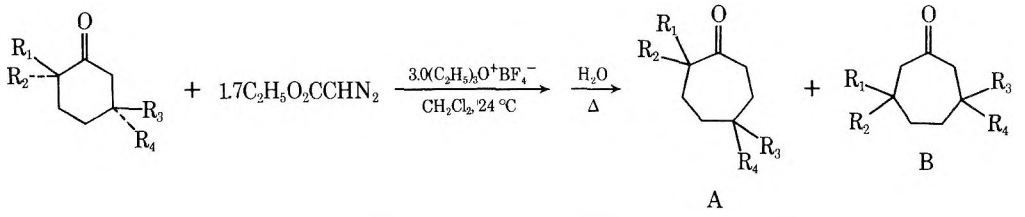
number of nonbonded interactions could be singled out as chiefly responsible for inducing the predominant direction of insertion. In order to facilitate interpretation, investigation was restricted to the conformationally well-defined cyclohexanone system.

A. Variation in the Vicinity of the Ketone. Product ratios (after hydrolysis and decarboxylation) from a series of 2-substituted cyclohexanones are recorded in Table II. The results are rather surprising, for the position of insertion is relatively insensitive to steric bulk adjacent to the carbonyl group. There is no obvious systematic variation within the series 2-methyl, 2-ethyl, 2-isopropyl, 2-*tert*-butyl, 2-phenyl, although in each case predominantly the $-CH_2-$ residue migrates. It might be hypothesized that the lack of a uniform transition among these examples should be attributed to variable amounts of axial substituent in the *reactive* conformation. However, 2,2-dimethylcyclohexanone (entry 6), in which both the axial and equatorial positions are occupied, did not give interpretationally different results. Furthermore, the isomers of menthone were examined. In the case of *trans*-2-isopropyl-5-methylcyclohexanone (entry 7), an equatorial isopropyl group may be assumed; the results are in accord with previous examples. With *cis*-2-isopropyl-5-methylcyclohexanone (entry 8), a substantial amount of the conformer with an axial isopropyl group has been postulated.[11] In this instance slightly less regioselectivity was noted, consistent with the hypothesis that an axial 2 substituent is sterically less significant than an equatorial one. However, the magnitude of the difference is scarcely convincing. Finally, in the case of norbornanone (entry 9, a particularly facile homologation, incidentally) no discrimination at all was noted between migration of CH_2C and CHC_2.

B. Variation in Catalyst. It seemed plausible that steric congestion involving the *O*-alkyl residue in the reactive intermediate carboxonium ion (eq 2) should contribute to product ratio determination. In Table III are the results of homologation of 2-methylcyclohexanone catalyzed by trimethyl-, triethyl-, and tripropyloxonium fluoroborates. It will be noted that no significant difference in the relative amounts of methylcycloheptanones is found. It should be observed that the steric requirements of these residues (methyl, ethyl, propyl) are likely too similar to allow an interpretation. Unfortunately, bulkier trialkyloxonium salts are unavailable. It can only be concluded that there is no evidence either indicating or disproving a substantial steric interaction at this site.

C. Variation in Diazo Ester. An equally plausible hypothesis is that nonbonded interactions between the *diazo ester* and various residues on the activated ketone are what determines product ratio. A strictly controlled variation in the steric requirements of the former moiety is not feasible. However, Table IV describes products obtained with 2-methylcyclohexanone and a series of diazo ester analogues,[3]

Table II. Products of Expansion of Substituted Cyclohexanones



Registry no.	Reactant[a] (R = H except as noted)	Reaction time, h	Intermediate keto esters total yield, %	Decarbethoxylation ratio (A:B)
583-60-8	1. $R_1 = CH_3$	4	72[b]	82:18
4423-94-3	2. $R_1 = C_2H_5$	14	94	80:20
1004-77-9	3. $R_1 = i\text{-}C_3H_7$	15	91	90:10
1728-46-7	4. $R_1 = t\text{-}C_4H_9$	19	~20[c]	73:27
1444-65-1	5. $R_1 = C_6H_5$	15	95	>95:5[d]
1193-47-1	6. $R_1 = CH_3$; $R_2 = CH_3$	19	39[c]	88:12
89-80-5	7. $R_1 = i\text{-}C_3H_7$; $R_4 = CH_3$	16	97	86:14
491-07-6	8. $R_1 = i\text{-}C_3H_7$; $R_3 = CH_3$	17	55	67:33
497-38-1	9. $R_1, R_3 = -CH_2-$ (norbornanone)	6[e]	92	51:49

[a] Standardized conditions (see Experimental Section). [b] Yield 96% at 0 °C (Table IV). [c] Incomplete conversion. [d] Only 2-phenylcycloheptanone detected. [e] Reaction temperature 0 °C instead of 24 °C.

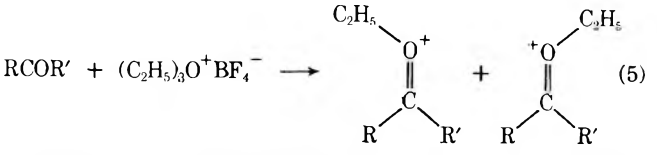
Table III. Expansion of 2-Methylcyclohexanone Catalyzed with Different Trialkyloxonium Salts

Catalyst[a]	Intermediate keto esters total yield, %	Decarbethoxylation ratio (2-CH_3:3-CH_3)[b]
1. $(CH_3)_3O^+BF_4^-$	96	83:17
2. $(C_2H_5)_3O^+BF_4^-$	96	85:15
3. $(n\text{-}C_3H_7)_3O^+BF_4^-$	97	81:19

[a] Conditions: 3.0 equiv of $R_3O^+BF_4^-$, 1.7 equiv of $C_2H_5O_2CCHN_2$, 0 °C, 3.5–4 h. [b] Cycloheptanone product.

listed in approximate order of their steric bulk. Diazoacetonitrile is a nearly symmetrical molecule (NNCHCN); perhaps significantly, it shows very little product discrimination. The probable increasing bulk in the series N_2CHCF_3, $N_2CHCO_2C_2H_5$, $N_2CHCO_2C(CH_3)_3$ results in progressively enhanced selectivity. Unfortunately, homologation of this ketone fails with dimethyl diazophosphonate, in which the substituent on the diazomethane reactant likely possesses greater steric requirements than in the latter three cases. While the evidence is less than convincing, an argument can be made that steric repulsions involving the carbethoxy group of ethyl diazoacetate (and corresponding group in analogues) are felt in the product-determining step of these homologations. This hypothesis will be developed in the Discussion.

D. Kinetic vs. Thermodynamic Control of Activation. Our deepest attempted divination of the mechanism of this reaction involves modification of the catalytic activation of the ketone. It has previously been established that the *rate-determining step* (as the homologation is normally conducted) is O-alkylation of the carbonyl group by triethyloxonum ion. In general, in the case of an unsymmetrical ketone this should result in a mixture of syn and anti intermediate carboxonium ion isomers (eq 5). We postulate (1) that these intermediates



should be formed in a *kinetically* determined ratio, (2) that their interconversion *may* be slow relative to the subsequent steps,[12] and (3) that the isomers *might* be expected to interact differently with ethyl diazoacetate in a *product-determining step* (to yield different diastereomer ratios; see Discussion). A test of these assumptions and their consequences has been devised.

We have also indicated that the intermediate carboxonium ions may be isolated in certain cases, using a more potent alkylating agent, and that they may subsequently be inserted into the reaction sequence. It is a reasonable proposition that if such an isolated carboxonium ion is allowed to equilibrate, it may form a *thermodynamic* distribution of syn and anti isomers, which differs from that obtained kinetically. Should the latter mixture (or perhaps single isomer) yield a different distribution of homologated products, then an inference may be drawn connecting the steric environment of the carboxonium ion with the product-determining step. Substances selected for such a test were acetophenone and norbornanone, which yield crystalline ions (e.g., upon alkylation with *O,O′*-dialkylformate hexachloroantimonate). The results are given in Table V. Comparison is drawn between the product ratios as the reaction is normally run, and ratios with independently generated (isolated) carboxonium ion. As previously indicated, with acetophenone no differences are noted between putative kinetically and thermodynamically controlled reactions. Likewise, in the case of norbornanone with O-ethylation yielding the reactive species, there is an insignificant shift in product isomer ratios ensuing from the manner of activation. It might be noted that these observations are independent of the counterion (BF_4^- or $SbCl_6^-$). The null results in these experiments neither confirm nor deny our postulates; i.e., the syn–anti ratios in the alkylation may be coincidentally invariant in the kinetic and thermodynamic instances, there may be rapid equilibration, etc.

However, in the third example (Table V) an experimentally significant difference is observed. With norbornanone and an *O-methyl* activating residue, a reversal in the major:minor isomer ratio is observed which is outside of error limits. We surmise the sought-after connection between syn–anti carboxonium ion ratio and homologation product. Steric interactions between diazoacetate and carboxonium ion in the bimolecular combination of these species (*following* the rate-determining step, O-alkylation), is product-*influencing* and may be exclusively product determining. In the Discussion we offer general speculations as to the details of these interactions. Even though the syn:anti ratio of an equilibrated solution of *O*-methylnorbornanone cation has been measured

Table IV. Expansions of 2-Methylcyclohexanone with Different Diazo Reagents, Yielding Substituted Methylcycloheptanones

Reactant[a]	Reaction time, h	Initial products,[b] total yield, %	Product isomer ratio (2-CH_3:3-CH_3)
1. N_2CHCN	5	89	53:47[c]
2. N_2CHCF_3	2.5	87	78:22[d]
3. $N_2CHCO_2C_2H_5$	4	96	85:15[d]
4. $N_2CHCO_2C(CH_3)_3$	4	92	88:12[d]
5. $N_2CHPO(OCH_3)_2$	>5	0[e]	

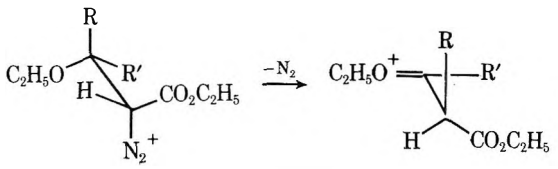
[a] Conditions: 1.7–2.5 equiv of N_2CHR, 3.0 equiv of $(C_2H_5)_3O^+BF_4^-$, 0 °C. [b] Homologated ketone, with CN, CF_3, etc. [c] Ratio of cyano ketones, determined directly (without hydrolysis and decarboxylation). [d] Ratio of methylcycloheptanones, after hydroysis and decarboxylation. [e] No keto phosphonate detected.

by NMR (FSO_3H solution, −68 °C, CH_3 syn to bridgehead is disfavored by 1:4;[13] SO_2 solution, 40 °C, ratio 1:3) there are too many variables to permit a justifiable fitting of the admittedly slight product differences to a particular model (for this single example—see Discussion, however). We are satisfied to claim, on the basis of present evidence, that a correlation probably exists between carboxonium ion stereochemistry and distribution of homologation products.

Discussion

In summary, our view of the mechanism of this homologation is as follows. A rate-determining O-alkylation of the ketone by triethyloxonium fluoroborate precedes a rapid coordination with ethyl diazoacetate. The diazonium ion thus formed probably loses nitrogen concertedly with alkyl or aryl migration to the incipient cationic site adjacent to the carbethoxy group. A new carbethoxycarboxonium ion is thus formed, which promptly yields an ethyl residue to some acceptor in the medium (eq 2). We should like to focus on the product-determining step, in an attempt to understand the unconventional distribution of homologation products in the cases of unsymmetrical ketones. It would appear that the position of insertion is not determined directly by the structure of the migrating group. Primary centers move in preference to secondary and tertiary centers in this cationic rearrangement, methyl competes effectively with phenyl, and the substituent effect in aryl migrations is small. These observations are consistent with a very early transition state for the rearrangement step, which is reasonable in that it avoids accumulation of positive charge adjacent to the carbethoxy group and is generally precedented in diazonium ion chemistry. Since other considerations tend to be excluded, we suggest that the *conformation* of the diazonium ion is that which determines the products of this reaction. We propose that analysis of nonbonded interactions provides a rationale for the stereoselectivities observed.

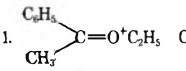
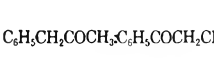
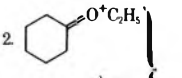
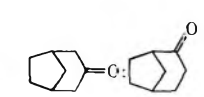
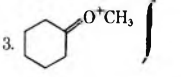
Even with the exclusive assumption of an antiperiplanar transition state for nitrogen expulsion–concerted rearrangement (eq 6), a number of conformations need to be considered



(6)

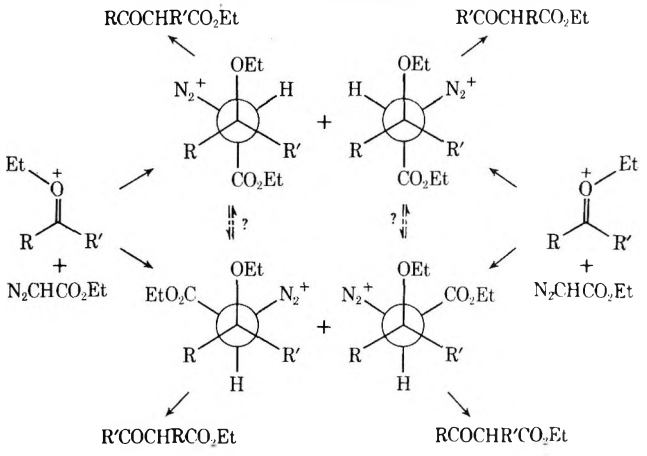
in the case of unsymmetrical ketones. As summarized in Scheme I, there should be syn and anti forms of the carboxonium ions, each of which may give rise to either of two diastereomeric diazonium ions, which individually may exist in either of two reactive conformations. The resulting four theoretically significant complexes may collapse to yield the observed two products as shown (Scheme I). Since either product may arise from either carboxonium ion via either

Table V. Ketone Homologation Ratios as a Function of Mode of Generation of Carboxonium Ion

Reactant (intermediate)	Decarbethoxylation product, ratio of homologated material (i) from isolated carboxonium ion[a] (ii) from in situ generated carboxonium ion[b]
1. 	 (i) 89:11, (ii) 89:11
2. 	 (i) 47:53, (ii) 49:51
3. 	(i) 58:42, (ii) 46:54

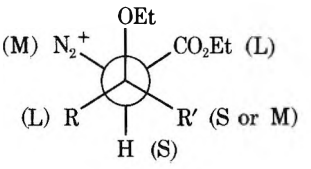
[a] Counterion: $SbCl_6^-$. [b] Counterion: BF_4^-.

Scheme I. Kinetically Significant Diazonium Ions



diastereomeric diazonium ion, the selection of a preferred reaction path to fit the observed product distribution may not be done unequivocally. However, the generalization may be made that partitioning between the diastereomeric diazonium ions (and hence population of the reactive conformations) *should* be a function of the syn–anti ratio of the original carboxonium ion. Therefore, the ultimate product distribution should in part be a function of the kinetically controlled alkylation of the ketone by triethyloxonium ion. Evidence consistent with this conclusion was cited in the Results section (*O*-methylnorbornanone cation).

It may then be further assumed that conformations which minimize gauche steric repulsions will be favored. Conventional small–medium–large (SML) analysis rationalizes preferred migration of the least bulky group. Of the four conformations in Scheme I, the least congested is **3**, which situates the largest substituents in an anti relationship. However, it should in general be accompanied by a diastereomer, for which



3

a clear conformational preference cannot be specified (pair of conformers on left, Scheme I). On the assumption that *conformation* controls migration (i.e., intrinsic differences in the activation energies for migration of various groups are small and the free energies of the transition states therefore correlate with conformational stabilities[4q] or, alternatively, the internal rotational barrier is greater than that for rearrangement), the expectation should be for both possible products with a predominance of insertion into the less substituted bond (3, C–R′). In other words, the larger of the ketone substituents, being preferentially gauche to the departing diazonium moiety, migrates least.

In support of this steric interpretation we would chiefly cite the regioselectivity trend exhibited with the diazo ester analogues (Table IV). Diazoacetonitrile (similar bulk of –C≡N, –N≡N) was indiscriminant, whereas the trifluoromethyl and carboxylate reactions gave greater specificities. It is troublesome, however, that all substituted cyclohexanones gave similar product distributions (Table II). Increasing bulk adjacent to the carbonyl should likewise produce enhanced selectivity. A reasonable rationalization of this noneffect may be found in the kinetically controlled syn–anti O-alkylation yielding the initial carboxonium ions. We postulate that bulky equatorial substituents direct the O-alkylation preferentially to the anti position. Not unreasonably, this could produce an internal steric *compensation*, such that the diastereomeric diazonium ions (all conformers) are produced in a ratio that yields a *roughly constant product isomer distribution.*

The foregoing has been a speculative interpretation, built largely on inference. We justify such conjecturing on the grounds that the peculiar pattern of regioselectivity demands some explanation before the mechanism of this reaction may be taken to be established. Several minor considerations were glossed over, which at least require acknowledgment. The most obvious deviation from our steric explanation is the acetophenones (Table I), in which the major product consistently results from aryl migration (factor of 9:1). However, it should be noted that in more hindered phenyl ketones a reversal does occur. In isobutyrophenone aryl migration is the minor reaction path.[3] The apparent relative ease of insertion into the carbonyl–phenyl bond may be a consequence of an intrinsically lower activation energy for aryl participation, as is well documented for genuine cationic rearrangements.[14] Alternatively, unique dispersion (London) forces between the diazoacetate moiety and the aromatic ring may preferentially favor conformations of the intermediate diazonium ion leading to the observed products. In discussion of the substituted cyclohexanones, a distinction was not drawn between equatorial or axial attack by diazoacetate upon the (chair conformation) carboxonium ion. Upon the assumption of competing pathways of diazo ester approach,[4n,o,t] yet another parameter is added to explain the puzzling 2-substituent effects.[15] For reasons of brevity we have not considered relevant literature examples of *diazomethane* (CH_2N_2) homologations.[4] Such reactions are experimentally not so clean (corrections for multiple expansions and by-products have not always been made) and regioselectivities are generally reduced in comparison, but a similarity of ketone substituent effects is noted for the most part.[4b,d-g,i,l,n-q] Although our conformational explanation requires some modification and supplementary assumptions, it may be similarly applied to many of these cases, as has been done in specific instances.[4r,u] For example, altered regioselectivity of diazoethane compared with diazomethane conforms to our interpretation.[4q] However, the substantially smaller steric demands of diazomethane (which occasionally gives moderate regioselectivity[4]) suggest that we should duly note the reservation that additional factors than those we have considered could be operative in diazo ester homologations. Nevertheless, the reactions are sufficiently different that our interpretation may stand on its own.

In conclusion, this mechanistic investigation was undertaken with the hope of developing a technique for improving or controlling the regioselectivity of the homologation. This has not materialized. However, the numerous examples which we describe provide an empirical guide to the expected isomer ratios for most synthetic applications. While unquantitative steric-factor explanations are notorious as the last refuge of the perplexed organic chemist, it does appear that nonbonded interactions provide the most plausible rationalization for the peculiar product distributions observed in the present instances. We suggest that the elaborateness of this investigation should encourage further application of the conformational control concept to other reaction mechanisms involving diazonium ion intermediates.

Experimental Section

General directions for carrying out homologations are presented in an accompanying article.[3] Full details for many of the experiments which cannot be described here are to be found in the Ph.D. Thesis of M.E.H.[1a]

Kinetic Measurements. Standard homologation conditions for cyclohexanone[2,3] were approximated, except that all of the ethyl diazoacetate was added initially. Progress of reaction was monitored by withdrawal of aliquots followed by quenching with ethanolic ferric chloride solution, with subsequent spectroscopic (583 nm) determination of keto ester concentration. Appropriate calibrations and adjustments of concentrations were carried out. In one set of experiments the concentration of only triethyloxonium fluoroborate was varied systematically from 2.5 to 1.75 to 1.0 equiv (relative to cyclohexanone). In the first case reaction was practically instantaneous (over in a few minutes); in the last case the reaction took several hours for completion (half consummated at ca. 60 min). Although smooth time and concentration dependencies were observed, no attempt to fit a rate expression was made. In a second set of experiments the concentration of ethyl diazoacetate was varied, with other parameters held constant. Reaction with 1.0 equiv was actually slightly faster than with 1.25 equiv, which in turn was faster than with 1.75 equiv. However, total (ultimate) conversion to keto ester was greater in the latter instances; apparently side reactions consume diazo ester. Although extent of conversion varied smoothly with time in all cases, fitting to a rate expression was deemed impractical. Nevertheless, there is clearly an apparent small *inverse* rate dependency upon ethyl diazoacetate concentration, which is perhaps associated with a base or solvent effect.[16] This phenomenon was not further investigated. However, a practical conclusion ensues; preparatively it is preferable to slowly add the diazo ester during the course of the reaction.

Substituted Acetophenones. The homologations listed in Table I were carried out under standardized conditions (100 ml of methylene chloride, 25 mmol of ketone, 1.7 equiv of ethyl diazoacetate, 3 equiv of triethyloxonium fluoroborate, 24 °C, 3-h reaction duration). Since the purpose of this study was to examine relative proportions of aryl and methyl migration (and this could not be determined directly with the keto esters in general) great care was taken in ensuring that total hydrolysis and decarboxylation was induced (by checking that product ratios did not vary under increasingly severe conditions of hydrolysis).[3] Details of the individual experiments and product characterization (involving preparative GLC where necessary) may be found elsewhere.[1a]

Substituted Cyclohexanones. For homologations listed in Table II, the critical experimental parameters are incorporated in the table. For the individual substances, the following notes apply (all final products fully characterized spectroscopically). (1) 2-Methylcyclohexanone, experimental procedure given previously.[3] (2) 2-Ethylcyclohexanone gave a keto ester mixture, bp 121–135 °C (4.5 mm), yielding (after decarbethoxylation and preparative GLC) 2-ethylcycloheptanone, semicarbazone mp 139–140 °C,[17] and 3-ethylcycloheptanone, semicarbazone mp 175–176 °C.[18] (3) 2-Isopropylcyclo-

hexanone gave a keto ester mixture, bp 91–96 °C (0.2 mm), yielding (after decarbethoxylation and preparative GLC) 2-isopropylcycloheptanone, semicarbazone mp 174–175 °C,[19] and 3-isopropylcycloheptanone. (4) 2-*tert*-Butylcyclohexanone gave a keto ester mixture indicating only partial conversion, bp 92–105 °C (0.4 mm), yielding (after decarbethoxylation and preparative GLC) 2- and 3-*tert*-butylcycloheptanones, identified by NMR (comparison with earlier examples). (5) 2-Phenylcyclohexanone gave apparently a single keto ester, bp 131–145 °C (0.1 mm), yielding 2-phenylcycloheptanone only, identified from published spectra[4b] and by deuterium exchange experiments. (6) 2,2-Dimethylcyclohexanone gave a keto ester mixture indicating only partial conversion, bp 83–90 °C (0.3 mm), yielding (after decarbethoxylation and preparative GLC) 2,2- and 3,3-dimethylcycloheptanone, distinguished by their NMR spectra ($-CH_2CO-$ integral). (7) *trans*-2-Isopropyl-5-methylcyclohexanone (menthone) gave a keto ester mixture, bp 85–96 °C (0.25 mm), yielding (after decarbethoxylation and preparative GLC) 2-isopropyl-5-methylcycloheptanone, 2,4-DNP derivative mp 105–107 °C,[20] and 3-isopropyl-6-methylcycloheptanone, 2,4-DNP derivative mp 88–93 °C (minor amount).[21] (8) *cis*-2-Isopropyl-5-methylcyclohexanone (isomenthone, contaminated with 10% menthone) gave a keto ester mixture indicating only partial conversion, bp 86–110 °C (0.2 mm), yielding (after decarbethoxylation and preparative GLC) 2-isopropyl-5-methylcycloheptanone, 2,4-DNP derivative mp 91–92 °C, and 3-isopropyl-6-methylcycloheptanone, 2,4-DNP derivative (amorphous) mp 52–56 °C. The respective cycloheptanone isomers obtained from menthone and isomenthone were spectrally identical; the disparity in derivative melting points is attributed to differing optical purities (which were not examined), and/or to cis–trans isomerism (certainly in the case of the 3,6 isomer and possibly in the case of the 2,5 isomer, which is susceptible to epimerization during hydrolysis and decarboxylation). A correction for the contaminating menthone is not incorporated in Table II. (9) Bicyclo[2.2.1]heptanone (norbornanone) gave a keto ester mixture, bp 69–82 °C (0.1 mm), yielding (after decarbethoxylation and preparative GLC) bicyclo[3.2.1]-octan-3-one, semicarbazone mp 190–191 °C,[22] and bicyclo[3.2.1]-octan-2-one, semicarbazone mp 170–172 °C.[23]

Homologation with Trimethyl- and Tripropyloxonium Fluoroborates.[24] Expansions of methylcyclohexanone were carried out with pure homologues of triethyloxonium fluoroborate. Insofar as possible conditions for the reactions were kept invariant; however, the insolubility of the trimethyloxonium salt resulted in a heterogeneous reaction mixture. Results are recorded in Table III.

Homologations with Diazo Ester Analogues. For the methylcyclohexanone expansions listed in Table IV, reaction conditions were as given for cyclohexanone in the accompanying article.[3] It might be noted that yields were uniformly higher in these cases (excepting fifth entry). For the individual substances the following notes apply (all final products fully characterized spectroscopically). (1) Diazoacetonitrile gave a mixture of 2-cyano-3-methyl- and 2-cyano-6-methylcycloheptanone, bp 67–71 °C (0.2 mm), directly separated by preparative GLC (ratio 47:53). (2) 2,2,2-Trifluorodiazoethane gave a mixture of expansion products (plus contaminants), bp 86–108 °C (55–60 mm), which could not be separated by GLC. Basic hydrolysis yielded the methylcycloheptanones as previously described.[3] (3) Ethyl diazoacetate, note that discrepancy from Table II is a consequence of reaction temperature. (4) *tert*-Butyl diazoacetate gave a mixture of keto esters, bp 73–76 °C (0.2 mm), yielding the corresponding methylcycloheptanones upon acid treatment ($CH_3C_6H_4SO_3H$, C_6H_6, 80 °C, 12 h).

Carboxonium Ion Isolation and Reaction. The O-alkylation products of acetophenone and norbornanone have been described.[7,13] As given under Results, a solution of *O*-ethylacetophenone hexachloroantimonate[7] in methylene chloride at 0 °C was treated dropwise with 5 equiv of ethyl diazoacetate. After 0.5 h, aqueous sodium bicarbonate workup yielded a much contaminated product which was submitted to acidic hydrolysis–decarboxylation directly. A mixture (19%) of phenylacetone and propiophenone (89:11) plus acetophenone was obtained.

An experimentally more convenient procedure was applied for preparation of the cations from norbornanone, as will be exemplified for O-methylation. A solution of 4.0 g (0.025 mol) of 2,2-dimethoxynorbornane in 15 ml of methylene chloride was cooled to −78 °C in a dry flask protected with a drying tube under a nitrogen atmosphere. To the magnetically stirred solution, 15 g (0.05 mol) of antimony pentachloride was added. After a few minutes, the dark reaction mixture was allowed to warm to room temperature and the precipitate (CH_3OSbCl_4?) which formed during the reaction was removed by filtration. The precipitate was discarded and 150 ml of carbon tetrachloride was added to the filtrate. Another precipitate was formed which was collected on a rigorously dried sintered glass funnel in a stream of dry nitrogen. The brownish solid was dried by passing dry nitrogen through the filter. The solid was identified from its NMR spectrum as *O*-methylnorbornanone hexachloroantimonate: NMR (SO_2) δ ca. 1.4 (m, 6), ca. 2.3 (m, 3), ca. 3.3 (m, 1), and 4.3 ppm (s, 3). The resonance at 4.3 ppm may be resolved into two singlets occurring in a ratio of ca. 3:1. A peak at slightly higher chemical shift is the predominant signal. In addition to the signals given, small (i.e., less than one proton) resonances were observed at 4.7 and 8.4 ppm, attributed to an unidentified impurity.

The hexachloroantimonate of *O*-methylnorbornanone was added to 100 ml of methylene chloride cooled to 0 °C in a dry flask protected with a drying tube under a nitrogen atmosphere. A solution of 5.2 g of ethyl diazoacetate in 5 ml of diethyl ether was rapidly added dropwise to the magnetically stirred solution. Nitrogen was rapidly evolved. After a total reaction period of 5 min, the reaction was quenched with 150 ml of saturated sodium bicarbonate. The precipitated antimony salt was removed and the aqueous layer was separated and washed twice with 25 ml of methylene chloride. The combined methylene chloride extract was dried over anhydrous magnesium sulfate, solvent was removed, and the residue was distilled at reduced pressure. After a forerun of 0.7 g of an unidentified product mixture, 1.0 g (20%, from the ketal) of keto ester was obtained, bp 75–87 °C (0.1 mm). The product was decarbethoxylated in the usual way; GLC analysis revealed bicyclo[3.2.1]octan-3-one and bicyclo[3.2.1]octan-2-one, ratio 58:42. The hydrolysis procedure also produced a small amount of white, acid-soluble material, which was not identified.

Homologation in the normal manner using trimethyloxonium fluoroborate gave a keto ester mixture (68%) yielding the same products in the ratio 46:54 (Table V). An analogous set of experiments involving O-ethylation yielded an essentially invariant product ratio (48:52 ± 1, see Tables II and V). In this case separate NMR signals from isomeric carboxonium ions were unobservable.

Acknowledgment. This work was partially funded through the National Science Foundation. Particular thanks are given to PPG Industries for financial support (to M.E.H.) and to the A. P. Sloan Foundation for a fellowship (to W.L.M.).

Registry No.—Ethyl diazoacetate, 623-73-4; triethyloxonium fluoroborate, 368-39-8; 2-isopropyl-5-methylcycloheptanone 2,4-DNP, 60705-58-0; 3-isopropyl-6-methylcycloheptanone 2,4-DNP, 60705-59-1; trimethyloxonium fluoroborate, 420-37-1; tripropyloxonium fluoroborate, 621-67-0; diazoacetonitrile, 13138-21-1; 2,2,2-trifluorodiazoethane, 371-67-5; *tert*-butyl diazoacetate, 35059-50-8; 2,2-dimethoxynorbornane, 10395-51-4; antimony pentachloride, 7647-18-9; *O*-methylnorbornanone hexachloroantimonate, 60705-61-5.

References and Notes

(1) (a) Taken from the Ph.D. Thesis of M. E. Hartman, Carnegie-Mellon University, 1972; *Diss. Abstr. Int. B*, **33**, 3553 (1973). (b) Address inquiries to Department of Chemistry, University of Illinois at Chicago Circle, Box 4348, Chicago, Ill. 60680.
(2) W. L. Mock and M. E. Hartman, *J. Am. Chem. Soc.*, **92**, 5767 (1970).
(3) W. L. Mock and M. E. Hartman, *J. Org. Chem.*, preceding paper in this issue.
(4) C. D. Gutsche and D. Redmore, "Carbocyclic Ring Expansion Reactions", Academic Press, New York, N.Y., 1968; (b) C. D. Gutsche, *J. Am. Chem. Soc.*, **71**, 3513 (1949); (c) C. D. Gutsche and H. H. Peter, *ibid.*, **77**, 5971 (1955); (d) C. D. Gutsche, H. F. Strohmayer, and J. M. Chang, *J. Org. Chem.*, **23**, 1 (1958); (e) H. O. House, E. J. Grubbs, and W. F. Gannon, *J. Am. Chem. Soc.*, **82**, 4099 (1960); (f) R. A. Barnes and W. J. Houlihan, *J. Org. Chem.*, **26**, 1609 (1961); (g) C. D. Gutsche and C. T. Chang, *J. Am. Chem. Soc.*, **84**, 2263 (1962); (h) E. Müller and R. Heischkeil, *Tetrahedron Lett.*, 1023 (1962); (i) C. Djerassi, B. F. Burrows, C. G. Overberger, T. Takekoshi, C. D. Gutsche, and C. T. Chang, *J. Am. Chem. Soc.*, **85**, 949 (1963); (j) J. N. Bradley, G. W. Cowell, and A. Ledwith, *J. Chem. Soc.*, 4334 (1964); (k) E. Müller, B. Zeeh, and R. Heischkeil, *Justus Liebigs Ann. Chem.*, **677**, 47 (1964); (l) E. Müller, H. Kessler, and B. Zeeh, *Fortschr. Chem. Forsch.*, **7**, 128 (1966); (m) C. D. Gutsche and J. E. Bowers, *J. Org. Chem.*, **32**, 1203 (1967); (n) R. G. Carlson and N. S. Behn, *ibid.*, **33**, 2069 (1968); (o) J. A. Marshall and J. J. Partridge, *ibid.*, **33**, 4090 (1968); (p) J. B. Jones and P. Price, *Chem. Commun.*, 1478 (1969); (q) N. J. Turro and R. B. Gagosian, *J. Am. Chem. Soc.*, **92**, 2036 (1970); (r) T. Gibson, *J. Org. Chem.*, **37**, 700 (1972); (s) M. A. McKinney and P. P. Patel, *ibid.*, **38**, 4059, 4064 (1973); (t) J. B. Jones and P. Price, *Tetrahedron*, **29**, 1941 (1973); (u) E. Volpi, F. D. Cima, and F. Pietra, *J. Chem. Soc., Perkin Trans. 1*, 703 (1974).
(5) H. Meerwein in Houben-Weyl, "Methoden der Organischen Chemie", Vol. VI, E. Müller, Ed., Georg Thieme Verlag, Stuttgart, 1965, p 359; H. Pest, "Oxonium Ions in Organic Chemistry", Academic Press, New York, N.Y., 1971, pp 70, 129; R. P. Quirk and C. R. Gambill, *J. Chem. Soc., Chem. Commun.*, 503 (1974).

(6) E. M. Arnett, R. P. Quirk, and J. J. Burke, *J. Am. Chem. Soc.*, **92**, 1260 (1970); E. M. Arnett, R. P. Quirk, and J. W. Larsen, *ibid.*, **92**, 3977 (1970).
(7) S. Kabuss, *Angew. Chem., Int. Ed. Engl.*, **5**, 675 (1966).
(8) This latter homologation in the presence of ether was more rapid than in the normal triethyloxonium catalyzed reaction, indicating kinetic competence for the proposed intermediate, as well as that $C_2H_5O_2CCHN_2$ competes effectively with $(C_2H_5)_2O$ as a nucleophile.
(9) D. J. Pasto and P. W. Wojtkowski, *Tetrahedron Lett.*, 215 (1970); *J. Org. Chem.*, **36**, 1790 (1971).
(10) We chose σ over σ^+ values, for reasons given by G. A. Olah, M. Tashiro, and S. Kobayashi, *J. Am. Chem. Soc.*, **92**, 6369 (1970). Our conclusion is not altered by choice of substituent constant scale.
(11) C. Djerassi, P. A. Hart, and C. Beard, *J. Am. Chem. Soc.*, **86**, 85 (1964).
(12) R. K. Lustgarten, M. Brookhart, and S. Winstein, *Tetrahedron Lett.*, 141 (1971). This work suggests a velocity of syn–anti interconversion which is at least an order of magnitude slower than the rate at which the carboxonium ion must be consumed by ethyl diazoacetate (see ref 1a for computation).
(13) A. Nickon and Y. Lin, *J. Am. Chem. Soc.*, **91**, 6861 (1969).
(14) W. E. Bachmann and J. W. Ferguson, *J. Am. Chem. Soc.*, **56**, 2081 (1934). On the other hand, semipinacol deamination gives results similar to our own: D. Y. Curtin and M. C. Crew, *ibid.*, **76**, 3719 (1954).
(15) Successful homologation of adamantanone (ref 3) demonstrates the feasibility of axial attack. For an exemplary study of reactivity in conformationally mobile cyclohexanones see D. C. Wigfield and D. J. Phelps, *J. Am. Chem. Soc.*, **96**, 543 (1974).
(16) K. Bott, *Tetrahedron*, **22**, 1251 (1966).
(17) V. A. Barkhash, G. P. Smirnova, and I. V. Machinskaya, *Zh. Obshch. Khim.*, **31**, 3197 (1962).
(18) T. Nozoe, T. Mukai, and S. Matsumoto, *Proc. Jpn. Acad.*, **27**, 110 (1951).
(19) I. Elphimoff-Felkin and Y. Gault, *C. R. Acad. Sci.*, **246**, 1871 (1958).
(20) E. Müller, W. Lürken, and M. Bauer, *Tetrahedron Lett.*, 775 (1962).
(21) T. M. Jacob and S. Dev, *J. Indian Chem. Soc.*, **34**, 327 (1957).
(22) W. Kraus, *Chem. Ber.*, **97**, 2719 (1964).
(23) D. M. Bailey, J. E. Bowers, and C. D. Gutsche, *J. Org. Chem.*, **28**, 610 (1963).
(24) T. J. Curphey, *Org. Synth.*, **51**, 142 (1971); H. Meerwein, E. Battenberg, H. Gold, E. Pfeil, and G. Willfang, *J. Prakt. Chem.*, **154**, 83 (1939).

The Mechanism of Amine-Catalyzed Halohydrin Formation from α-Chloro Ketones and Phosphonate Diesters

Bleecker Springs and Paul Haake*

Department of Chemistry, Wesleyan University, Middletown, Connecticut 06457

Received November 3, 1975

The formation of halohydrin in the triethylamine-catalyzed reaction of dimethyl phosphonate and chloroacetone was followed by NMR. In benzene the kinetics appear to be complex due to solvent effects and aggregation, and the results cannot be summarized by any simple rate law. The reaction in methanol is approximately first order in phosphonate and first order in triethylamine. The results suggest a rate-determining, tautomeric conversion of the phosphonate to the corresponding phosphite with rate law $v = 1.42 \times 10^{-2}\ M^{-1}\ s^{-1}$ [phosphonate][triethylamine].

The chemistry of bond formation between phosphorus and carbon is a significant problem; it underlies the synthesis of new structures which may be used to extend our knowledge of the chemistry of phosphorus, to furnish useful reagents for new synthetic methods, to investigate biologically important reactions through isosteric similarity to phosphates, and to provide medically useful drugs such as the antibiotic fosfomycin.[1-4] As part of our study on epoxyphosphonate synthesis, we have investigated the kinetics of formation of halohydrin phosphonates which are intermediates in some synthetic sequences.[1,5] The halohydrin **3** is formed by the base-catalyzed reaction of dimethyl phosphonate (**1**) and chloroacetone (**2**). This reaction (eq 1) was studied in methanol and

$$\underset{\mathbf{1}}{(MeO)_2P(O)H} + \underset{\mathbf{2}}{CH_3COCH_2Cl} \xrightarrow[CH_3OH \text{ or } C_6H_6]{(C_2H_5)_3N} \underset{\mathbf{3}}{(MeO)_2P(OOH)CH(CH_3)Cl} \quad (1)$$

benzene by observation of the changes in the C–CH_3 signals in ^1H NMR spectra which were taken as the reaction proceeded.

Experimental Section

Kinetics. *In solutions of methanol,* the appropriate concentration of dimethyl phosphonate and chloroacetone was prepared in a 5-ml volumetric flask. A 0.5-ml aliquot was injected into an NMR tube and spun in the probe for 5 min to bring it to constant temperature. To the NMR tube was then added the appropriate amount of triethylamine or buffer stock solution in methanol. The concentrations were corrected for total volume. The reaction was followed by the disappearance of the methyl singlet of chloroacetone, **2**, at τ 7.75 and the appearance of a doublet for the C–CH_3 in **3** (J_{PCCH} = 15 Hz) at τ 8.48.[5] The reaction was followed with a 50 Hz sweep width of the singlet and one peak of the doublet. The area under each peak was determined by multiplying the peak height by the width at half the height. The area of the singlet over the sum of the area of the singlet and two times the area of one doublet peak gives the fraction of chloroacetone remaining at that time.

For experiments in benzene, triethylamine was added neat. The rate was determined by relative *integrations* of the methyl peaks using a Varian A-60A spectrometer. The average result of three integrations was used with the time recorded in the middle of the second integration. For some runs the reaction was also followed by a 50 Hz sweep width and the above described calculation of area. Results from the two methods were in good agreement. All reactions appeared to proceed to completion based on NMR spectra.

Results

Treatment of Rates. Since we followed the concentration of chloroacetone (**2**), it was necessary to express the rate law in terms of **2**. In all reactions the concentration of chloroacetone was less than or equal to that of phosphonate, so the stoichiometry demands that

$$-d[2]/dt = k[2]^a([2] + \Delta)^b[(C_2H_5)_3N]^c \quad (2)$$

where $\Delta = ([1] - [2])$. The concentration of triethylamine remains constant because it is a catalyst. In methanol as solvent we found that when the rate law was reduced to

$$v = -d[2]/dt = k'([2] + \Delta) \quad (3)$$

and integrated to give

$$\ln([2] + \Delta) = -k't + \text{constant} \quad (4)$$

we could fit the observed data and we obtained the first-order rate constants in Table I. Therefore, in methanol the reaction is first order in phosphite and zero order in chloroacetone (Table I). Dividing the k' values in Table I by $[(C_2H_5)_3N]$ gave a constant value for a second-order rate constant (eq 5, 6)

Table I. Kinetics of Phosphonate Halohydrin Formation in Methanol

Reactants, M				
$[(MeO)_2P(O)H]$	$[CH_3CO\text{-}CH_2Cl]$	$[Et_3N]$	$10^4\,k'$, s^{-1}	$10^2\,k_1 = k'/[(C_2H_5)_3N]$, $M^{-1}\,s^{-1}$
1.28	1.28	2.55×10^{-2}	4.09	1.60
1.27	1.27	3.80×10^{-2}	5.42	1.42
1.28	1.28	5.11×10^{-2}	9.15	1.79
1.27	1.27	7.59×10^{-2}	12.05	1.59
1.28	1.28	2.55×10^{-2}	3.60	1.41
0.64	0.64	2.55×10^{-2}	3.70	1.45
2.56	2.56	2.55×10^{-2}	2.09	0.82
1.28	0.64	2.55×10^{-2}	3.45	1.35
1.28	0.64	2.55×10^{-2}	3.46	1.36
Buffered; $(C_2H_5)_3N/(C_2H_5)_3NH^+ = 1/1$				
1.28	1.28	2.55×10^{-2}	1.38	0.54
1.23	1.23	7.38×10^{-2}	3.83	0.52
1.23	1.23	7.38×10^{-2}	3.83	0.52

Table II. Kinetics of Phosphonate Halohydrin Formation in Benzene

Reactants, M				
$[(MeO)_2P(O)H]$	$[CH_3CO\text{-}CH_2Cl]$	$[Et_3N]$	$10^4\,k'$, s^{-1}	$k_1 = 10^4\,k'/[R_3N]$, $M^{-1}\,s^{-1}$
1.19	1.19	0.595	3.35	5.6
1.19	1.19	0.595	2.80	4.7
1.10	1.10	1.10	5.12	4.7
2.38	1.19	0.595	3.94	6.6
1.19	0.595	0.595	1.06	1.8
1.19	1.19	0.595	2.23	3.8
1.19	1.19	0.595	2.45	4.1
1.19	1.19	0.595	2.44	4.2
1.19	1.19	0.595	2.29	3.9
1.10	1.10	1.10	4.62	4.2
1.10	1.10	1.10	4.61	4.2
1.10	1.10	1.10	4.57	4.2
2.38	1.19	0.595	3.74	6.3
2.38	1.19	0.595	3.82	6.4
2.38	1.19	0.595	3.67	6.2
2.38	1.19	0.595	3.56	6.0

$$v = k_1[1][(C_2H_5)_3N] \quad (5)$$

$$k_1 = k'/[(C_2H_5)_3N] \quad (6)$$

with the exception of one run at high concentrations of phosphite and chloroacetone. The average value of k_1 is $1.42 \times 10^{-2}\ M^{-1}\ sec^{-1}$. The deviant value, $k_1 = 0.82 \times 10^{-2}\ M^{-1}\ s^{-1}$, is included in this average. Because of the poor temperature control and the speed of these reactions, considerable error is expected in the observed rate constants.

The kinetics in benzene were more complicated and did not appear to be simple first order in phosphite. Therefore, the data were treated without prejudice regarding the order of the reaction. Since $[(C_2H_5)_3N]$ is constant, any individual reaction will show total order = $a + b$ (eq 2). Reactions with $\Delta = 0$ were examined for total order; they plotted best as first order but there was curvature late in the reaction. We also determined $a + b$ directly by fitting [2] to a polynomial dependence on t using a computer program (Figure 1). Since $\Delta = 0$, eq 2 reduces to eq 7 and the log of eq 7 is eq 8.

$$-d[2]/dt = k[2]^{a+b} \quad (7)$$

$$\log(-d[2]/dt) = \log k + (a + b)\log[2] \quad (8)$$

The polynomial fit, [2] vs. t (eq 9), made it possible to evaluate $d[2]/dt$ (eq 10).

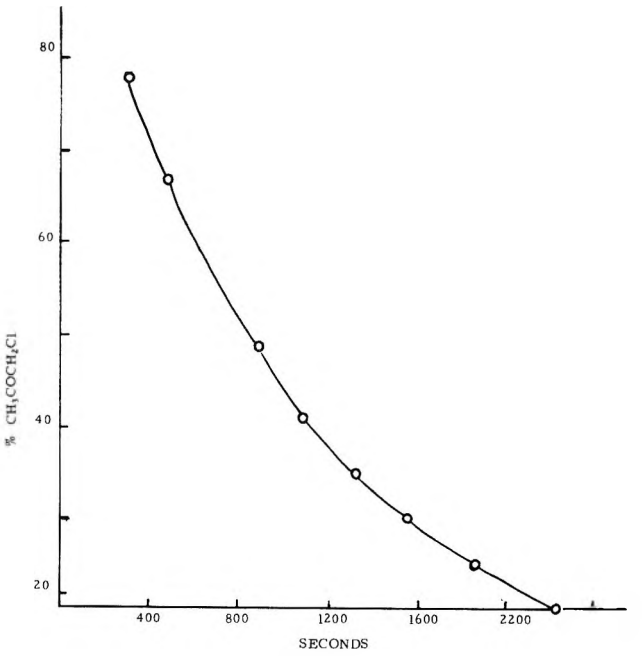


Figure 1. Plot of data for phosphonate halohydrin formation in benzene using a polynomial equation; the date points are circles and the line is the equation of the polynomial (eq 9).

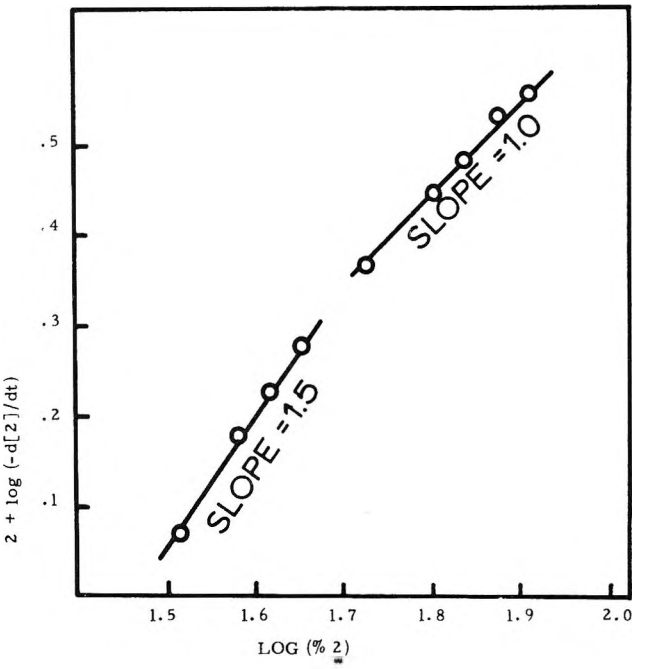


Figure 2. Graphical solution of eq 8.

$$[2] = 99.46 - 0.0802t + 0.294 \times 10^{-4}\,t^2 - 0.426 \times 10^{-8}\,t^3 \quad (9)$$

$$v = -d[2]/dt = 0.802 - 0.588 \times 10^{-4}\,t + 1.278 \times 10^{-8}\,t^2 \quad (10)$$

Graphical solution of eq 8 gives an initial slope (Figure 2) very close to 1.0. The points on Figure 2 were calculated for the times at which [2] was determined in the experiment. However, late in the reaction the order appears to increase. Therefore, in all runs, first-order rate constants were determined (eq 4) and appear in Table II.

Discussion

A very common method for synthesis of P–C bonds is nucleophilic attack of a tricoordinated phosphorus compound,

such as a phosphine or phosphite, on a reactive carbon compound. This mechanism is the basis of synthesis of phosphonium compounds and is the first step in the Arbuzov reaction in which a trialkyl phosphite is transformed into a dialkyl alkylphosphonate:

$$(RO)_3P: + R'X \longrightarrow (RO)_3\overset{+}{P}R'X^- \longrightarrow RX + (RO)_2\overset{O}{\overset{\|}{P}}R' \quad (11)$$

These nucleophilic reactions of trialkyl phosphites have been extensively studied.[2,3] With α-halo ketones, there are three possible products: phosphonate halohydrins, β-ketophosphonates (an Arbuzov reaction), and enolphosphates (the Perkow reaction[4]).

The compounds commonly referred to as dialkyl phosphites exist predominantly as the phosphonate tautomers, **1**; therefore, they are weakly acidic and have much less nucleophilicity than trialkyl phosphites, $(RO)_3P$.[2] In general, one can expect nucleophilic reactions of dialkyl phosphonates to proceed through the phosphite tautomer, **4**, or the phosphonate anion, **5** (eq 12).

$$\underset{\mathbf{4}}{(RO)_2\ddot{P}OH} \rightleftharpoons \underset{\mathbf{1}}{(RO)_2\overset{O}{\overset{\|}{P}}H} \rightleftharpoons \underset{\mathbf{5}}{(RO)_2PO^-} + H^+ \quad (12)$$

There has been considerable investigation on the reactions of the sodium salts of **5** which are formed by the reaction of sodium with **1**. In the reactions with α-halo ketones, three products are observable: epoxyphosphonates (probably formed through the halohydrin oxy anion[5]), β-ketophosphonates, and enol phosphates.[6]

Kinetics and Mechanism. This chemistry leads one to expect that the mechanism of the reaction we have studied would involve either base-catalyzed tautomerism of **1** into the phosphite tautomer (**4**) or formation of **5** as reactive intermediates. The observed first-order kinetics in [**1**] and the first-order dependence on triethylamine (eq 5, Table I) appear to confirm the scheme below in methanol:

$$\text{base} + \underset{\mathbf{1}}{(RO)_2\overset{O}{\overset{\|}{P}}H} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{\mathbf{4}}{(RO)_2\ddot{P}OH} \quad (13)$$

$$(RO)_2\ddot{P}OH + CH_3\overset{O}{\overset{\|}{C}}CH_2Cl \xrightarrow[\text{fast}]{k_2} (RO)_2\overset{O}{\overset{\|}{P}}-\underset{\displaystyle CH_2Cl}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}-OH \quad (14)$$

Since k_1 is not lowered by more than a factor of 3 in buffered solutions of triethylamine, the active intermediate cannot be the anion, **5**, the concentration of which would have to be proportional to $[CH_3O^-]$; there should be a large change in $[CH_3O^-]$ between unbuffered and buffered solutions. However, the comparison of k_1 in buffered and unbuffered solutions does indicate that in eq 13 both CH_3O^- and $(C_2H_5)_3N$ contribute to the rate. We expect that the pathway from **1** to **4** involves **5** as an intermediate.

In benzene, there is greater complexity. Increases of concentration of both **1** and **2** give increases in rate constants. Yet the reaction is first order in [**1**]. Two explanations seem possible. (1) Aggregation effects may be important. For example, either of the hydrogen-bonded complexes below might facilitate the reaction by increasing the rate of proton removal from **1**:

$$(CH_3O)_2\overset{H}{P}=O\cdots HCHC(O)CH_3 \quad (Cl) \qquad (CH_3O)_2\overset{H}{P}=O\cdots H-\overset{O}{\overset{\|}{P}}(OCH_3)_2$$

(2) The high concentrations of reactants can change the solvent character. Since both **1** and **2** are highly polar, they will contribute to a more polar medium and accelerate the reaction. The values of k_1 in benzene are roughly 1/100 of k_1 in methanol; this demonstrates the effect of solvent on rates and supports this explanation. The low rate constant at 0.595 M chloroacetone (Table II) and the high rate constants at 2.38 M phosphonate indicate that concentrations of both reactants affect the value of the first-order rate constant found in any individual run. The data in Table II support first-order dependence on triethylamine. In summary, we believe that the mechanism in eq 13 and 14 is followed in benzene but the observed rate is highly dependent on concentrations of reactants.

There are a number of other comments which may be relevant in this reaction: (1) The effect of competition between k_2 and k_{-1} on rates may explain some of the dependence of rates on concentration of reactants. (2) There may be other mechanisms for generation of **4** such as proton transfer in a dimer or polymer of **1**. (3) Although we expect this reaction to proceed by reaction with the chloro *ketone*, significant amounts of *enol* (**6**) should be present in both solvents and the keto $\rightarrow$ enol conversion will be catalyzed by R_3N. (4) In methanol, the chloro ketone will be partially in the form of the hemiketal (**7**) which will be unreactive.

$$\underset{\mathbf{6}}{CH_3-\overset{OH}{\overset{|}{C}}=CHCl} \rightleftharpoons 2 \rightleftharpoons \underset{\mathbf{7}}{CH_3-\underset{\displaystyle OCH_3}{\overset{\displaystyle OH}{\overset{|}{\underset{|}{C}}}}-CH_2Cl}$$

The insights gained from this investigation led us to devise a one-step synthesis of epoxyphosphonates.[1,5]

Acknowledgment. Part of this research was supported by a grant from Merck and Co., Inc. We thank a referee for a valuable, critical reading of an earlier draft.

Registry No.—**1**, 868-85-9; **2**, 78-95-5; **3**, 4185-83-5; Et_3N, 121-44-8.

References and Notes

(1) B. Springs, Ph.D. Thesis, Wesleyan University, 1975.
(2) (a) R. F. Hudson, "Structure and Mechanism in Organophosphorus Chemistry,", Academic Press, New York, N.Y., 1965, Chapters 4, 5; (b) A. J. Kirby and S. G. Warren, "The Organic Chemistry of Phosphorus", Elsevier, Amsterdam, 1967.
(3) S. Trippett, Ed., "Organophosphorus Chemistry", Vol. 1–5, The Chemical Society, London, 1970–1975, Chapter 5.
(4) F. W. Lichtenthaler, *Chem. Rev.*, **61**, 607 (1961).
(5) B. Springs and P. Haake, *J. Org. Chem.*, **41**, 1165 (1976); this paper includes additional NMR spectral data.
(6) (a) B. A. Arbuzov, V. S. Vinogradova, and N. A. Polezhaeva, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 41 (1959); (b) A. Meisters and J. M. Swan, *Aust. J. Chem.*, **18**, 168 (1965); (c) B. A. Arbuzov, V. S. Vinogradova, and N. A. Polezhaeva, *Dokl. Akad. Nauk SSSR*, **111**, 107 (1956); (d) B. A. Arbuzov in "Phosphoric Esters and Related Compounds", The Chemical Society, London, 1957, pp 47–55.

Catalysis of Reactions of *p*-Nitrobenzoyl Phosphate by Functional and Nonfunctional Micelles[1]

Clifford A. Bunton* and Michael McAneny

Department of Chemistry, University of California, Santa Barbara, California 93106.

Received August 30, 1976

Cationic micelles of cetyltrimethylammonium bromide (CTABr), $(n\text{-}C_{16}H_{33}N^+Me_2)_2(CH_2)_6\ 2Br^-$ (I), and $n\text{-}C_{16}H_{33}N^+Me_2CH_2CH_2OH\ Br^-$ (II) catalyze the spontaneous hydrolysis of *p*-nitrobenzoyl phosphate dianion by factors of up to 6, with little effect upon spontaneous hydrolysis of the monoanion. Nonfunctional micelles of CTABr and I catalyze attack of OH^- upon the dianion by factors of up to 10, but at high pH micelles of II are partially ionized and the zwitterion of II is an effective reagent. Choline is a more effective reagent than OH^- at high pH in the absence of surfactant. In micelles of CTABr *n*-octyloxyamine effectively deacylates *p*-nitrobenzoyl phosphate monoanion; and *n*-alkylamines, especially *n*-dodecylamine, react readily with the dianion. 1-Decylguanidinium bromide doubles the rate of attack of OH^- upon the dianionic substrate in CTABr, but it, and other guanidinium salts, have little effect on the other reactions.

The rate of hydrolysis of primary aryl phosphates ($RCOOPO_3H_2$ and their salts) in water or aqueous organic solvents is pH sensitive.[2-4] The reaction is acid catalyzed, and at pH >2 three reactions can be observed under appropriate conditions: (1) spontaneous decomposition of the monoanion with elimination of PO_3^-; (2) spontaneous decomposition of the dianion with elimination of PO_3^-, and (3) deacylation.

The relative importance of these reactions depends upon the substituents, and electron-withdrawing groups favor spontaneous reaction of the dianion over that of the monoanion.[4] Nucleophiles other than the lyate ion can attack either the mono- or dianion, and the rates of all these reactions should be affected by micelles.[5]

Micellar catalysis of reactions of phosphate esters has the following pattern: (1) the spontaneous decomposition of the dianion, but not the monoanion, of a monosubstituted phosphate ester is catalyzed by cationic micelles;[9,10] (2) attack of anionic nucleophiles upon di- and trisubstituted phosphate esters is catalyzed by cationic micelles and inhibited by anionic and nonionic micelles,[10,11] and (3) micelles of surfactants which contain nucleophilic or basic groups are good reagents toward di- and trisubstituted phosphate esters.[12,13] Deacylation of an acyl phosphate should be similar to reactions of carboxylic esters which are catalyzed by cationic micelles,[6-8] and functional mcelles are good reagents in this reaction.[6-8,14-16]

The aim of the present work was to compare micellar catalysis of reactions of *p*-nitrobenzoyl phosphate in the pH range 2–13 with that of uni- and bimolecular reactions of carboxylic and phosphoric esters and unimolecular decarboxylation.[17] Micelles can control reaction rates and products,[6-8,18-20] and our system is a model for acylation and phosphorylation,[2-4,21,22] and illustrates control of the mechanisms of reaction of acyl phosphates by a submicroscopic aggregate.

The surfactants were cetyltrimethylammonium bromide (CTABr), $n\text{-}C_{16}H_{33}N^+Me_3Br^-$; hexamethylenebis(hexadecyldimethylammonium) dibromide (I), $n\text{-}C_{16}H_{33}N^+Me_2(CH_2)_6N^+Me_2n\text{-}C_{16}H_{33}$, $2Br^-$; and hexadecyl(2-hydroxyethyl)dimethylammonium bromide (II), $n\text{-}C_{16}H_{33}N^+Me_2CH_2CH_2OH\ Br^-$. As nucleophiles we used *n*-alkylamines, 1-octyloxyamine, and hydroxide ion and the reactions were

$$ArCOOPO_3H^- \longrightarrow ArCO_2H + PO_3^-$$

$$\text{III} \xrightarrow{N} ArCON + Pi$$

$$ArCOOPO_3^{2-} \longrightarrow ArCO_2^- + PO_3^-$$

$$\text{IV} \xrightarrow{N} ArCON + Pi$$

$Ar = O_2N$–C$_6$H$_3$–; N = nucleophile

The hydroxyethyl moiety in II is a model for an enzymic serine residue.[12,15,16]

Experimental Section

Materials. *p*-Nitrobenzoyl phosphate was prepared as the dilithium salt from silver dihydrogen phosphate and *p*-nitrobenzoyl chloride by standard methods,[22] and the preparation and purification of the surfactants has been described.[11,12] 1-Octyloxyamine hydrochloride was prepared from benzohydroxamic acid and 1-bromooctane. After recrystallization (EtOH–EtOAc) it had mp 147–149 °C (lit.[23] 147–149 °C). 1-Decylguanidine hydrobromide was prepared from methylthioisourea hydrobromide and decylamine; after recrystallization (EtOH) and drying over P_2O_5 it had mp 64.5–66 °C. The picrate had mp 149–150 °C (lit.[24] 149–151 °C).

Kinetics. Reactions were followed spectrophotometrically at 265 nm, using a Gilford spectrophotometer with water jacketed cells at 25.0 °C. This wavelength gave the maximum absorbance changes during reaction, but because the absorbances of the substrate and *p*-nitrobenzoate ion are similar, the absorbance changes during reactions are small, ca. 0.08 absorbance units for 5×10^{-5} M substrate, and the 0.1 absorbance scale of the instrument was used. Runs were done in duplicate or triplicate and rate constants agreed within ±10%. The first-order rate constants, k_ψ, are in s^{-1} at 25.0 °C in water. The surfactants prevented use of the standard hydroxamic acid method of following the hydrolysis.[2-4]

Products. The products of hydrolysis and aminolysis of *p*-nitrobenzoyl phosphate were examined. The formation of *O*-octyl *p*-nitrobenzohydroxamate in the reaction of *p*-nitrobenzoyl phosphate (4×10^{-5} M) with 1.4×10^{-2} M 1-octyloxyamine in 0.02 M CTABr at pH 4.5 (0.02 M acetate buffer) was shown spectrophotometrically. The absorbance decreases at 268 nm and increase at 345 nm when the pH is increased to 12.5 (Figure 1) are typical of hydroxamate esters[25] including the *p*-nitrobenzoate, and the increase in absorbance at 345 nm corresponds to 90% conversion of *p*-nitrobenzoyl phosphate into hydroxamate ester. The hydroxamate ester and *p*-nitrobenzoic acid and their anions absorb at ca. 270 nm so this spectral region was not used for calculation of the product composition.

Reaction of *p*-nitrobenzoyl phosphate (1.5×10^{-4} M) with 4×10^{-3} M dodecylamine in 2×10^{-2} M CTABr and 0.001 M NaOH gave a mixture of *p*-nitrobenzoic acid and *N*-dodecyl *p*-nitrobenzamide, based on spectral and chromatographic evidence. After complete reaction the uv absorption was measured and the pH was then brought to 2. The absorbance maximum shifted from 270 to 262 nm as expected from the spectra of *p*-nitrobenzoic acid and its anion.[22b,26] The increase in absorbance was that expected for a concentration of *p*-nitrobenzoic acid of ca. 6.5×10^{-5} M. A sample of the original reaction mixture was then neutralized ($HClO_4$) and after addition of MeOH and $NaClO_4$ was extracted several times with hexane. The dried hexane layer had λ_{max} 255 nm, characteristic of *N*-dodecyl-*p*-nitrobenzamide,[26] and the absorbance corresponded to an amide concentration of ca. 9×10^{-5} M in the original reaction mixture. Thin layer chromatography, silica gel in $CHCl_3$–petroleum ether (bp 65–110 °C), 1:1, gave a spot, R_f 0.65, coincident with that of authentic amide.

Results and Discussion

Reactions in the Absence of Surfactant. The reactions were followed at 25.0 °C in three regions of pH: at pH 2 (dilute

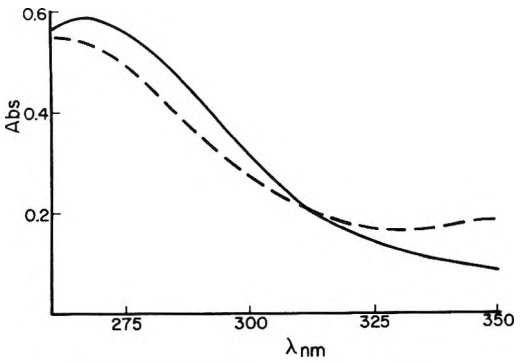


Figure 1. Uv spectra of the products of reaction of *p*-nitrobenzoyl phosphate monoanion with 1-octyloxyamine at pH 4.5 (solid line), and after pH increase to 12.5 (broken line).

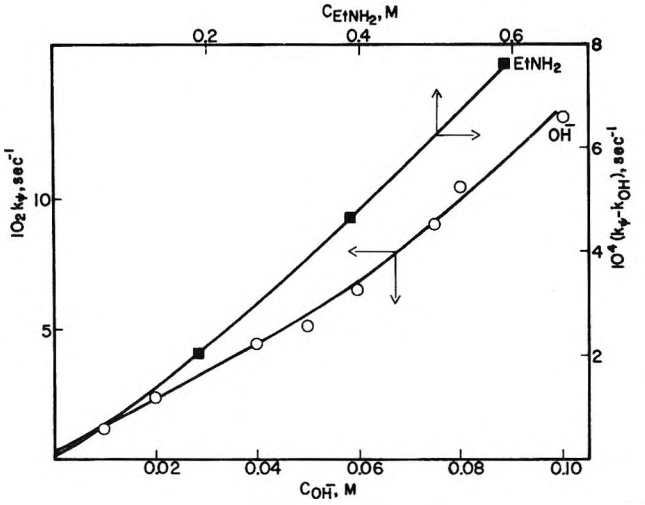


Figure 2. Reaction of *p*-nitrobenzoyl phosphate dianion with OH^- and $EtNH_2$ at 25.0.

Table I. Salt Effect upon Reactions of the Dianionic Substrate

Salt	$10^5 k_\psi$, s^{-1} [a]	Salt	$10^4 k_\psi$, s^{-1} [b]
	3.89		5.17
0.02 M $Me_3NCH_2CH_2OHCl$	4.57	0.08 M Me_4NCl	5.96
0.05 M $Me_3NCH_2CH_2OHCl$	4.62	0.016 M Me_4NCl	6.42
0.10 M $Me_3NCH_2CH_2OHCl$	4.70		

[a] At pH 8 in 1.25×10^{-2} M borate buffer. [b] In 0.05 M NaOH.

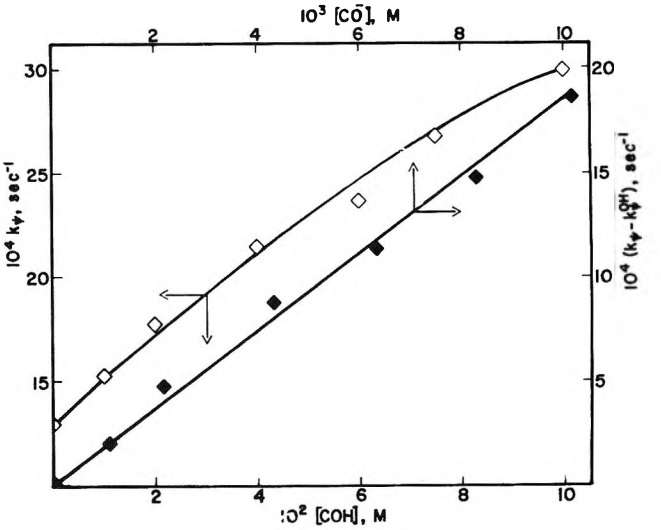


Figure 3. Reaction of *p*-nitrobenzoyl phosphate dianion with choline chloride at 25.0 °C, ◇; ◆, for reaction of zwitterion.

HCl) where the monoanion (III) is the bulk species, at pH 8.0 (1.25×10^{-2} M borate buffer) where the dianion (IV) is the bulk species, and in dilute alkali where the major reaction is attack of hydroxide ion upon the dianion.[2-4] The first-order rate constants in the absence of surfactant are, for the monoanion 3.80×10^{-5} s^{-1} and for the dianion 3.89×10^{-5} s^{-1}. Di Sabato and Jencks found the corresponding values to be 1.35×10^{-4} and 4.67×10^{-4} s^{-1} at 39 °C.[4] As is typical of these reactions of organic phosphates the activation energy is higher for hydrolysis of the dianion.[4,27]

Hydroxide ion attacks the carbonyl group, and the second-order rate constant (Figure 2) increases slightly with increasing hydroxide ion (initial value 9×10^{-3} M^{-1} s^{-1}), probably because there is a small positive salt effect as is found with Me_4NCl (Table I, cf. ref 28a).

Added amines attack the carbonyl group,[2,4] and our results for reaction of the dianion with ethylamine are in Figure 2. The concentrations of free amine and hydroxide ion were calculated from the total amine concentration and the pH of the solution (for $EtNH_2$ pK_a = 10.64). The second-order rate constants drift up slightly with increasing amine concentration, but the initial value of 10^{-3} M^{-1} s^{-1} is almost one-tenth that for reaction of OH^-. The upward drift in the second-order rate constants for reaction of amines has been ascribed to a general base catalysis,[4] although in some systems the rate varies linearly with amine concentration.[2] In many of these reactions it is necessary to separate the contributions of several independent reactions using dissociation constants and even when ionic strength is held constant, specific salt effects may complicate calculations of the individual rate constants.[28]

At pH 8.0 choline chloride has a small positive salt effect on hydrolysis of *p*-nitrobenzoyl phosphate dianion (Table I), but it is a very effective reagent at higher pH where the cholinate zwitterion is present (pK_a = 13.9 for choline[29]). The rate data are in Figure 3, where COH and CO^- denote choline and its zwitterion, respectively. The corrected first-order rate constants $k_\psi - k_\psi^{OH}$ (where k_ψ^{OH} is the first-order rate constant in the absence of choline) vary linearly with concentration of cholinate zwitterion and the second-order rate constant, $k_2 = 1.87 \times 10^{-2}$ M^{-1} s^{-1}, is larger than for reaction with hydroxide ion, as is found for reactions of triaryl phosphates,[12] triarylmethyl carbocations, and dihalonitrobenzenes.[30] The second-order rate constants for reactions in water are summarized in Table II.

Reactions of Mono- and Dianion (III and IV) in the Presence of Cationic Micelles. Hydrolysis of *p*-nitrobenzoyl phosphate monoanion at pH 2 ($k_\psi = 3.8 \times 10^{-5}$ s^{-1}) is slightly catalyzed by micelles of CTABr with $k_\psi = 5.36 \times 10^{-5}$ s^{-1} in both 0.025 and 0.05 M CTABr at 25.0 °C, although these micelles do not catalyze the hydrolysis of *p*-nitrophenyl phosphate monoanion.[9] Micellar effects should be small for reactions in which the transition state requires both proton transfer to the leaving aryloxy or carboxyl moiety and phosphorus–oxygen scission.

The spontaneous hydrolysis of the dianion is catalyzed by cationic micelles (Figure 4), as are the spontaneous hydrolyses of 2,4- and 2,6-dinitrophenyl phosphate dianions.[9] The values of k_ψ for hydrolysis of *p*-nitrobenzoyl phosphate dianion increase to plateaux values with increasing surfactant concentration as is typical of micellar catalyzed unimolecular reactions,[9,10,17,18] in contrast to the rate maxima which are gen-

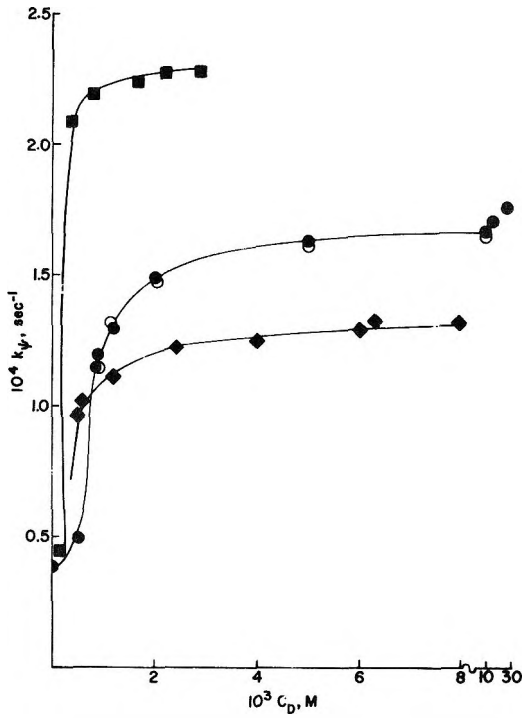
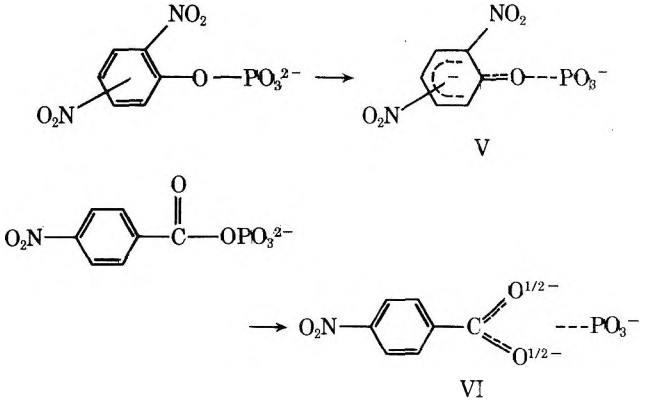


Figure 4. Micellar effects upon the spontaneous hydrolysis of *p*-nitrobenzoyl phosphate dianion at 25.0 °C. ●, CTABr; ■, I; ♦, II. The open points (○) are calculated values, eq 1.

erally found for micellar catalyzed bimolecular reactions.[6-8] These rate maxima and their significance are discussed in ref 6–8 and 31.

The micellar catalyses of several spontaneous hydrolyses and decarboxylations are compared in Table III. The rate enhancements for hydrolyses of the dinitrophenyl phosphate dianions are greater than for that of *p*-nitrobenzoyl phosphate dianion, although these reactions are formally very similar. Reduced solvation of the phosphate moiety in the substrate should increase the reaction rate,[4,27] and incorporation into a cationic micelle should both reduce this solvation and provide beneficial interactions between the cationic head groups of the micelle and the organic residue in the transition states V and VI.



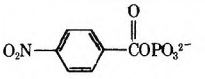
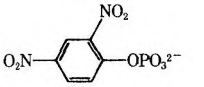
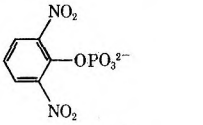
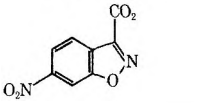
Aromatic compounds interact with both micellized and nonmicellized quaternary ammonium ions,[32,33] but the interactions should be stronger with a forming dinitrophenoxide ion with its delocalized charge than with a carboxylate ion with its localized charge. The micellar catalyses of decarboxylations of activated carboxylate anions are very much larger than those for hydrolysis of these dianionic organic phosphates (Table III) because of the strong interaction of the cationic head group of the surfactant with the carbanion-like transition state.[17] There is a similar pattern in the micellar catalyses of

Table II. Second-Order Rate Constants for Nucleophilic Attack upon the Dianion[a]

Nucleophile	Water	CTABr
OH^-	9×10^{-3}	77×10^{-3} [b]
$Me_3N^+CH_2CH_2O^-$	18.7×10^{-3}	
$EtNH_2$	10^{-3}	
$C_{12}H_{25}NH_2$		30×10^{-3} [c]

[a] Values of k_2, M^{-1} s^{-1} at 25.0 °C. [b] In 0.005 M CTABr and 0.01 M NaOH. [c] In 0.01 M CTABr.

Table III. Micellar Effects upon Spontaneous Reactions of Phosphate Dianions and Carboxylate Monoanions[a]

	Surfactant		
Substrate	CTABr	$(n\text{-}C_{16}H_{33}\text{-}N^+Me_2)_2\text{-}(CH_2)_6{\cdot}2Br^-$	$C_{16}H_{33}N^+\text{-}Me_2CH_2\text{-}CH_2OHBr^-$
	5	6	3.5
	21[b]		27[c]
	24[b]		
	95	400	90
$PhCH(CN)CO_2^-$ [d]	660		

[a] Values of k_{rel} compared with rate constant in the absence of surfactant. [b] Reference 9. [c] Reference 20. [d] Reference 17.

bimolecular reactions of phosphate and carboxylic esters and activated aryl halides.[6-8,11,30b]

The relation between rate constant and surfactant concentration for unimolecular micellar catalyzed and micellar inhibited reactions can be treated using a simple distribution model:[6-8,34]

$$S + D_n \overset{K}{\rightleftharpoons} SD_n$$
$$\downarrow k_w \qquad \downarrow k_m$$
$$\text{products}$$

where S is the substrate, D_n is the micelle of the surfactant (detergent) D, and k_w and k_m are the rate constants in the aqueous and micellar phases.

This scheme gives

$$k_\psi = [k_w + k_m K(C_D - \text{cmc})/N]/[1 + K(C_D - \text{cmc})/N] \quad (1)$$

where C_D is the surfactant concentration, cmc is the critical micelle concentration, and N is the aggregation number of the micelle.

Equation 1 can be rearranged to[11]

$$(k_\psi - k_w)/(k_m - k_\psi) = K(C_D - \text{cmc})/N \quad (2)$$

For the spontaneous reaction of the dianion in CTABr a plot of $(k_\psi - k_w)/(k_m - k_\psi)$ against C_D is linear (Figure 5), and the extrapolated value of cmc of 5×10^{-4} M is slightly lower than the literature value of 9×10^{-4} M for CTABr[35] probably because of substrate induced micellization.[11,36] The value of K/N

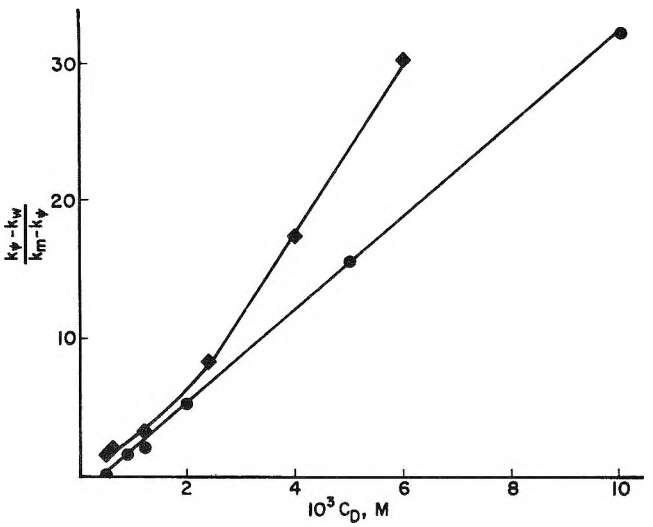


Figure 5. Estimation of association constants between *p*-nitrobenzoyl phosphate dianion and cationic micelles: ●, CTABr; ♦, hydroxyethyl surfactant (II).

Table IV. Salt Effects upon Reaction of the Dianion in CTABr[a]

Salt	C_{salt}, M	0.05	0.10	0.15
NaCl		1.26	1.08	0.97
NaBr		0.91	0.68	0.61

[a] Values of $10^4 k_\psi$ at 25.0 °C in 0.01 M CTABr at pH 8.0, in the absence of added salt $10^4 k_\psi = 1.7\ s^{-1}$.

is 3.4×10^3 and if N is ca. 60, and is unaffected by the substrate, K is ca. 2×10^5 and is similar to those of 1.1×10^5 and 3.9×10^4 for 2,4- and 2,6-dinitrophenyl phosphate dianions.[9] The values of k_ψ calculated using k_w, k_m, and K/N fit the experimental data (Figure 4).

Although we observe a plateau value of k_ψ for reaction in the presence of the hydroxyethyl surfactant (Figure 4), there is curvature in plots of $(k_\psi - k_w)/(k_m - k_\psi)$ against concentration of this surfactant (Figure 5). The intercept is close to zero surfactant concentration, suggesting that there is specific interaction between the dianionic substrate and the hydroxy group of II which should be a good hydrogen bonding donor.

We could not apply eq 1 and 2 to catalysis by the dicationic surfactant (I) because the rate reaches its plateau value at surfactant concentrations very close to the cmc (Figure 4) suggesting that the micelles bind the substrate very strongly.[11b] This surfactant is also a better catalyst than CTABr for spontaneous decarboxylation (Table III).

Added electrolytes typically reduce micellar catalysis by competing for the micelle with an ionic substrate,[6-8,37] and, so far as we know, unimolecular decarboxylations of carboxylate ions are the only exceptions to this generalization.[17] Added salts decrease the catalysis by CTABr of the spontaneous hydrolysis of *p*-nitrobenzoyl phosphate dianion (Table IV), and these salt effects follow the general pattern, with inhibition increasing with increasing hydrophobicity of the counterion to the surfactant.

Micellar Effects upon Reactions at High pH. Micelles of CTABr and the dicationic surfactant (I) speed the reaction of *p*-nitrobenzoyl phosphate dianion with hydroxide ion (Figure 6), as is general for deacylation.[6-8] The rate enhancements are small, even with micelles of I, probably because each anionic reagent hinders incorporation of the other into the Stern layer of the micelle. There is a problem in the

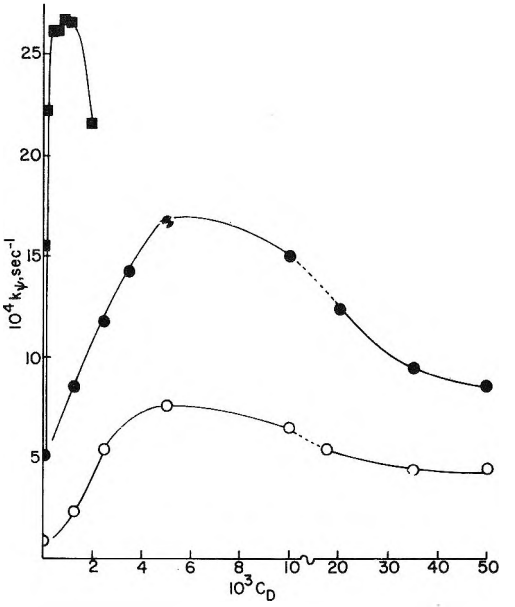


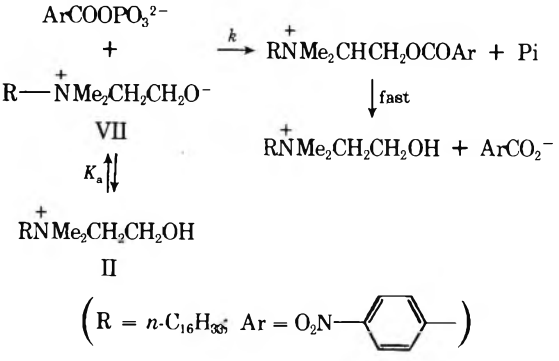
Figure 6. Effects of nonfunctional micelles on the reaction of *p*-nitrobenzoyl phosphate dianion at 25.0 °C: ○, 0.01 M OH^- in CTABr; ●, 0.05 M OH^- in CTABr; ■, 0.05 M OH^- in I.

distribution of ionic reagents between water and the micelle,[8,31,38] so that rate maxima are found in plots of k_ψ against surfactant concentration, and in CTABr the reaction is less than first order with respect to hydroxide ion.

These results for deacylation are similar to those for decomposition of *p*-nitrophenyl diphenyl phosphate and ethyl *p*-nitrophenyl phosphate monoanion, where nucleophilic attack was on the phosphoryl group.[12]

Attack by the alkoxide moiety in VII upon the acyl phosphate is shown in Scheme I, and the relation of rate to pH was analyzed, following the approach used for dephosphorylation.[12]

Scheme I



In Scheme I k is the first-order rate constant for reaction of VII with the substrate in the micelle. The kinetic form was treated making certain simplifying assumptions,[12] to give

$$k_m = \frac{kC_{OH^-}(K_a/K_w)}{1 + C_{OH^-}(K_a/K_w)} \qquad (3)$$

where k_m is the observed first-order rate constant when all the substrate is incorporated into the micelle. Some of the assumptions, for example, that ionization of the hydroxyl group of II does not materially decrease the hydroxide ion concentrations, are easily satisfied but others are less certain. For example, the value of K_w for water may not be applicable on the micellar surface, and we do not know the distribution of hydroxide ion between aqueous and micellar phases. Therefore the values of k and K_a, calculated using eq 3, are appar-

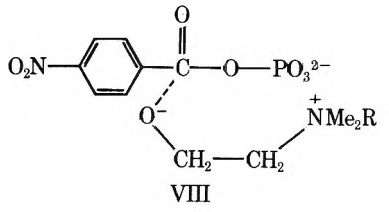
ent[12] but the value of K_a should be the same for reactions of different substrates in micellized II except for salt effects by the reagents, and we can test the relation between k_m and hydroxide ion concentration (eq 3) by using it for different reactions.

Equation 3 can be rewritten as

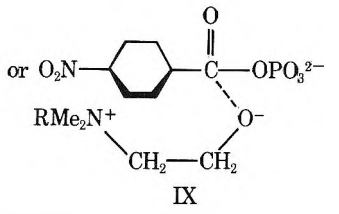
$$1/k_m = 1/k + K_w/kK_aC_{OH^-} \quad (4)$$

and a plot of k_m vs. $1/C_{OH^-}$ gives $k = 0.036\ s^{-1}$ and $pK_a = 12.1$ (this estimate is based on $K_w = 10^{-14}$). The value of pK_a agrees with that of 12.4 from reactions of di- and triaryl phosphates in the presence of micellized II,[12] and of 12.3 from reactions of 2,4-dinitrohalobenzenes.[30] These values of K_a and k lead to calculated rate constants which agree with the experimental values (Figure 7).

Catalysis by micelles of a functional surfactant is akin to the so-called "intramolecular catalysis" whose effectiveness is often measured by comparing the first-order rate constant for the intramolecular reaction with the second-order rate constant for the corresponding intermolecular reaction.[39] For reaction of hydroxide ion with p-nitrobenzoyl phosphate dianion $k_2 = 9 \times 10^{-3}\ M^{-1}\ s^{-1}$, so that our k value of $0.036\ s^{-1}$ corresponds to an effective hydroxide ion concentration of ca. 4 M. For the intermolecular reaction with cholinate zwitterion $k_2 = 1.9 \times 10^{-2}\ M^{-1}\ s^{-1}$, so that the k value corresponds to the hypothetical reaction rate in 2 M cholinate zwitterion suggesting that in both intermolecular and micellar reactions the quaternary ammonium ion center assists reaction by bringing together the substrate and the cholinate zwitterion or VII as in VIII or IX by interacting with anionic or aromatic



VIII



IX

residues in the transition state.[17,30b,32,33] Similar results were obtained in the reactions of the cholinate zwitterion with p-nitrophenyldiphenyl phosphate[12] and with carbocations and 2,4-dinitrohalobenzenes,[30] although in these systems the rate enhancements in micelles of II over the intermolecular reactions of OH^- and the cholinate zwitterion were much larger than those found here; e.g., for reactions in micelles of II the effective hydroxide ion concentrations were for p-nitrophenyldiphenyl phosphate, 8 M;[12] for 2,4-dinitrochlorobenzene, 410 M; and for 2,4-dinitrofluorobenzene, 170 M.[30b] These observations suggest that in the transition states for both deacylation and spontaneous hydrolysis the p-nitrobenzoyl moiety interacts less effectively with the cationic head groups than does an aryloxy or carbanion-like moiety,[12,17,30b] because negative charge is extensively delocalized into the aryl group in aromatic nucleophilic substitution, is less delocalized when a p-nitrophenoxide ion leaves a phosphoryl group, and is not delocalized into an aryl group in nucleophilic attack upon p-nitrobenzoyl phosphate.

Attack of II upon p-nitrobenzoyl phosphate dianion generates the p-nitrobenzoate but this compound, like other choline derived esters,[40] is very reactive in dilute alkali and undetectable under our reaction conditions.[41] (In 5×10^{-3} M II and 0.02 M NaOH $k_\psi = 12.5\ s^{-1}$ at 25.0 °C for the decomposition of the p-nitrobenzoate of II.[41]) However, an ether can be detected in the corresponding reactions of 2,4-dinitrohalobenzenes,[30b] and "burst" experiments have shown that acetylation of the hydroxyethyl moiety is the first step in the saponification of p-nitrophenyl acetate in micelles of a hydroxyethyl derived surfactant.[16,42]

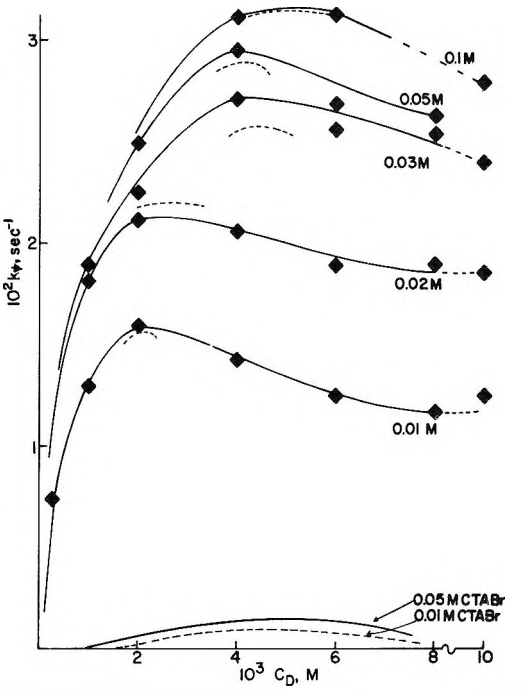


Figure 7. Reaction of p-nitrobenzoyl phosphate dianion with micelles of the hydroxyethyl surfactant (II), and CTABr at the indicated hydroxide ion molarities. The broken lines for II are calculated using eq 3.

All the evidence shows that micelles of hydroxyethyl derived surfactants related to II react as nucleophilic alkoxide ions, and proton loss is an equilibrium step and not concerted with making of the new bond.[12c] However, the magnitude of the micellar catalysis increases as the negative charge in the transition state is delocalized into an aryl group where it interacts favorably with the cationic head groups of the micelle.

Micellar Effects upon the Apparent pK_a of p-Nitrobenzoyl Phosphate. Added amines deacylate phosphates (ref 2, 4, and Figure 2), and, in the absence of surfactants, the various reactions can be separated using the dissociation constants of the amines and phosphates. The problem is more complicated for reactions in the presence of micelles which alter dissociation constants,[6-8,33,43] and complicate the use of buffers and the electrochemical determination of dissociation constants. We could not determine the dissociation constants of p-nitrobenzoyl phosphate spectrophotometrically, and therefore we used kinetic methods.

The hydrolysis of p-nitrobenzoyl phosphate was followed over a pH range in 0.01 M CTABr, where the substrate should be wholly in the micelles (Figure 4). At low pH the monoanion is the main reactant, and at high pH it is the dianion whose spontaneous hydrolysis is catalyzed by CTABr, and the midpoint value of k_ψ (Table V) corresponds to an apparent $pK_a = 4$ for the second dissociation in micelles of CTABr. (It is an apparent dissociation constant because we do not know the ionic distribution between water and the micelles.) In water at 39 °C $pK_a = 4.3$,[4] and a cationic micelle should decrease pK_a.[6-8,33,43]

Micellar Effects upon Amine Reactions. In order to examine attack of amine upon the monoanion in a micelle we

Table V. pH Dependence of the Hydrolysis of *p*-Nitrobenzoyl Phosphate[a]

pH	$10^4 k_\psi$, s^{-1}	pH	$10^4 k_\psi$, s^{-1}
1.0	0.54	4.0	1.21
2.0	0.54	4.5	1.51
2.5	0.60	5.0	1.70
3.5	0.81	8.0	1.76

[a] At 25.0 °C in 0.01 M CTABr; pH 1–2 in dilute HCl; pH 2.5–5 in 10^{-2} M acetate buffer; pH 8 in 1.25×10^{-2} M borate buffer.

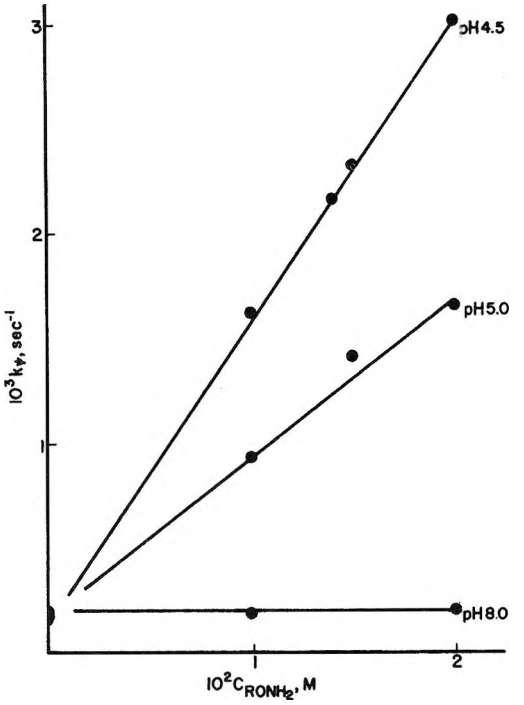


Figure 8. Reaction of 1-octyloxyamine with *p*-nitrobenzoyl phosphate monoanion in CTABr at 25.0 °C in 0.02 M CTABr. Buffers: pH 4.5 and 5.0 0.02 M acetate; pH 8.0 0.125 M borate.

needed an amine which is not extensively protonated at pH where the substrate is monoanionic, but we could not use aromatic amines which interfere with the spectrophotometric determination of reaction rate. Alkoxyamines are suitable reagents (for *n*-alkoxyamines pK_a = 4.6[44]), and we used octyloxyamine, which should be readily incorporated into micelles of CTABr. Alkoxyamines are α-effect nucleophiles, and they are often more nucleophilic than predicted by their basicity.[45]

The reaction was carried out at pH 4.5 in 0.02 M CTABr and 1.4×10^{-2} M octyloxyamine, where at least 90% of the product was hydroxamate ester (Experimental Section), and the first-order rate constant, $k_\psi = 2.17 \times 10^{-3}$ s^{-1}. This rate constant is approximately 14 times greater than that of hydrolysis under these conditions, $k_\psi = 1.55 \times 10^{-4}$ s^{-1}, in agreement with the product composition.

The first-order rate constants for reaction with octyloxyamine in CTABr are in Figure 8. The decreasing slopes of plots of k_ψ against oxyamine concentration with increasing pH show that nucleophilic attack upon *p*-nitrobenzoyl phosphate dianion is relatively unimportant. Under these conditions

$$k_\psi[S_T] = k'[S] + k''[S^{2-}] + k_N[S^-][RONH_2] \quad (5)$$

where S_T is stoichiometric substrate, k', k'' are first-order rate constants with respect to substrate mono- and dianion, respectively, and k_N is the second-order rate constant for nucleophilic attack.

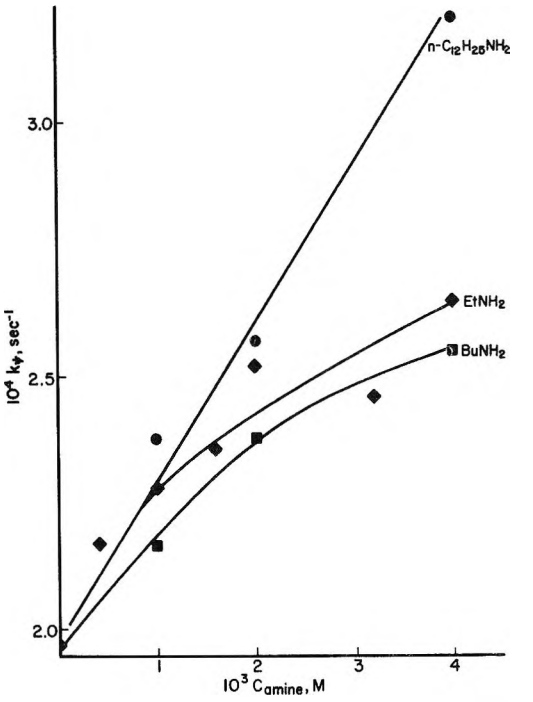


Figure 9. Micellar effects upon the reactions of *n*-alkylamines with *p*-nitrobenzoyl phosphate dianion at 25.0 °C in 0.02 M CTABr and 10^{-3} M NaOH.

Equation 5 can be simplified to

$$(k_\psi - k_0)[S_T] = k_N[S^-][RONH_2] \quad (6)$$

where k_0 is the first-order rate constant in the absence of alkoxyamine.

If K_N and K_s are respectively the ionization constants for octyloxyamine and the substrate *in the micelle* we can write

$$k_N = \frac{(k_\psi - k_0)([H^+] + K_N)([H^+] + K_s)}{K_N[H^+][N_T]} \quad (7)$$

The values of k_N and K_N in eq 7 can be estimated from the values of $k_\psi - k_0$ and K_s at pH 4.5 and 5 provided that k_N is independent of pH. Substituting the appropriate values from Figure 8 into eq 7 and simplifying gives

$$(K_N - 2.27 \times 10^{-5})(K_s - 2.27 \times 10^{-5}) = 1.77 \times 10^{-9} \quad (8)$$

The form of equation 8 is reasonable because both K_N and K_s must be greater or less than 2.27×10^{-5}, and we estimated pK_s = 4.0 in CTABr ($K_s = 10^{-4}$). Provided that we can use this value of K_s for comicelles of CTABr and octyloxyamine we calculate $K_N = 4.6 \times 10^{-5}$, i.e., pK_N = 4.34 (in water pK_N = 4.6[44]), and k_N = 10.1 M^{-1} s^{-1}. In this as in other reactions functional micelles or comicelles containing hydroxylamine moieties are very effective reagents at both carbonyl and phosphoryl centers.[14a,46] As a test of the assumption that there is no attack on the dianion and using eq 5, we calculate the following values of k_ψ at pH 8.0 in 0.02 M CTABr: with 0.014 M $C_8H_{17}ONH_2$, $10^3 k_\psi = 0.19$ s^{-1} (obsd 0.183) and with 0.0186 M $C_6H_{17}ONH_2$ 0.194 s^{-1} (obsd 0.198). Micelles of CTABr markedly catalyze the reaction of octyloxyamine so that at pH 4.5 and 5 it overwhelms the spontaneous hydrolyses of the mono- and dianions.

Although octyloxyamine does not attack the dianion even in CTABr, we can observe such a reaction by using more nucleophilic amines (Figure 9). In most micellar catalyzed reactions, first-order rate constants do not increase linearly with increasing reagent concentration[6-8,11,31,38] in part because the reagent is distributed between the micelles and bulk solvent.

Table VI. Effect of Decylguanidinium Bromide on Reactions of the Dianion[a]

pH	10^3 [$C_{10}H_{21}NHC(NH_2)_2$ Br], M	10^3 [CTABr], M	k_{rel}
8.0	4	2	0.96
8.0	4	4	0.98
10.6	15	40	0.86
12[b]	5	5	1.31
12[b]	7.5	7.5	1.57
12[b]	10.0	10.0	1.87
12[b]	10.4	10.4	2.05

[a] Values of k_{rel} to rate constant in the absence of decylguanidinium bromide at 25.0 °C. [b] 0.01 M NaOH.

But k_ψ increases linearly with amine concentration for reactions of dodecylamine with p-nitrobenzoyl phosphate dianion (and octyloxyamine with the monoanion), probably because of strong interactions between the cationic micelles and these hydrophobic nucleophiles. In low concentration ethyl-, butyl-, and dodecylamine have similar reactivities in CTABr solutions.

The second-order rate constant for reaction of dodecylamine with the dianion in CTABr is 3×10^{-2} M^{-1} s^{-1}, as compared with that of 10^{-3} M^{-1} s^{-1} for reaction of ethylamine in water. Dodecylamine could not be used in water, but it should have a similar reactivity to ethylamine, and this 30-fold rate enhancement of amine attack by micellized CTABr is considerably larger than that for attack of hydroxide ion (Table II and Figure 6). This difference could be due to the greater micellar incorporation of dodecylamine as compared with hydroxide ion, and the absence of electrolyte effects. In water hydroxide ion is considerably more reactive than ethylamine toward the dianion (Figure 2).

Effects of Alkylguanidinium Ions. Guanidinium moieties modify the biological properties of organic phosphates,[24] and we hoped that guanidinium salts would affect micellar reactions of p-nitrobenzoyl phosphate by hydrogen bonding to the phosphate group,[47] and assisting nucleophilic attack at carbonyl or phosphoryl groups. Such assistance would be similar to that of alkaline earth cations which catalyze neutral and basic hydrolysis probably by coordinating with the phosphate group.[2,4,22a] Guanidinium ion should also hinder spontaneous dephosphorylation. Relatively low concentrations of guanidinium halides were used because they could have a negative salt effect and disrupt the micelles by perturbing water structure. In CTABr decylguanidinium bromide slightly hinders spontaneous hydrolysis of p-nitrobenzoylphosphate dianion, but it assists attack of hydroxide ion (Table VI). The guanidinium salts generally inhibited the reactions with octyloxyamine and functional micelles of II (Table VII), by the usual salt effect or by disrupting the micelles. Decylguanidinium bromide should comicellize and deactivate octyloxyamine or the zwitterion (VII) by hydrogen bonding which would offset any rate assistance by hydrogen bonding to p-nitrobenzoyl phosphate.

Relation between Micellar Catalysis and Substrate Structure. Micelles assist bimolecular reactions by bringing reactants together into a small volume element and in a medium in which they can react, and it is difficult to separate the "concentration" and "medium" effects.[6-8,31] But for unimolecular reactions, only the second effect is important once the substrate is brought into the micelles, and as we noted earlier the catalysis is greatest when a localized charge in the initial state is delocalized in the transition state.[17] The quaternary ammonium ion in a cationic micelle can be regarded as a very soft acid which interacts best with a soft base,[48] e.g., better with a delocalized carbanion than with a carboxylate ion, and these principles should also apply to micellar catalyzed bimolecular reactions. It is difficult to compare data obtained under different conditions, but it appears that micellar catalysis is greater for reactions in which anionic attack generates transition states with a highly delocalized charge, as compared with those having their charge localized on oxygen atoms. For example, micellar catalysis appears to be smaller for reactions in which small anions attack acyl or phosphoryl centers than for those in which attack is on an aromatic moiety,[6-8,38,50] even under conditions in which reaction occurs wholly in the micelles.

Table VII. Effect of Guanidinium Salts on Reactions of Mono- and Dianionic Substrate[a]

Salt	Reagent: 0.02 M $C_8H_{17}ONH_2$[b]	Reagent: 0.008 M $C_{16}H_{33}N^+Me_2CH_2CH_2O$-HBr$^-$[c]
0.02 M $(NH_2)_3CCl$	0.95	
0.04 M $(NH_2)_3CCl$		0.66 (0.81)
0.08 M $(NH_2)_3CCl$	0.90	
0.02 M MeNHC-$(NH_2)_2Cl$	1.04	
0.04 M MeNHC-$(NH_2)_2Cl$		0.55 (0.80)
0.08 M MeNHC-$(NH_2)_2Cl$	0.64	
0.04 M $C_{10}H_{21}NHC$-$(NH_2)_2Br$		1.04
0.1 M $C_{10}H_{21}NHC$-$(NH_2)_2Br$	0.45	

[a] Values of k_{rel} compared with rate constant in the absence of the guanidinium salt. [b] pH 4.5 and 0.02 M CTABr. [c] At pH 10.6; the values in parentheses are at pH 8.3.

Registry No.—I, 15590-96-2; II, 20317-32-2; IV, 60646-46-0; CTABr, 57-09-0.

References and Notes

(1) Support of this work by the Arthritis and Metabolic Diseases Institute of the U.S. Public Health Service is gratefully acknowledged.
(2) D. E. Koshland, *J. Am. Chem. Soc.*, **73**, 4103 (1951); **74**, 2286 (1952).
(3) D. R. Phillips and T. H. Fife, *J. Am. Chem. Soc.*, **90**, 6803 (1968).
(4) S. DiSabato and W. P. Jencks, *J. Am. Chem. Soc.*, **83**, 4395, 4400 (1961).
(5) For discussions of micellar catalysis and inhibition see ref 6-8.
(6) (a) E. H. Cordes and C. Gitler, *Prog. Bioorg. Chem.*, **2**, 1 (1973); (b) E. H. Cordes, Ed., "Reaction Kinetics in Micelles", Plenum Press, New York, N.Y., 1973.
(7) E. J. Fendler and J. H. Fendler, *Adv. Phys. Org. Chem.*, **8**, 271 (1970).
(8) C. A. Bunton, *Prog. Solid State Chem.*, **8**, 239 (1973).
(9) C. A. Bunton, E. J. Fendler, L. Sepulveda, and K-U. Yang, *J. Am. Chem. Soc.*, **90**, 5512 (1968).
(10) G. J. Buist, C. A. Bunton, L. Robinson, L. Sepulveda, and M. Stam, *J. Am. Chem. Soc.*, **92**, 4072 (1970).
(11) (a) C. A. Bunton and L. Robinson, *J. Org. Chem.*, **34**, 773 (1969); (b) C. A. Bunton, L. Robinson, J. Schaak, and M. J. Stam, *ibid.*, **36**, 2346 (1971).
(12) (a) C. A. Bunton, L. Robinson, and M. Stam, *J. Am. Chem. Soc.*, **92**, 7393 (1970); (b) C. A. Bunton and L. G. Ionescu, *ibid.*, **95**, 2912 (1973); (c) C. A. Bunton and S. Diaz, *J. Org. Chem.*, **41**, 33 (1976).
(13) J. M. Brown, C. A. Bunton, and S. Diaz, *J. Chem. Soc., Chem. Commun.*, 971 (1974).
(14) (a) I. Tabushi, Y. Kuroda, and S. Kita, *Tetrahedron Lett.*, 643 (1974); (b) R. A. Moss, R. C. Nahas, S. Ramaswami, and W. J. Sanders, *ibid.*, 3379 (1973); P. Heitman, R. Husung-Bublitz, and H. J. Zunft, *Tetrahedron*, **30**, 4137 (1974).
(15) G. Meyer, *Tetrahedron Lett.*, 4581 (1972); V. Gani, C. Lapinte, and P. Viout, *ibid.*, 4435 (1973); M. Chevion, J. Katzhendler, and S. Sarel, *Isr. J. Chem.*, **10**, 975 (1972).
(16) K. Martinek, A. V. Levashov, and I. V. Berezin, *Tetrahedron Lett.*, 1275 (1975).
(17) C. A. Bunton, M. J. Minch, J. Hidalgo, and L. Sepulveda, *J. Am. Chem. Soc.*, **95**, 3262 (1975); C. A. Bunton, A. Kamego, and M. J. Minch, *J. Org. Chem.*, **37**, 1388 (1972); C. A. Bunton, A. Kamego, M. J. Minch, and J. L. Wright, *ibid.*, **40**, 1321 (1975).
(18) E. J. Fendler and J. H. Fendler, *J. Org. Chem.*, **33**, 3852 (1968); E. J. Fendler, R. R. Liechti, and J. H. Fendler, *ibid.*, **35**, 1658 (1970); J. H. Fendler, E. J. Fendler, and L. W. Smith, *J. Chem. Soc., Perkin Trans. 2*, 2097 (1972).
(19) C. A. Bunton, A. A. Kamego, and P. Ng, *J. Org. Chem.*, **39**, 3469

(1974).
(20) C. A. Bunton, S. Diaz, J. M. Hellyer, Y. Ihara, and L. G. Ionescu, *J. Org. Chem.*, **40**, 2313 (1975).
(21) H. R. Mahler and E. H. Cordes, "Biological Chemistry", 2d ed, Harper and Row, New York, N.Y., 1971, p 383.
(22) (a) F. Lipmann and L. C. Tuttle, *J. Biol. Chem.*, **153**, 571 (1944); (b) G. Ramponi, C. Treves, and A. Guerritore, *Arch. Biochem. Biophys.*, **115**, 129 (1966).
(23) P. Mamalis, J. Green, and D. McHale, *J. Chem. Soc.*, 229 (1960).
(24) B. C. Pressman, *J. Biol. Chem.*, **238**, 401 (1963).
(25) O. Exner and J. Holubek, *Collect. Czech. Chem. Commun.*, **30**, 941 (1965).
(26) H. C. Brown, D. H. McDaniel, and O. Hafliger in "Determination of Organic Structures by Physical Methods", E. C. Braude and F. C. Nachod, Ed., Academic Press, New York, N.Y., 1955.
(27) A. J. Kirby and A. G. Varvoglis, *J. Am. Chem. Soc.*, **89**, 413 (1967); C. A. Bunton, E. J. Fendler, and J. H. Fendler, *ibid.*, **89**, 1221 (1967).
(28) (a) C. A. Bunton, S. J. Farber, and E. J. Fendler, *J. Org. Chem.*, **33**, 29 (1968); (b) C. A. Bunton and S. K. Huang, *J. Am. Chem. Soc.*, **94**, 3436 (1972); M. J. Postle and P. A. H. Wyatt, *J. Chem. Soc., Perkin Trans. 2*, 474 (1972); (c) P. Salomaa, A. Kankaanpera, and M. Lahti, *J. Am. Chem. Soc.*, **93**, 2084 (1971).
(29) R. M. C. Dawson, D. C. Elliott, W. H. Elliott, and K. M. Jones, "Data for Biochemical Research", Clarendon Press, Oxford, 1959.
(30) (a) C. A. Bunton and C. H. Paik, *J. Org. Chem.*, **41**, 40 (1976); (b) C. A. Bunton and S. Diaz, *J. Am. Chem. Soc.*, **98**, 5663 (1976).
(31) (a) C. A. Bunton and B. Wolfe, *J. Am. Chem. Soc.*, **95**, 3742 (1973); (b) A. K. Yatsimirski, K. Martinek, and I. V. Berezin, *Tetrahedron*, **27**, 2855 (1971).
(32) E. M. Arnett, M. Ho, and L. L. Schaleger, *J. Am. Chem. Soc.*, **92**, 7039 (1970); E. F. J. Duynstee and E. Grunwald, *Tetrahedron*, **21**, 2401 (1965); J. Gordon, J. C. Robertson, and R. L. Thorne, *J. Phys. Chem.*, **74**, 957 (1970); J. W. Larsen and L. J. Magid, *ibid.*, **78**, 834 (1974); *J. Am. Chem. Soc.*, **96**, 5774 (1974).
(33) C. A. Bunton and M. J. Minch, *J. Phys. Chem.*, **78**, 1490 (1974).
(34) F. M. Menger and C. E. Portnoy, *J. Am. Chem. Soc.*, **89**, 4968 (1967).
(35) P. Mukerjee and K. J. Mysels, "Critical Micelle Concentrations of Aqueous Surfactant Systems", National Bureau of Standards, Washington, D.C., 1971.
(36) T. C. Bruice, J. Kazhendler, and L. R. Fedor, *J. Am. Chem. Soc.*, **90**, 1333 (1968); R. J. Williams, J. N. Phillips, and K. J. Mysels, *Trans. Faraday Soc.*, **51**, 728 (1955).
(37) C. A. Bunton in ref 6b, p 73.
(38) C. A. Bunton and L. Robinson, *J. Am. Chem. Soc.*, **90**, 5972 (1968).
(39) (a) T. C. Bruice and S. J. Benkovic, "Bioorganic Chemistry", W. A. Benjamin, New York, N.Y., 1966, Chapter 1; (b) W. P. Jencks, "Catalysis in Chemistry and Enzymology", McGraw-Hill, New York, N.Y., 1969, Chapter 1.
(40) J. J. Zimmerman and J. E. Goyan, *J. Med. Chem.*, **13**, 492 (1970).
(41) C. A. Bunton and M. McAneny, *J. Org. Chem.*, **41**, 36 (1976).
(42) It was necessary to use an excess of substrate in these "burst" experiments,[16] so that the situation was different from those generally used in studies of micellar catalysis where the surfactant concentration is much greater than that of the substrate.[6-8]
(43) M. T. A. Behme and E. H. Cordes, *J. Am. Chem. Soc.*, **87**, 260 (1965); C. A. Bunton and L. Robinson, *J. Phys. Chem.*, **73**, 4237 (1969); **74**, 1062 (1970).
(44) T. C. Bissot, R. W. Perry, and W. H. Campbell, *J. Am. Chem. Soc.*, **79**, 796 (1957); W. P. Jencks, *ibid.*, **80**, 4581 (1958).
(45) J. E. Dixon and T. C. Bruice, *J. Am. Chem. Soc.*, **93**, 3248, 6592 (1971); 2052 (1972); cf. C. D. Ritchie, *ibid.*, **97**, 1170 (1975).
(46) Y. Ihara, unpublished results.
(47) For discussion of hydrogen bonding by the guanidinium ion see ref 39b, Chapter 6.
(48) For discussion of the hard–soft classification of reagents see ref 49.
(49) R. G. Pearson and J. Songstad, *J. Am. Chem. Soc.*, **89**, 1827 (1967).
(50) C. A. Bunton and L. Robinson, *J. Am. Chem. Soc.*, **92**, 356 (1970); J. Baumrucker, M. Calzadilla, M. Centeno, G. Lehrmann, M. Urdaneta, P. Lindquist, D. Dunham, M. Price, B. Sears, and E. H. Cordes, *ibid.*, **94**, 8164 (1972).

Reaction of Saturated (5α- and 5β-) 19-Hydroxy Steroids with Mixed Phosphorus and Halogen Containing Reagents[1a]

Enzo Santaniello[1b] and Eliahu Caspi*

The Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts 01545

William L. Duax* and Charles M. Weeks

Medical Foundation of Buffalo, Buffalo, New York 14203

Received July 6, 1976

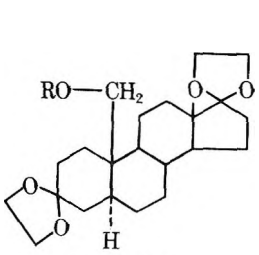
Attempts to convert saturated (5α- and 5β-) 19-hydroxylated steroids to 19-halogenated analogues with the use of mixed phosphorus and halogen containing reagents are described. The 19-halogenated analogues were not obtained, but certain transformations in the 5α series and rearrangements in the 5β series were noted and are discussed.

Previously, we have described the unsuccessful attempts to prepare saturated (5α- and 5β-) 10β-methyl sterols from 19-hydroxylated analogues via the hydrogenolysis of the corresponding sulfonate esters.[2a] In a search for an alternative approach, we considered the possibility of converting the 19 alcohol to a 19 halide (e.g., iodide) which, in turn, could be hydrogenolyzed to the 10β methyl. This approach suggested itself by the observations on the efficient conversion of numerous alcohols to halides with the use of mixed phosphorus and halogen containing reagents.[2b,3-9]

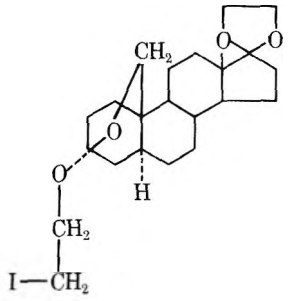
The attractiveness of the method was further enhanced by the observation that even alcohols prone to rearrangements gave unrearranged halides.[2b,8-10] For example, (1*S*)-neopentyl-*1-d* alcohol, on treatment with $(C_6H_5)_3P$–CCl_4, was transformed to presumably optically pure (1*R*)-neopentyl-*1-d* chloride.[11] In most instances, when the reaction is not assisted by a neighboring group, inversion of configuration takes place.[6,11] Retention of configuration in cases involving neighboring group participation was reported.[3,7] We have tested one of the procedures and obtained 17α-iodoestra-1,3,5(10)-trien-3-ol and 5α-cholestane 3α-iodide by treatment of estradiol and 5α-cholestan-3β-ol with $(C_6H_5O)_3P$–CH_3I, respectively.[12]

The preparation of the required 19-hydroxy-5α-androstane-3,17-bis(ethylene dioxide) (**1**) was previously described.[2a] Treatment of a dimethylformamide solution of **1a** with $(C_6H_5)_3P$ and bromine for 16 h at room temperature in the air resulted in the 19 formate **1b**. Formate ester formation under similar reaction conditions was previously observed.[13] Only starting material was recovered when the above mixture was refluxed (48 h) under nitrogen. Similarly, starting material was recovered when **1a** was refluxed (48 h) under nitrogen with $(C_6H_5)P_3$ in CCl_4.

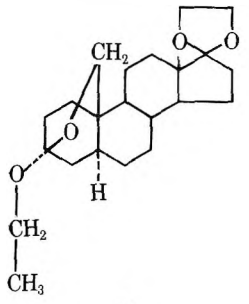
The reaction of **1a** with triphenyl phosphite–methyl iodide [$(C_6H_5O)_3P$–CH_3I] (MTPI) gave an iodide, but did not proceed in the desired manner. When **1a** was stirred at room temperature with MTPI in formamide for 3 h under nitrogen, 3α-(2-iodo)ethoxy-3β,19-oxido-5α-androstan-17-ethylene dioxide (**2**) was obtained (60% yield). The mass spectrum of **2** showed peaks at *m/e* 502 (M^+), 348 (M − 154), and 99. The



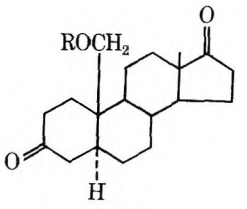
1a, R = H
b, R = HCO



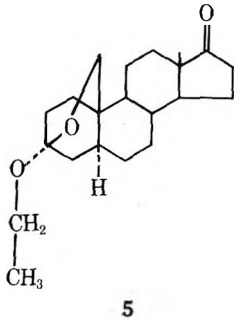
2



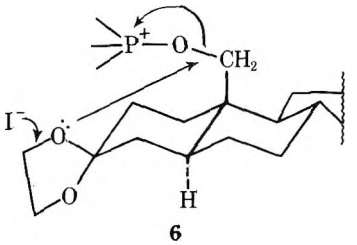
3



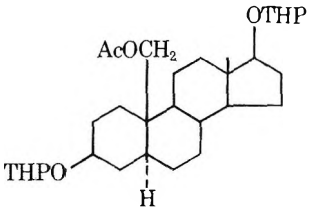
4a, R = H
b, R = Me



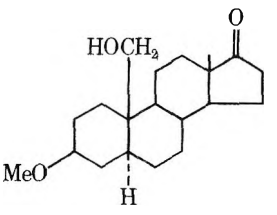
5



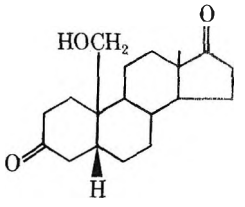
6



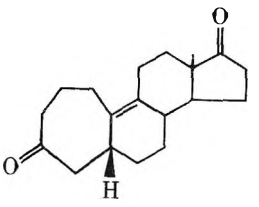
7



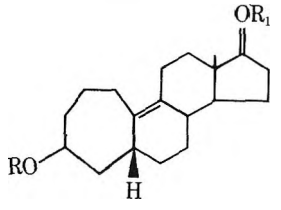
8



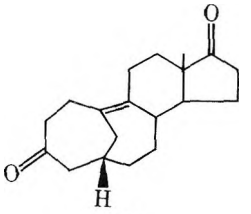
9a, H
b, *p*-Ts



10



11a, R = R1 = H
b, R = *p*-BrC6H4CO; R1 = H
c, R = R1 = Ac



12

molecular ion of **2** (*m/e* 502) indicated that "the equivalent of a hydroxyl group" of **1a** was displaced with an iodine atom and that the product retained a ketal group (*m/e* 99). However, the fragment at *m/e* 348 (M − 154) was clearly inconsistent for a 19-iodo compound which was expected to have peaks at *m/e* 374 (M^+ − 128) and/or 360 (M − 142). Also, the NMR spectrum, which had a complex signal at ca. 4.12 ppm, was not in accord with the 19-iodo-3,17-diketal structure. These results indicated that, very likely, a transformation involving both carbon 19 and the 3-ketal moiety of **1a** occurred during the reaction. Treatment of **2** with $LiAlH_4$ resulted in the 3α-ethoxy product **3** [*m/e* 376 (M^+)]. The NMR spectrum of **3** had signals at 1.17 (t, 3 H) and 3.60 ppm (q, 2 H) and is in accord with the 3α-ethoxy structure. Hydrolysis of **3** gave **4a** which, on treatment with ethanol and *p*-toluenesulfonic acid, gave **5**. The obtained **5** was identical with an authentic sample.

It is likely that formation of **2** proceeds in a manner indicated in **6**. It is worthy of note that the ω-iodination proceeded only when rings A and B had the trans junction. This was evidenced by the fact that, when 19-hydroxy-5β-androstane-3,17-bis(ethylene dioxide) was treated with MTPI and DMF, even after 6 days, only starting material was recovered. Whether in the A/B cis series the reaction did not proceed because of steric factors or due to the lack of anchimeric assistance of the C-3 ketal moiety is not clear. As indicated in **6**, the anchimeric assistance of the C-3 ketal in the A/B trans series is very likely. However, the possibility of a 19-hydroxy → C-3β oxide formation occurring in the course of the reaction and resulting in 3α-(2-hydroxy)ethoxide 3β,19-oxide which, in turn, is converted to the iodide **2** cannot be ruled out.

In view of the negative results described above, the possibility that the 3-ketal may have a detrimental influence on the C-19 halogenation was considered. Therefore, 5α-androstane-3β,17β,19-trihydroxy-3,17-bis(tetrahydropyranyl ether) was prepared and the iodination reaction was tested on this compound. Unfortunately, when **7** was treated with MTPI in DMF, a complex mixture of at least seven products was obtained. One of the products (ca. 8%) apparently contained iodine, but proved most unstable and decomposed on purification.

We have then tested the reaction on 19-hydroxy-5α-androstane-3β-methoxy-17-one (**8**). However, treatment of **8** with MTPI in DMF, under nitrogen for 7 h, gave a mixture of three products which were not investigated further because they did not contain iodine.

For studies in the 5β series, 19-hydroxy-5β-androstan-3,17-one (**9a**)[14] was used. When **9a** was treated (2 h) with MTPI in DMF at room temperature, a rearranged product later identified as **10** was obtained in ca. 40–50% yield. The unknown [mp 114–116 °C, MS *m/e* 286 (M^+)] was devoid of iodine and its IR spectrum had no bands for hydroxyls, but showed bands at 1740 and 1695 cm^{-1} for the C-17 and C-3 ketones. The NMR spectrum was lacking absorption for vinylic protons and had a signal at 1.00 ppm for the C-13 methyl and at 2.54 ppm (s, 2 H). The presence of a tetrasubstituted double bond in **10** was demonstrated by hydrogenation (EtOH–Pd/C) which was accompanied by the uptake of 1 equiv of hydrogen. The NMR of the saturated residue of the hydrogenation (*m/e* 288) indicated the presence of several isomers which were not investigated.

Reduction of **10** with $NaBH_4$ gave the diol **11a** which could be reoxidized to **10**. Treatment of **10** with base or acid resulted in the recovery of starting material. The presented evidence indicated that **10** has a tetrasubstituted double bond which apparently is not located at the C-5 (**10**) position.

The results were consistent with the possibility that the unknown may have structure **10** or **12**. Dauben and Ben Efraim[15] in the course of studies of the solvolysis of the 19 tosylester **9b** obtained a small amount of a product to which they assigned structure **10**. The reported[15] physical constants for **10** [mp 105–106.5 °C; IR ν_{max} 1740, 1705 cm^{-1}; NMR τ 9.04

Table I. Fractional Atomic Coordinates and Estimated Standard Deviations

Atom	X/A	Y/B	Z/C
C(1)	0.23192 (29)	0.4586 (12)	0.58746 (31)
C(2)	0.26004 (39)	0.2350 (14)	0.58514 (41)
C(3)	0.22004 (52)	0.0486 (13)	0.59623 (47)
C(4)	0.13804 (49)	0.0546 (12)	0.55453 (42)
C(4A)	0.10500 (37)	0.1869 (13)	0.59302 (37)
C(5)	0.12041 (27)	0.4308 (11)	0.60264 (33)
C(6)	0.08674 (27)	0.5370 (15)	0.64406 (35)
C(7)	0.13059 (25)	0.4821 (18)	0.73080 (30)
C(8)	0.20870 (27)	0.5653 (10)	0.76506 (30)
C(9)	0.24138 (24)	0.5370 (10)	0.71405 (29)
C(10)	0.20175 (23)	0.4803 (11)	0.64042 (27)
C(11)	0.32212 (28)	0.5940 (13)	0.75056 (32)
C(12)	0.36941 (25)	0.4904 (16)	0.82900 (30)
C(13)	0.33856 (26)	0.5356 (11)	0.88195 (28)
C(14)	0.25838 (27)	0.4559 (12)	0.84175 (32)
C(15)	0.23985 (32)	0.4614 (20)	0.90379 (34)
C(16)	0.31145 (41)	0.4045 (18)	0.97688 (41)
C(17)	0.36955 (32)	0.3978 (13)	0.95379 (37)
C(18)	0.34607 (43)	0.7729 (14)	0.90304 (40)
C(20)	0.07780 (28)	0.0187 (13)	0.41778 (33)
C(21)	0.05384 (25)	0.1345 (11)	0.34630 (29)
C(22)	0.00581 (29)	0.0335 (13)	0.27720 (34)
C(23)	−0.01830 (32)	0.1377 (12)	0.20833 (36)
C(24)	0.00526 (30)	0.3447 (15)	0.20971 (35)
C(25)	0.05279 (28)	0.4478 (11)	0.27795 (33)
C(26)	0.07651 (28)	0.3459 (11)	0.34471 (33)
Br(24)	−0.02884 (4)	0.5000 (0)	0.11700 (4)
O(4B)	0.10843 (32)	0.1472 (9)	0.47742 (25)
O(17B)	0.43953 (25)	0.4597 (11)	1.01526 (23)
O(20)	0.07263 (31)	−0.1735 (9)	0.42337 (31)

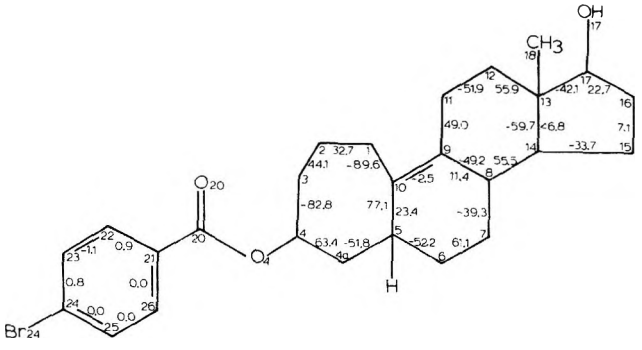


Figure 1. Endocyclic torsion angles. A torsion angle α–β–γ–δ is positive if, when viewed down the β–γ bond, the α–β bond will eclipse the γ–δ bond when rotated less than 180° in a clockwise direction.

(s, 3 H)] differed from those of the unknown obtained by us. This, at first, suggested that the rearranged product may have structure **12**.

The determination of the structure was carried out by x-ray crystallography on the 4-*p*-bromobenzoate **11b**.

The fractional atomic coordinates are given in Table I, and the atomic numbers, as well as the endocyclic torsion angles, are illustrated in Figure 1. The seven-membered A ring has a twist chair conformation as shown by the torsion angles, which agree quite closely with the theoretical values reported by Hendrickson[16] for a seven-membered twist chair ring. Beginning with the C(4a)–C(5) bond and proceeding in either direction around the ring, the theoretical values are −54.3, 72.3, −88.1, 39.1, 39.1, −88.1, and 72.3°. Another view of the A-ring conformation is provided by Figure 2. Figure 3 shows two ORTEP[17] drawings which illustrate the overall conformation of the molecules as well as the configurations at all asymmetric centers.

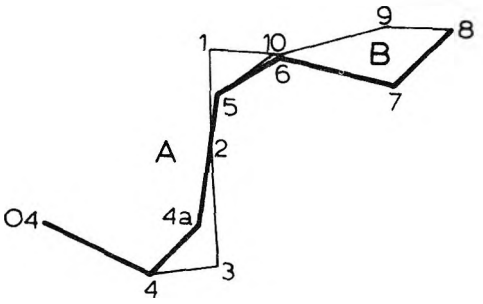


Figure 2. The seven-membered twist chain A ring looking from the midpoint of the C(4a)–C(5) bond to C(2).

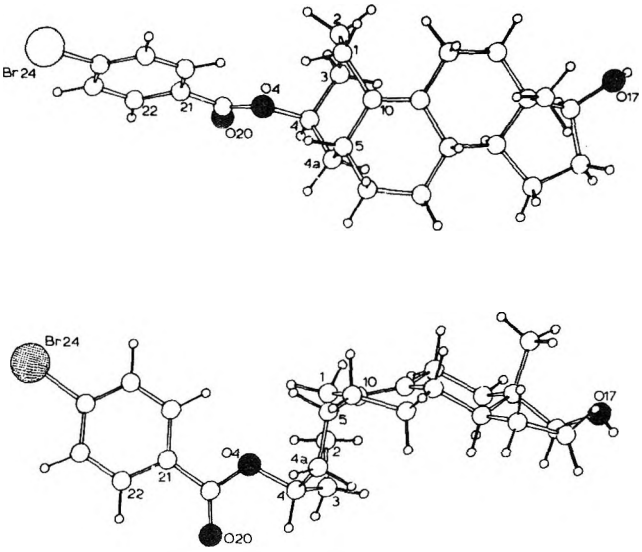


Figure 3. Perspective drawings of the *A*-homo-19-nor-5β-androst-9(10)-ene-4β,17β-diol 4-*p*-bromobenzoate molecule.

Experimental Section

Physical Measurements. Melting points were taken on a hot stage apparatus and are corrected. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 237 spectrophotometer as KBr wafers; absorption frequencies are quoted in reciprocal centimeters. Ultraviolet (UV) spectra were recorded on a Perkin-Elmer Model 202 spectrophotometer in methanol solutions.

Unless otherwise indicated, nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ on a Varian DA-60 spectrometer at 60 MHz. Chemical shifts are quoted in parts per million downfield from tetramethylsilane as internal standard (s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet). Mass spectra were recorded on a Du Pont 21-491 instrument, using the direct probe insertion system with a temperature of source of 210 °C and an ionization voltage of 70 eV. The masses of eliminated fragments are given in parentheses after the molecular ion.

Chromatography. Analytical thin layer chromatography (TLC) was carried out on precoated silica IB-F Baker Flex sheets in the indicated solvent systems. The products were detected under ultraviolet light and/or by spraying with an ethanolic solution of phosphomolybdic acid (10%) and heating to 105 °C for visualization.

Preparative layer chromatography was carried out on plates coated with silica gel (Merck HF 254-366). Column chromatography was carried out on silica gel (Merck, 70–230 mesh). The purity of steroidal samples was tested by gas–liquid chromatography (GLC) on a Hewlett-Packard 7620 A instrument using a 6-ft glass column (o.d. 6 mm, i.d. 2 mm) packed with SE-30 1% on Gas-Chrom (80–100 mesh) support. The temperature was set isothermally at 210–250 °C and the helium flow was 30 ml/min.

19-Hydroxy-5α-androstane-3,17-bis(ethylene dioxide) 19-Formate (1b). To a solution of $(C_6H_5)_3P$ (150 mg) in dry DMF (distilled from CaH_2 and stored over a molecular sieve) (2 ml) a solution of **1a** (180 mg) in DMF (3 ml) and bromine (27 μl) were added. The mixture was stored for 16 h in the air, then the pH was adjusted to 7 with a dilute solution of sodium hydrogen carbonate. After dilution

with water (10 ml), the product was recovered with ethyl acetate (3 × 10 ml), and processed in the usual manner. The obtained residue was fractionated on TLC [silica gel, benzene–ethyl acetate (4:1)] to yield the 19 formate (120 mg).

A sample was crystallized from methanol–water and showed mp 52–54 °C; IR ν_{max} 1715, 1175 cm^{-1}; NMR δ 0.83 (s, 3 H, 13-CH_3), 3.88 [m, 4 H, (17-$OCH_2)_2$], 4.40 (s, 2 H, 19-CH_2), 8.1 (s, 1 H, HCOO); MS *m/e* 420 (M^+) (−30, −44, −72, −89), 125, 99.

When the reaction was carried at reflux (48 h) under *nitrogen*, only starting material was recovered.

Treatment of 1a with $(C_6H_5)_3P$ in CCl_4.[6] A solution of **1a** (200 mg) and $(C_6H_5)_3P$ in CCl_4 (10 ml) was refluxed (48 h) under nitrogen. Following the usual workup, only starting material was obtained.

3α-(2-Iodo)ethoxy-3β,19-oxido-5α-androstan-17-ethylene Dioxide (2). To a stirred under nitrogen solution of **1a** (150 mg) in dry formamide (10 ml), MTPI[18] (260 mg) was added. The mixture was stirred for 3 h at ambient temperature, neutralized with aqueous sodium hydrogen carbonate, and diluted with water. The product was recovered with ethyl acetate, and the extract was washed with 5% $Na_2S_2O_3$ and water, dried, and concentrated to a residue. The residue was fractionated on TLC [silica gel, benzene–ethyl acetate (4:1)] to yield **2** (120 mg).

A sample was crystallized from ethyl acetate and showed mp 148–150 °C; IR ν_{max} 2920, 1450 cm^{-1}; NMR δ 0.80 (s, 3 H, 13-CH_3), 3.17 [t, 2 H, 3α-(-OCH_2–), J = 8 Hz], 3.90 [m, 4 H, 17-$(OCH_2)_2$], 4.12 [d, 2 H, 19-(CH_2O–), J = 2 Hz]; MS *m/e* 502 (M^+) (−154, −215), 155, 141, 99.

3α-Ethoxy-3β,19-oxido-5α-androstan-17-ethylene Dioxide (3). A solution of **2** (100 mg) in dry tetrahydrofuran (THF, 3 ml) was added to a stirred suspension of $LiAlH_4$ (100 mg) in THF (3 ml). The mixture was stirred (16 h) with the exclusion of moisture and, after a conventional workup, a crude residue (80 mg) was obtained. Following TLC purification [silica gel, benzene–ethyl acetate (4:1)] homogenous **3** (72 mg) was obtained.

A sample was crystallized from ethyl acetate–methanol and showed mp 165–167 °C; IR ν_{max} 2920, 2860 cm^{-1}; NMR δ 0.80 (s, 3 H, 13-CH_3), 1.17 [t, 3 H, 3α-(-OCH_2CH_3), J = 8 Hz], 3.60 [q, 2 H, 3α-(-OCH_2CH_3), J = 8 Hz], 3.98 [m, 4 H, 17-$(-OCH_2)_2$], 4.12 [d, 2 H, 19-(OCH_2–), J = 2 Hz]; MS *m/e* 376 (M^+) (−15, −29, −45, −87), 99.

3α-Ethoxy-3β,19-oxido-5α-androstan-17-one (5). The previously prepared 19-acetate **4b** (200 mg) was saponified [methanol (10 ml), water (5 ml), K_2CO_3 (100 mg), 4 h at room temperature] to yield **4a** (180 mg).

The obtained **4a** (170 mg) was immediately dissolved in absolute ethanol (5 ml), *p*-toluenesulfonic acid (40 mg) was added, and the mixture was stored (6 h) at room temperature. The ethanol was removed in a stream of nitrogen and the residue was fractionated on TLC [silica gel, benzene–ethyl acetate (4:1)] to afford **5** (120 mg): NMR δ 0.83 (s, 3 H, C-13 CH_3), 1.18 [t, 3 H, 3α-(-OCH_2CH_3), J = 6 Hz], 3.62 [q, 2 H, 3α-(-OCH_2CH_3), J = 6 Hz], 3.88 [d, 1 H, 19(CH_2), J = 8 Hz], 4.20 [d, 1 H, 19(CH_2), J = 8 Hz].

Treatment of a solution of **3** in aqueous acetone with *p*-toluenesulfonic acid (16 h at room temperature) gave **4a**, which was converted to **5** as above described.

3β,17β,19-Trihydroxy-5α-androstane-3,17-bis(tetrahydropyranyl Ether) 19-Acetate (7). The previously prepared 3β,19-dihydroxy-5α-androstan-17-one 19-acetate was used.[2a] The diol 19-acetate (1 g) was dissolved in dry methanol (20 ml) and then $NaBH_4$ (300 mg) was added in small portions. The reaction was allowed to proceed for 1 h when the mixture was made slightly acidic by the addition of 0.2 M hydrochloric acid. The mixture was diluted with water, and the obtained solid was collected by filtration and dried (0.85 g). The recrystallized sample (chloroform–hexane) of the 19-acetoxy-5α-androstane-3β,17β-diol showed mp 186–188 °C; IR ν_{max} 3400, 2940, and 1740 cm^{-1}; NMR δ 0.74 (s, 3 H, 13-CH_3), 2.10 (s, 3 H, 19-acetate-CH_3), 3.50 [m, 1 H, 17α-(H)], 4.31 [s, 2 H (19-CH_2)]; MS *m/e* 350 (M^+) (−18, −30, −48, −81, −112).

The above 19-acetoxy-3β,17β-diol (800 mg) was dissolved in dry THF (30 ml), then dihydropyran (1 ml) and *p*-toluenesulfonic acid (60 mg) were added and the mixture was stored for 6 h at ambient temperature. The reaction was terminated with solid sodium hydrogen carbonate, then a saturated solution of sodium hydrogen carbonate (70 ml) was added and the product was recovered with ethyl acetate. After the conventional workup, 3β,17β,19-trihydroxy-5α-androstane-3,17-bis(tetrahydropyranyl ether) 19-acetate (0.9 g) was obtained: IR 2920, 1740 cm^{-1}; NMR δ 0.78 [C-13 (CH_3)], 1.63 (m, THP-methylene H), 2.05 [s, 19-acetate (-CH_3)], 3.80 (m, 5 H, -CH_2O– of THP and 17α-H), 4.32 (s, 2 H, 19-CH_2O–), 4.70 (m, 2 H, CHO– of THP). The crude material (0.8 g) was dissolved in ether (30 ml) and added dropwise to a stirred suspension of $LiAlH_4$ (800 mg) in ether (20 ml). The mixture was refluxed (2 h) and processed in the conventional manner to yield a residue (680 mg). Following TLC fractionation [silica gel, benzene–ethyl acetate (7:3)] homogenous **7** (500 mg) was obtained.

A sample was crystallized from ethyl acetate and showed mp 165–167 °C; IR ν_{max} 3470, 2920 cm^{-1}; NMR δ 0.83 [s, 3 H, C-13 (CH_3)], 1.67 (m, THP methylene H), 3.62 (m, CH_2O– of THP and 17α-H), 3.90 (s, 2 H, 19-CH_2O), 4.72 (m, 2 H, CHO– of THP); MS *m/e* 476 (M^+), 392 (M − 102, −124, −134, −144, −156, −169), 85.

Treatment of 7 with MTPI in DMF. A mixture of **7** (300 mg), MTPI (350 mg), and DMF (5 ml) was stirred (7 h) under nitrogen at room temperature. The mixture was diluted with brine, and the products were collected by filtration and purified by TLC (benzene). A complex mixture of at least seven products was detected. The least mobile product showed IR ν_{max} 2910, 2870 cm^{-1}; NMR (all signals were broad) δ 0.87 (s, 3 H, 13-CH_3), 1.62 (m, THP methylene H), 3.62 (m, CH_2O of THP and 17α-H), 4.16 (m, 2 H,19-CH_2O), 5.00 (m, 2 H, CHO of THP); MS *m/e* 586 (M^+) 430 (M − 156) (M − 186, −204, −260, −314, −331). The product decomposed rapidly during purification.

19-Hydroxy-3β-methoxy-5α-androstan-17-one (8). The required starting material 19-acetoxy-3β-hydroxyandrost-5-en-17-one was prepared as described by Djerassi and Kielczewski.[19]

To a solution of 19-acetoxy-3β-hydroxyandrost-5-en-17-one (760 mg) in purified dioxane (10 ml) containing 70% perchloric acid (5 drops), methyl orthoformate (2.5 ml) was added dropwise. The solution was stored at room temperature and, as soon as it started to turn dark, the reaction was terminated by the addition of solid $NaHCO_3$. The mixture was diluted with water, and the product recovered (ethyl acetate) and processed in the usual manner. The residue was chromatographed on a column packed with Alox III. The fractions eluted with benzene–ethyl acetate (7:3) gave the 19-acetoxy-3β-methoxyandrost-5-en-17-one (420 mg): NMR δ 0.90 (13-CH_3), 2.03 (19-acetate CH_3) 3.38 (s, 3 H, OCH_3), 3.82 (d, 1 H, 19-CH_2–, J = 12 Hz), 4.52 (d, 1 H, 19-CH_2–, J = 12 Hz), 5.70 (m, 1 H, C-6 vinylic H).

The above 5-en-3-methyl ether (300 mg) was dissolved in dry methanol (30 ml), then 5% Pd on charcoal catalyst (200 mg) was added and the mixture was shaken (16 h) in an atmosphere of H_2 at room temperature. The catalyst was removed by filtration and the filtrate was concentrated to yield the 19-acetoxy-3β-methoxy-5α-androstan-17-one (269 mg): NMR δ 0.85 (13-CH_3), 2.04 (19-acetate CH_3), 3.34 [s, 3 H, 3β-(OCH_3)], 4.14 (d, 1 H, 19-CH_2–, J = 12 Hz), 4.42 (d, 1 H, 19-CH_2–, J = 12 Hz).

A mixture of the saturated (5α)-19-acetoxy-3-methyl ether (269 mg), methanol (10 ml), and 2 N NaOH (2 ml) was refluxed (30 min) under nitrogen. After neutralization with 1 N HCl, water was added and the product was recovered (ether) and processed in the usual manner. The obtained residue was fractionated on TLC (silica gel, benzene-ethyl acetate (7:3)] to yield 8 (200 mg): IR ν_{max} 3450, 2900, 1740 cm^{-1}; NMR δ 0.90 (13-CH_3), 1.90 (OH, exchangeable with D_2O), 3.38 [s, 3 H, 3β-(OCH_3)], 3.87 (2 H, 19-CH_2–).

Treatment of 8 with MTPI in DMF. A mixture of 8 (90 mg) and MTPI (180 mg) in DMF (4 ml) was stored (7 h) at room temperature. The reaction mixture was worked up to yield a residue (51 mg) whose NMR indicated that it was a mixture of at least three products (δ 0.83, 0.85, 0.93, three singlets at a ratio of 1.6:1:1.1). The mixture was not investigated further because it did not contain iodine.

19-Nor-*A*-homo-5β-androst-9(10)-ene-4,17-dione (10). The 19-hydroxy-5β-androstane-3,17-dione (**9a**) was prepared by the method of Knox et al.[14] A mixture of **9a** (100 mg) and MTPI (225 mg) in dry DMF (10 ml) was stirred (2 h) under nitrogen at room temperature. After dilution with brine, the products were recovered with ethyl acetate. The extract was washed with 10% aqueous $Na_2S_2O_3$, brine, and water, dried and concentrated to a residue (120 mg). The residue was fractionated on TLC [silica gel, benzene–ethyl acetate (4:1)] to yield **10** (42 mg).

A sample was crystallized from ether–pentane and showed mp 114–116 °C; IR ν_{max} 2910, 1735, 1695 cm^{-1}; NMR δ 1.0 (s, 3 H, 13-CH_3), 2.54 (s, 2 H); MS *m/e* 286 (M^+) (−15, −43); UV end absorption at 220 nm.

A mixture of **10** (13 mg), ethanol (1 ml), and 2 N NaOH (5 drops) was refluxed (1 h) under nitrogen. After the conventional workup, starting material was recovered. Similarly, only starting material was recovered from a solution of **10** (15 mg) in methanol (2 ml) containing concentrated HCl (5 drops) which was refluxed for 4 h, then diluted with water and processed as usual.

A mixture of **10** and 5% Pd on charcoal (20 mg) in ethanol (10 ml) was shaken (16 h) in an atmosphere of hydrogen at room temperature. The NMR of the recovered saturated residue indicated the presence

of several compounds (isomers): NMR δ 0.83 (s), 0.91 (s), 0.96 (s) (ratio 0.2:2:1); MS *m/e* 288 (M^+) (−44, −58, −103).

The mixture was not investigated further.

A-Homo-19-nor-5β-androst-9(10)-ene-4β,17β-diol (11a). A solution of **10** (40 mg) and $NaBH_4$ (50 mg) in methanol (2 ml) was stored (15 min) at room temperature. The recovered product was purified by TLC [silica gel, benzene–ethyl acetate (7:3)] to yield the diol **11a** (32 mg): IR no carbonyl absorption; NMR (pyridine) δ 1.03 (s, 3 H, 13-CH_3), 3.90 (broad m, 1-H), 4.15 (broad m, 1-H).

The diacetate **11c** was prepared in the conventional manner, using **11a** (25 mg), pyridine (2 ml), and acetic anhydride (1 ml). The obtained **11c** was purified on TLC [silica gel, benzene–ethyl acetate (7:3)]: NMR δ 0.92 (s, 3 H, 13-CH_3), 2.06 (s, 6 H, 2-acetate methyls), 4.60 (broad m, 1 H), 4.80 (broad m, 1 H).

A-Homo-19-nor-5β-androst-9(10)-ene-4β,17β-diol 4-*p*-Bromobenzoate (11b). A mixture of **11a** (75 mg), *p*-bromobenzoyl chloride (250 mg), methylene chloride (distilled from a molecular sieve) (4 ml), and triethylamine (1.2 ml) was stirred (16 h) at room temperature. Water (10 ml) was then added and the recovered product was purified by TLC [silica gel, hexane–ethyl acetate (3:1)] to yield a homogenous material which was later identified by x-ray crystallography as **11b**. The sample was slowly crystallized from ethanol and showed mp 166–168 °C; NMR δ 0.87 (s, 3 H, 13-CH_3), 3.65 (broad m, 1 H), 5.20 (broad m, 1 H), 7.55 (d, 2 H, J = 8 Hz, aromatic H), 7.90 (d, 2 H, J = 8 Hz, aromatic).

A single crystal having dimensions 0.1 × 0.2 × 0.4 mm was used for the x-ray measurements of the lattice parameters and intensities. The systematic absences in the diffraction pattern indicated the space group to be C2. The unit cell constants were determined from least-squares analysis of the θ values for 30 reflections to be a = 21.196 (2), b = 6.223 (1), c = 20.340 (1) Å, and β = 120.34° resulting in a unit cell volume of 2316 Å^3. The density was calculated to be 1.36 g cm^{-3} based on the presence of four molecules (Z = 4) in the cell. Integrated intensities for 1989 independent reflections having θ <75° were measured on an Enraf-Nonius CAD-4 diffractometer using Cu Kα radiation. After the Lorentz and polarization corrections [$(1 + \cos^2 2\theta)/2 \sin 2\theta$] had been applied to the intensity data, normalized structure factor amplitudes were computed, and the structure was solved by straightforward application of heavy atom techniques and found to be **11b** ($C_{26}H_{33}O_3Br$, mol wt 473.5).

The positional and anisotropic thermal parameters of all nonhydrogen atoms were refined by full-matrix least squares using the 1353 reflections for which the observed intensity was greater than twice the corresponding standard deviation. These reflections were regarded as having intensities significantly greater than the background. The weights used were the quantities ($1/\sigma_F^2$) where σ_F is defined by equation H.14 of Stout and Jensen[20] using 0.06 rather than 0.01 as the instability correction. The hydrogens bonded to carbons were placed at their geometrically expected positions and included in the final three refinement cycles although their parameters were not refined. The hydroxyl hydrogen was located on a Fourier difference map. The final reliability index, R (defined as $\Sigma||F_o| - |F_c||/\Sigma|F_o|$), was 4.9% for the 1353 reflections used in the refinement and 6.0% for all data.

Registry No.—**1a,** 2220-69-1; **1b,** 60803-07-8; **2,** 60803-08-9; **3,** 60803-09-0; **4a,** 2229-24-5; **4b,** 14550-51-7; **5,** 17916-20-0; **7,** 60803-10-3; **8,** 60803-11-4; **9a,** 2059-53-2; **10,** 60803-12-5; **11a,** 60803-13-6; **11b,** 60803-14-7; **11c,** 60803-15-8; $(C_6H_5)_3P$, 603-35-0; MTPI, 4387-41-1; 3β,19-dihydroxy-5α-androstan-17-one, 14456-03-2; 19-acetoxy-5α-androstane-3β,17β-diol, 60803-16-9; dihydropyran, 25512-65-6; 19-acetoxy-3β-hydroxyandrost-5-en-17-one, 13328-60-4; methyl orthoformate, 149-73-5; 19-acetoxy-3β-methoxyandrost-5-en-17-one, 2857-43-4; bromobenzoyl chloride, 586-75-4.

Supplementary Material Available. Tables of the anisotropic thermal parameters of the nonhydrogen atoms, coordinates of the hydrogens, and interatomic distances and valency angles (3 pages). Ordering information is given on any current masthead page.

References and Notes

(1) (a) The work at the Worcester Foundation for Experimental Biology was supported by NIH Grant GM 19882. The work at the Medical Foundation of Buffalo was supported by NIH Grant CA 10906. (b) Postdoctoral Fellow, 1973–1975. On leave of absence from the Institute of Chemistry, School of Medicine, University of Milano, Milano, Italy.
(2) (a) E. Santaniello and E. Caspi, *J. Steroid Biochem.*, **7**, 223 (1976); (b) N. Kornblum and P. C. Iffland, *J. Am. Chem. Soc.*, **77**, 6653 (1955).
(3) S. R. Landauer and N. H. Rydon, *J. Chem. Soc.*, 2224 (1953).
(4) G. J. Karabatsos, C. E. Orzech, Jr., and S. Meyerson, *J. Am. Chem. Soc.*, **86**, 1994 (1964).
(5) G. A. Wiley, R. L. Hershkowitz, B. M. Rein, and B. C. Chung, *J. Am. Chem. Soc.*, **86**, 964 (1964).
(6) R. G. Weiss and E. I. Snyder, *J. Org. Chem.*, **36**, 403 (1971).
(7) J. H. P. Verheyden and J. G. Moffat, *J. Am. Chem. Soc.*, **86**, 2093 (1964).
(8) I. M. Downie, J. B. Holmes, and J. B. Lee, *Chem. Ind. (London)*, 900 (1966).
(9) C. S. L. Baker, P. D. Landor, and A. N. Patel, *J. Chem. Soc.*, 4348 (1965).
(10) J. P. Schaefer and D. S. Weinberg, *J. Org. Chem.*, **30**, 2635 (1965).
(11) H. S. Mosher, *Tetrahedron*, **30**, 1733 (1974).
(12) T. Arunachalam, E. Santaniello, and E. Caspi, to be published.
(13) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 3, Wiley, New York, N.Y., 1972, p 321, and references cited therein.
(14) L. H. Knox, E. Blossey, H. Carpio, L. Cervantes, P. Crabbe, E. Velarde, and J. A. Edwards, *J. Org. Chem.*, **30**, 2198 (1965).
(15) W. G. Dauben and D. A. Ben Efraim, *J. Med. Chem.*, **11**, 287 (1968).
(16) J. B. Hendrickson, *J. Am. Chem. Soc.*, **89**, 7036 (1967).
(17) C. K. Johnson, ORTEP, ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965.
(18) J. P. H. Verheyden and J. G. Moffat, *J. Org. Chem.*, **35**, 2319 (1970).
(19) C. Djerassi and M. A. Kielczewski, *Steroids*, **2**, 125 (1963).
(20) G. H. Stout and L. H. Jensen, "X-Ray Structure Determination", Macmillan, New York, N.Y., 1968, p 457.

Steroid Oxetanones. 3. Synthesis of 5,7α-Epoxy-5α-cholestan-6-ones[1,2]

A. T. Rowland,* Robert S. Drawbaugh, and James R. Dalton

Department of Chemistry, Gettysburg College, Gettysburg, Pennsylvania 17325

Received July 12, 1976

Bromination of 5α-hydroxy-6-oxo cholestanes with pyridinium hydrobromide perbromide in hot acetic acid gave the corresponding 7α-bromo derivatives accompanied by significant amounts of by-products. Epimerization at C-7 by lithium bromide in dimethylformamide produced the 7β-bromo isomers which, upon treatment with methanolic potassium hydroxide in dimethyl sulfoxide, gave 5,7α-epoxy-5α-cholestan-6-ones and 5-hydroxy-7α-methoxy-5α-cholestan-6-ones. Spectroscopic data verify the structural assignments for the bromo ketones, oxetanones, and methoxy ketones. Among the few literature reports concerning the preparation of steroid oxetanones, this is the first to describe the production of α-methoxy ketones as competing products.

Since our report[3] on the synthesis of 5,7β-epoxy-5β-cholestan-6-one (1) and its ring A derivatives, few additional examples of this class of compounds have appeared in the literature. "As yet, there is no convenient general synthesis of oxetan-3-ones" is a statement[4] that accurately represents the situation regarding the preparation of this interesting class of compounds. The success of the method involving the bromination of steroidal α-ketols, followed by ring closure to the oxetanone upon treatment of the trans bromohydrin with base,[3] is often stymied in simplier acyclic compounds by cleavage of the α-ketol during the bromination reaction.[4] The bromination of 5-hydroxy-5β-cholestan-6-ones with pyridinium hydrobromide perbromide (PHP) produced no such complications.[3] We now report that similar treatment of the 5-hydroxy-5α-cholestan-6-ones invariably gives side products that decrease the yield of the desired 7α-bromo derivatives. However, the bromohydrins produced are readily converted to the corresponding oxetanones after epimerization to the 7β-bromo compounds.

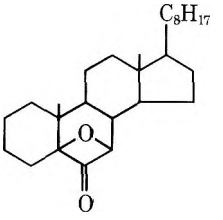
Bromination of 5-hydroxy-5α-cholestan-6-one (**2a**) with 1 equiv of PHP in hot acetic acid gave the 7α-bromo derivative (**2b**) in 39% yield along with unidentified material(s) that contained no hydroxy group. While brominations in the 5β-hydroxy series lead directly to 7α-bromo compounds that possess the trans relationship of bromine and hydroxyl necessary for oxetanone formation,[3] conversion of **2b** to the 7β-bromo epimer **2c** was essential. Attempted epimerization by hydrogen bromide in acetic acid[5] failed but treatment of **2b** with excess lithium bromide in dimethylformamide (DMF)[6] for an extended period at room temperature resulted in the production of **2c** in high yield. This procedure, although involving a long reaction period, did not produce an α,β-unsaturated ketone as occurred in the reported epimerization of 7α-bromo-6-oxo steroids utilizing a hot lithium carbonate–DMF mixture.[6] Treatment of **2c** with methanolic potassium hydroxide solution in dimethyl sulfoxide (Me_2SO)[3,6a] gave 5,7α-epoxy-5α-cholestan-6-one (**3a**) in moderate yield plus a small amount of 5-hydroxy-7α-methoxy-5α-cholestan-6-one (**4d**). The latter compound presumably arose by displacement with inversion of the 7β-bromine by methoxide ion formed from the equilibrium

$$KOH + MeOH \rightleftharpoons KOMe + H_2O$$

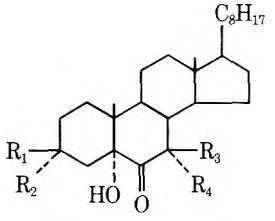
There was no indication of α-methoxy ketone formation in the reaction with base of 7α-bromo steroids in the 5β-hydroxy series,[3] probably owing to the typical inhibition to attack from the top side of the molecule.

That a trans relationship of the hydroxy and bromo substituents is needed for oxetanone formation is indicated by the fact that reaction of the 7α-bromo compound **2b** with methanolic potassium hydroxide–Me_2SO gave 5,7β-dihydroxy-5α-cholestan-6-one (**4b**) as the sole product. It appears likely that the conversion of **2b** to **4b** proceeded through an intermediate epoxy alcohol or ether (a pathway known to be taken by some α-bromo ketones[7]) since the crude reaction product before acidification contained little carbonyl absorption in its IR spectrum. The 7β-hydroxy compound **4b** was converted to the 7β-tosyloxy derivative (**4c**). Upon treatment with base, **4c** gave a low yield of oxetanone **3a** and unreacted **4c**. Thus, no advantage was found in using the tosyloxy substituent as a leaving group.

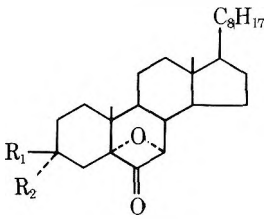
When the 7β-bromo steroid **2c** was treated with sodium bicarbonate in hot Me_2SO, the major product was 5,7α-dihydroxy-5α-cholestan-6-one (**4a**), accompanied by a trace of



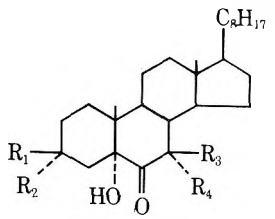
1



2a, $R_1 = R_2 = R_3 = R_4 = H$
b, $R_1 = R_2 = R_3 = H$; $R_4 = Br$
c, $R_1 = R_2 = R_4 = H$; $R_3 = Br$
d, $R_1 = OAc$; $R_2 = R_3 = R_4 = H$
e, $R_1 = OAc$; $R_2 = R_3 = H$; $R_4 = Br$
f, $R_1 = OAc$; $R_2 = R_4 = H$; $R_3 = Br$
g, $R_1 = R_3 = R_4 = H$; $R_2 = OAc$
h, $R_1 = R_3 = H$; $R_2 = OAc$; $R_4 = Br$
i, $R_1 = R_4 = H$; $R_2 = OAc$; $R_3 = Br$



3a, $R_1 = R_2 = H$
b, $R_1 = OH$; $R_2 = H$
c, $R_1 = OAc$; $R_2 = H$
d, $R_1 = H$; $R_2 = OH$
e, $R_1 = H$; $R_2 = OAc$



4a, $R_1 = R_2 = R_3 = H$; $R_4 = OH$
b, $R_1 = R_2 = R_4 = H$; $R_3 = OH$
c, $R_1 = R_2 = R_4 = H$; $R_3 = OTs$
d, $R_1 = R_2 = R_3 = H$; $R_4 = OCH_3$
e, $R_1 = OH$; $R_2 = R_3 = H$; $R_4 = OCH_3$

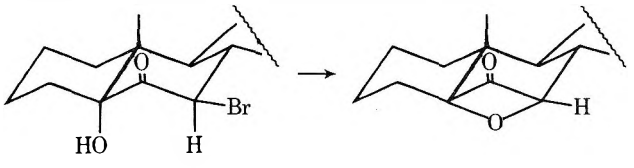
oxetanone **3a**. Displacement of bromine by hydroxyl with inversion of configuration at C-7 was a minor side reaction in the 7α-bromo-5β-hydroxy series[3] and the course of the reaction with **2c** illustrates the preference for displacement vs. oxetanone formation when a weak base is used and the bromine-bearing carbon is open to attack.

Hanna has reported[6a] that the reaction of 3β-acetoxy-5-hydroxy-7α-bromo-5α-cholestan-6-one (**2e**) with lithium carbonate–DMF gave the 7β-bromo epimer (**2f**) in 33% yield accompanied by a trace of 3β-acetoxy-5,7α-epoxy-5α-cholestan-6-one (**3c**) and significant amounts of conjugated ketones. Alternately, the hydroxy oxetanone **3b** was obtained in 50% yield by treatment of **2f** with methanolic potassium hydroxide in Me_2SO. It was assumed in the former reaction that the oxetanone **3c** arose from the bromo ketones **2f** produced by epimerization of **2e**. We reinvestigated this sequence in order to optimize the yield of oxetanone **3c** and and to determine if an α-methoxy ketone is also formed in the reaction of **2f** with base. Attempts at the bromination of 3β-acetoxy-5-hydroxy-5α-cholestan-6-one (**2d**) by the only recorded procedure[5,6a,8] were unsuccessful in our hands. However, PHP treatment of **2d** in hot acetic acid gave **2e** in good yield, accompanied by unidentified side products. Epimerization of **2e** with *hot* lithium bromide–DMF gave a complex mixture from which the desired 7β-bromo compound **2f** was readily separated by column chromatography. Treatment of **2f** with methanolic potassium hydroxide in Me_2SO resulted in the isolation of the oxetanone **3b** and a second compound not previously detected,[6a] 3β,5-dihydroxy-7α-methoxy-5α-cholestan-6-one (**4e**). These results were consistent with those observed for the reaction of **2c** with base.

The physical constants (melting point, $[\alpha]D$) we found for **3b** were quite different from those reported by Hanna.[6a] Spectroscopic and analytical data verify our structural assignment (see Experimental Section). Acetylation of **3b** gave **3c**.

Bromination of 3α-acetoxy-5-hydroxy-5α-cholestan-6-one (**2g**) with PHP gave the 7α-bromo derivative **2h** in moderate yield along with the usual unidentified by-products. Attempts at isomerization of **2h** to **2i** with lithium bromide–DMF at room temperature for 91 h produced little reaction but epimerization did occur at elevated temperatures within 18 h. The crystallized product, 3α-acetoxy-5-hydroxy-7β-bromo-5α-cholestan-6-one (**2i**), was contaminated by a small amount of an impurity that was removed by column chromatography. Treatment of **2i** with methanolic potassium hydroxide–Me_2SO gave much 3α-hydroxy-5,7α-epoxy-5α-cholestan-6-one (**3d**) according to the IR spectrum of the crude product but separation of **3d** from other products by column or thick layer chromatography was only mildly successful. The oxetanone **3d** was finally obtained by fractional crystallization of column fractions rich in **3d**. Acetylation of a portion of the crude product resulted in an acetate mixture that stubbornly refused separation as well, but a small amount of the acetate (**3e**) of **3d** was obtained. Although no α-methoxy ketone was obtained in a pure state from this reaction, its presence in some chromatographic fractions was indicated by the characteristic absorption in the NMR spectrum at ca. 206 Hz (cf. spectral data for **4d** and **4e** in Experimental Section).

The conversion of 5-hydroxy-7β-bromo-5α-cholestan-6-ones to the corresponding oxetanones does not involve a major conformational change such as that necessitated in the production of the isomeric oxetanones from the 5β-hydroxy compounds.[3] Whereas in the latter cases the change in the environment of a C-3 hydrogen is readily observed by NMR analysis,[3] no significant change in the half-band width of the C-3 hydrogen is noted in the 5α-hydroxy compounds. The ultraviolet data show the usual bathochromic shifts and hyperchromic effects due to the bromine substituents in the 7α-bromo compounds and the IR and NMR data are in complete accord with all assignments.[3]



Rearrangements of simple oxetanones by Grignard reagents[9] and by acid[10] have been reported. We intend to investigate the behavior of steroid oxetanols (derived from the ketones reported here) under similar conditions.

Experimental Section

Melting points were taken in open capillaries in a Mel-Temp apparatus and are uncorrected. Optical rotations were determined in ca. 1% $CHCl_3$ solutions and are accurate to ±2°. Infrared spectra were taken on a Perkin-Elmer Model 735 spectrometer in CCl_4 solutions unless otherwise indicated. Ultraviolet spectra were obtained on a Bausch and Lomb Spectronic 505 spectrometer in absolute ethanol solutions. NMR spectra were determined on a Varian T-60 spectrometer in $CDCl_3$ solutions containing Me_4Si as an internal standard; chemical shifts are in hertz relative to Me_4Si. Microanalyses were conducted by Micro-Analysis, Inc., Wilmington, Del. Preliminary examinations of crude products and column fractions were carried out by TLC on Baker-flex silica gel 1B sheets and spectroscopically. Solutions were dried with anhydrous Na_2SO_4. Dimethyl sulfoxide (Me_2SO) and dimethylformamide (DMF) were Baker reagent grade and used as purchased. Alumina refers to Merck acid-washed grade and silica gel to Baker Analyzed reagent.

Preparation of 7α-Bromo Ketones. General Procedure. The given volume of glacial acetic acid was heated to the indicated temperature. Pyridinium hydrobromide perbromide (PHP) and the steroid were then added immediately and the solution was swirled vigorously with no further heating. After 4–11 min, the light yellow solution was diluted with water and the product was collected, washed with much water, and recrystallized as noted.

A. 5-Hydroxy-7α-bromo-5α-cholestan-6-one (2b). Reaction of 16.169 g (40.22 mmol) of **2a**[11] with 12.947 g (40.47 mmol) of PHP in 400 ml of HOAc at 70 °C gave, after successive recrystallizations from aqueous acetone and acetone–methanol, 5.855 g of **2b** as white needles: mp 148.5–150.5 °C, dec 177 °C; $[\alpha]D$ +7°; IR ($CHCl_3$) 3571, 1709 cm^{-1}; UV 336 nm (ε 98); NMR 40 (s, 3, 18-H), 47.5 (s, 3, 19-H), 136 (s, 1, OH), 252 Hz (d, J = 3 Hz, 1, C-7 H). Column chromatography (silica gel) of the mother liquor residue yielded an additional 1.674 g of **2b** from ether–methanol, mp 151.5–152.5 °C (total yield, 39%).

Anal. Calcd for $C_{27}H_{45}BrO_2$ (481.55): C, 67.34; H, 9.42; Br, 16.60. Found: C, 67.37; H, 9.23; Br, 16.76.

B. 3β-Acetoxy-5-hydroxy-7α-bromo-5α-cholestan-6-one (2e). Treatment of 50.73 g (110.1 mmol) of **2d**[8] with 35.60 g (111.3 mmol) of PHP in 1550 ml of HOAc at 90 °C gave a crude product that was recrystallized from acetone–methanol to yield 36.67 g (62%) of **2e** as fluffy, white needles with double mp 151–153 °C, 167.5–168 °C, dec 197 °C. Recrystallization of a sample from petroleum ether gave mp 171–172.5 °C; $[\alpha]D$ +8°; IR ($CHCl_3$) 3575, 3430, 1720, 1710 cm^{-1}; UV 334 nm (ε 97); NMR 42 (s, 3, 18-H), 49.5 (s, 3, 19-H), 120.5 (s, 3, AcO), 195 (s, 1, OH), 252 (d, J = 3 Hz, 1, C-7 H), 307 Hz (m, $W_{1/2}$ = 22 Hz, 1, C-3 H) [lit. mp 170–171 °C; $[\alpha]D$ +7.5° (dioxane);[8] $[\alpha]D$ +7° ($CHCl_3$); UV 333.5 nm (ε 109)[5]].

C. 3α-Acetoxy-5-hydroxy-7α-bromo-5α-cholestan-6-one (2h). Reaction of 11.716 g (25.432 mmol) of **2g**[12] with 8.267 g (25.84 mmol) of PHP in 300 ml of HOAc at 95 °C yielded, from petroleum ether, 5.858 g (43%) of **2h** as small, white needles, mp 142–143 °C, dec 195 °C. Recrystallization of a sample from ether–petroleum ether gave mp 144–144.5 °C; $[\alpha]D$ +15°; IR 3571, 1751, 1721 cm^{-1}; UV 334.5 nm (ε 101); NMR 42 (s, 3, 18-H), 48.5 (s, 3, 19-H), 125 (s, 3, AcO), 211 (s, 1, OH), 253 (d, J = 3 Hz, 1, C-7 H), 318 Hz (m, $W_{1/2}$ = 9 Hz, 1, C-3 H).

Anal. Calcd for $C_{29}H_{47}BrO_4$ (539.60): C, 64.55; H, 8.78; Br, 14.81. Found: C, 64.55; H, 8.76; Br, 14.62.

5-Hydroxy-7β-bromo-5α-cholestan-6-one (2c). A solution of 7.111 g (14.77 mmol) of **2b** and 7.74 g (89.4 mmol) of anhydrous LiBr[6a] in 200 ml of DMF was stirred magnetically at room temperature for 166.5 h.[13] The colorless solution was treated with 9 ml of glacial HOAc and diluted with 250 ml of water. The mixture was extracted twice with ether and the combined extracts were washed twice with water, once (rapidly) with 0.1 N aqueous KOH, and again with water, and dried. The white solid obtained by removal of the solvent was chro-

matographed on 125 g of silica gel. Elution with benzene gave 738 mg of unchanged **2b** which was recrystallized from methanol to yield 570 mg as white needles with mp 151–152.5 °C. Further elution with benzene gave 6.166 g (87%) of **2c** as a white solid. Recrystallization of a 190-mg sample from aqueous methanol and then methanol gave 106 mg of **2c** as small, white plates: mp 143.5–144 °C dec; $[\alpha]_D$ +35°; IR ($CHCl_3$) 3600, 3450, 1730 cm^{-1}; UV 299.5 nm (ϵ 56); NMR 41.5 (s, 3, 18-H), 46 (s, 3, 19-H), 121 (s, 1, OH), 312 Hz (d, J = 9 Hz, 1, C-7 H).

Anal. Calcd for $C_{27}H_{45}BrO_2$) (481.55): C, 67.34; H, 9.42; Br, 16.60. Found: C, 67.37; H, 9.43; Br, 16.33.

3β-Acetoxy-5-hydroxy-7β-bromo-5α-cholestan-6-one (2f). A mixture of 27.68 g (51.30 mmol) of **2e** and 54.53 (629.7 mmol) of LiBr in 1 l. of DMF was maintained at 75 ± 2 °C for 24 h. The burgundy colored solution was cooled, then poured into a mixture of crushed ice and 120 ml of glacial HOAc. The orange solid was collected, washed with water, dried, and chromatographed on 454 g of alumina. The material eluted with 10% ether–benzene was recrystallized from CCl_4–methanol, giving 10.20 g of **2f** as off-white needles: mp 172.5–174 °C dec; $[\alpha]_D$ +4°; IR ($CHCl_3$) 3585, 3460, 1725, 1720 cm^{-1}; UV 300.5 nm (ϵ 50); NMR 42 (s, 3, 18-H), 48 (s, 3, 19-H), 120 (s, 3, AcO), 236 (s, 1, OH), ~302 (m, $W_{1/2}$ = 22 Hz, 1, C-3 H), 312 Hz (d, J = 8 Hz, 1, C-7 H) [lit.[6a] mp 176–177 °C; $[\alpha]_D$ 0°; IR 3580, 3460, 1728 cm^{-1}; UV 300 nm (ϵ 54); NMR 309 Hz (C-7 H)]. Concentration of mother liquor produced 1.623 g of **2f**, mp 170–173 °C dec.

A fraction (6.332 g) eluted with 25% ether–benzene was crystallized from CCl_4–methanol and recrystallized from methanol to give an additional 2.478 g of **2f** as white needles, mp 171–173 °C, dec 175.5 °C (total yield of **2f**, 52%).

3α-Acetoxy-5-hydroxy-7β-bromo-5α-cholestan-6-one (2i). A mixture of 4.619 g (8.560 mmol) of **2h** and 9.44 g (109 mmol) of LiBr in 140 ml of DMF was heated at 81 ± 3 °C for 18 h. The product was isolated in the manner employed for **2f**. Two recrystallizations from aqueous ethanol gave 3.534 g (77%) of **2i**, mp 159.5–161.5 °C, dec 205 °C. The product (UV, ϵ ~132) contained a small amount of some impurity which was removed by chromatography of a 327-mg sample on 20 g of alumina. Elution with benzene, combination of identical fractions, and recrystallization from 95% ethanol gave 184 mg of pure **2i** as white plates: mp 156–157 °C, dec 224 °C; $[\alpha]_D$ +24; IR 3560, 1750, 1740 cm^{-1}; UV 298.5 nm (ϵ 51); NMR 41.5 (s, 3, 18-H), 45 (s, 3, 19-H), 126 (s, 3, AcO), 192 (s, 1, OH), 309 (d, J = 9 Hz, 1, C-7 H), 321 Hz (m, $W_{1/2}$ = 9 Hz, 1, C-3 H).

Anal. Calcd for $C_{29}H_{47}BrO_4$ (539.60): C, 64.55; H, 8.78; Br, 14.81. Found: C, 64.64; H, 8.83; Br, 14.71.

5,7α-Dihydroxy-5α-cholestan-6-one (4a). A mechanically stirred solution of 910 mg (1.89 mmol) of **2c** and 1.00 g of $NaHCO_3$ in 35 ml of Me_2SO was heated at 98–99 °C for 4.75 h. Crushed ice was added to the hot solution and the resulting precipitate was collected, dried, and recrystallized from chloroform–petroleum ether to yield 485 mg of **4a**: mp 177–178 °C; $[\alpha]_D$ −49°; IR ($CHCl_3$) 3590, 3370, 1718 cm^{-1}; UV 325.5 nm (ϵ 71); NMR 38.5 (s, 3, 18-H), 46 (s, 3, 19-H), 234 (s, 2, OH), 234 Hz (d, J ~ 2 Hz, 1, C-7 H).

Anal. Calcd for $C_{27}H_{46}O_3$ (418.64): C, 77.46; H, 11.07. Found: C, 77.34; H, 11.02.

The solid obtained from the mother liquor was chromatographed on 25 g of silica gel. Elution with benzene yielded 62 mg of a white solid that was recrystallized from ether–methanol to give 35 mg (4.6%) of the oxetanone **3a** as white needles with mp 96–97 °C. Elution with ether produced an additional 104 mg of **4a** (74%).

5,7β-Dihydroxy-5α-cholestan-6-one (4b). A suspension of 2.434 g (5.054 mmol) of **2b** in 60 ml of Me_2SO was magnetically stirred as 15 ml of 1.03 N methanolic potassium hydroxide solution was added in one portion. The steroid dissolved within 2 min and after a total reaction time of 17 min, the yellow solution was poured into a mixture of crushed ice and salt. The product was extracted twice with ether and the combined extracts were washed twice with water and dried. The colorless oil (very weak C=O in IR) obtained by removal of the solvent was dissolved in 65 ml of acetone and 5 ml of water, then treated with 7 ml of 10% H_2SO_4. After 30 min, water was added and the precipitate was collected by filtration. Recrystallization from ether–petroleum ether gave 1.208 g of **4b** with mp 180–182 °C; $[\alpha]_D$ +4°; IR 3605, 3495, 3425, 1715 cm^{-1}; UV 294 nm (ϵ 55); NMR 39.5 (s, 3, 18-H), 44.5 (s, 3, 19-H), 179 (s, 2, OH), 276 Hz (d, J = 7 Hz, 1, C-7 H). One further recrystallization from the same solvents gave mp 183–184.5 °C. A further 519 mg of **4b** with mp 174–178 °C was obtained by recrystallization of the solid deposited from the first mother liquor (total yield, 82%).

Anal. Calcd for $C_{27}H_{46}O_3$ (418.64): C, 77.46; H, 11.07. Found: C, 77.52; H, 11.12.

5-Hydroxy-7β-tosyloxy-5α-cholestan-6-one (4c). A solution of 929 mg (2.22 mmol) of **4b** and 1.958 g (10.27 mmol) of *p*-toluenesulfonyl chloride in 5 ml of pyridine was allowed to remain at room temperature for 19 h. The gum that separated upon the addition of crushed ice and 5 ml of concentrated HCl was worked with a rod until it solidified. The product was filtered, washed with water, dried, and crystallized from petroleum ether yielding 1.235 g (97%) of **4c** with mp 157–161.5 °C, dec ~200 °C. Recrystallization from ether–cold methanol gave mp 167.5–169 °C, dec 215 °C; $[\alpha]_D$ +4°; IR 3605, 3510, 1744, 1600, 1185, 1175 cm^{-1}; NMR 37 (s, 3, 18-H), 42 (s, 3, 19-H), 144 (s, 3, ArMe), 164 (s, 1, OH), 350 (d, J = 8 Hz, 1, C-7 H), 433 (d, J = 8 Hz, 2, ArH), and 473 Hz (d, J = 8 Hz, 2, ArH).

Anal. Calcd for $C_{34}H_{52}O_5S$ (572.86): C, 71.29; H, 9.15; S, 5.60. Found: C, 71.01; H, 9.33; S, 5.42.

Reaction of 7β-Bromo and 7β-Tosyloxy Ketones with Methanolic Potassium Hydroxide. General Procedure. To a magnetically stirred suspension of the steroid in Me_2SO was added a volume of standardized methanolic potassium hydroxide solution ("base").[3,6a] After a time at room temperature, the pale yellow solution was poured into an ice–salt–water mixture. The mixture was extracted twice with ether and the combined extracts were washed twice with salt water, dried, and evaporated. The products were isolated as indicated.

A. Bromo Ketone 2c. Treatment of 3.338 g (6.932 mmol) of **2c** with 4.60 ml of 1.21 N base in 115 ml of Me_2SO for 21 min gave a yellow oil that was chromatographed on 45 g of silica gel. Elution with 63% benzene–petroleum ether gave a white solid that was recrystallized from ether–methanol, yielding 1.475 g of 5,7α-epoxy-5α-cholestan-6-one (**3a**) as long, white needles: mp 96.5–97.5 °C; $[\alpha]_D$ −34°; IR 1810, 880, 855 cm^{-1}; UV 289.5 nm (ϵ 47); NMR 39 (s, 3, 18-H), 51 (s, 3, 19-H), 290 Hz (s, 1, C-7H).

Anal. Calcd for $C_{27}H_{44}O_2$ (400.62): C, 80.94; H, 11.07. Found: C, 80.78; H, 11.09.

Elution with 85% benzene–petroleum ether gave 169 mg of 5-hydroxy-7α-methoxy-5α-cholestan-6-one (**4d**) as an oil containing a trace of the oxetanone **3a**.

The solid eluted with benzene was recrystallized from methanol, yielding 304 mg of unreacted starting material 2c, mp 141–142.5 °C, dec 145 °C.

Fractions containing mixtures were combined and rechromatographed on 40 g of silica gel. Recovered were an additional 86 mg of oxetanone **3a**, mp 96.5–97.5 °C; 208 mg of bromo ketone **2c**, mp 142–143 °C, dec 143.5 °C; and 133 mg of the pure methoxy ketone **4d** as an oil that resisted crystallization but which gave the correct analysis: $[\alpha]_D$ −48°; IR 3495, 1720, 1075, 1060 cm^{-1}; UV 330.5 nm (ϵ 85); NMR 38 (s, 3, 18-H), 46 (s, 3, 19-H), 205 (s, 3, MeO), ~208 (d, J ~ 2 Hz, 1, C-7 H), 296 Hz (s, 1, OH).

Anal. Calcd for $C_{28}H_{48}O_3$ (432.66): C, 77.72; H, 11.18. Found: C, 77.81; H, 11.20.

Based upon recovered **2c**, total yields were 66% for **3a** and ~12% for **4d**.

B. Bromo Ketone 2f. Reaction of 9.172 g (17.00 mmol) of **2f** with 28.60 ml of 1.19 N base in 300 ml of Me_2SO for 7 min gave an oil that was chromatographed on 300 g of alumina. Elution with 25% ether–benzene gave semicrystalline material that crystallized from methanol, giving 3.753 g of 3β-hydroxy-5,7α-epoxy-5α-cholestan-6-one (**3b**) as white needles with double mp 70–75, 108–110 °C. Recrystallization from petroleum ether gave white prisms of **3b**: mp 108–110 °C; $[\alpha]_D$ −29°; IR 3630, 3440, 1812, 910, 885 cm^{-1}; UV 288.5 nm (ϵ 44); NMR 40.5 (s, 3, 18-H), 54 (s, 3, 19-H), 141 (s, 1, OH), 228 (m, $W_{1/2}$ = 24 Hz, 1, C-3 H), 297 Hz (s, 1, C-7 H) [lit.[6a] mp 174–177 °C; $[\alpha]_D$ 0°; IR 3612, 3430, 1815 cm^{-1}].

Further elution with 25% ether–benzene gave 1.275 g of solid that was recrystallized from petroleum ether, yielding 817 mg of 3β,5-dihydroxy-7α-methoxy-5α-cholestan-6-one (**4e**): mp 147–148 °C; $[\alpha]_D$ −48°; IR 3630, 3485, 1712, 1080, 1060 cm^{-1}; UV 331 nm (ϵ 34); NMR 39 (s, 3, 18-H), 48 (s, 3, 19-H), 206 (s, 3, MeO), ~208 (d, J ~ 2 Hz, 1, C-7 H), 244 (m, $W_{1/2}$ = 26 Hz, 1, C-3 H), ~244, 296 Hz (s, 2, OH).

Anal. Calcd for $C_{28}H_{48}O_4$ (448.66): C, 74.95; H, 10.78. Found: C, 74.72; H, 10.77.

The residues from all mother liquors were combined and rechromatographed on 50 g of alumina. Recovered were 523 mg of oxetanone **3b**, mp 111.5–113 °C, and 215 mg of the methoxy ketone **4e**, mp 145–147 °C.

Total yields: **3b**, 60%; **4e**, 14%.

C. Bromo Ketone 2i. The reaction of 2.699 g (5.002 mmol) of **2i** with 6.20 ml of 1.21 N base in 90 ml of Me_2SO for 7 min gave a colorless oil that was chromatographed on 40 g of silica gel. All fractions contained mixtures of oxetanone **3d** and other products. The fraction (259 mg) containing oxetanone of highest purity was recrystallized twice from 95% ethanol, giving 126 mg of pure 3α-hydroxy-5,7α-epoxy-

5α-cholestan-6-one (**3d**) as small, white needles: mp 112.5–114 °C; $[\alpha]_D$ −37°; IR 3610, 3480, 1810, 910, 885 cm^{-1}; UV 286.5 nm (ε 57); NMR 40.5 (s, 3, 18-H), 52 (s, 3, 19-H), 129 (s, 1, OH), 245 (m, $W_{1/2}$ = 8 Hz, 1, C-3 H), 299.5 Hz (s, 1, C-7 H).

Anal. Calcd for $C_{27}H_{44}O_3$ (416.62): C, 77.83; H, 10.65. Found: C, 78.00; H, 10.63.

Evaporation of the first mother liquor gave an additional 69 mg of **3d**, mp 110.5–112.5 °C. Other fractions (686 mg) rich in **3d** were combined and recrystallized twice from 95% ethanol, giving 48 mg of **3d**, mp 110.5–111.5 °C.

The remaining fractions and mother liquor residues were combined and acetylated in the usual manner.[7] The resulting mixture of acetates could not be resolved by thick layer chromatography on silica gel, hence was chromatographed on 120 g of alumina. Elution with benzene gave six homogeneous fractions which were combined and recrystallized from methanol, yielding 239 mg of 3α-acetoxy-5,7α-epoxy-5α-cholestan-6-one (**3e**) as soft, white needles, mp 93–95 °C. Recrystallization from aqueous methanol gave mp 94–95.5 °C; $[\alpha]_D$ −37°; IR 1810, 1738, 918, 885 cm^{-1}; UV 289.5 nm (ε 61); NMR 40.5 (s, 3, 18-H), 53 (s, 3, 19-H), 125 (s, 3, AcO), 296 (s, 1, C-7 H), 304 Hz (m, $W_{1/2}$ = 10 Hz, 1, C-3 H).

Anal. Calcd for $C_{29}H_{46}O_4$ (458.66): C, 75.94; H, 10.11. Found: C, 75.82; H, 10.18.

Total yield of oxetanone (**3d** + **3e**) 22%. All other fractions contained inseparable mixtures.

D. Tosyloxy Ketone 4c. A suspension of 346 mg (0.604 mmol) of **4c** in 16 ml of Me_2SO was treated with 0.50 ml of 1.179 N base for 10 min. The resulting oil was chromatographed on 14 g of silica gel. Elution with 80% benzene–petroleum ether produced 71 mg of a solid that was recrystallized from ether–methanol to give 50 mg (21%) of oxetanone **3a**, mp 95–96 °C. Further fractions contained mixtures of starting material and unidentified products.

3β-Acetoxy-5,7α-epoxy-5α-cholestan-6-one (3c). A sample (138 mg, 0.331 mmol) of oxetanone **3b** was acetylated in the usual manner.[6a] Recrystallization of the product from methanol gave 107 mg (70%) of **3c**: mp 110–110.5 °C; $[\alpha]_D$ −36°; IR 1810, 1740, 910, 885 cm^{-1}; UV 287.5 nm (ε 44); NMR 40.5 (s, 3, 18-H), 54 (s, 3, 19-H), 121.5 (s, 3, AcO), 290 (m, $W_{1/2}$ = 24 Hz, 1, C-3 H), 295 Hz (s, 1, C-7 H) [lit.[6a] mp 108–111 °C; $[\alpha]_D$ −23.3°; IR 1815, 1730 cm^{-1}]. Recrystallization from aqueous ethanol did not alter the melting point.

Registry No.—**2a**, 19043-54-0; **2b**, 60009-78-1; **2c**, 60803-76-1; **2d**, 1258-38-4; **2e**, 50630-98-3; **2f**, 50631-05-5; **2g**, 60803-77-2; **2h**, 60803-78-3; **2i**, 60803-79-4; **3a**, 60803-80-7; **3b**, 50631-08-8; **3c**, 50801-48-4; **3d**, 60803-81-8; **3e**, 60803-82-9; **4a**, 60803-83-0; **4b**, 60803-84-1; **4c**, 60803-85-2; **4d**, 60803-86-3; **4e**, 60803-87-4; PHP, 39416-48-3.

References and Notes

(1) This work was supported, in part, by grants from the Merck Co. Foundation and the Committee on Educational Aid of E. I. du Pont de Nemours and Co. The competent technical assistance of Thomas P. Demuth, Jr., Robert B. Nachbar, Jr., and Scott R. Wilson is gratefully acknowledged.
(2) Part 2: S. R. Funk and A. T. Rowland, *Steroids*, **14**, 477 (1969).
(3) A. T. Rowland, P. J. Bennett, and T. S. Shoupe, *J. Org. Chem.*, **33**, 2426 (1968).
(4) J. A. Donnelly and R. O'Donnell, *J. Chem. Soc., Perkin Trans. 1*, 1875 (1972).
(5) R. C. Cookson and S. H. Dandegaonker, *J. Chem. Soc.*, 352 (1955).
(6) (a) R. Hanna, G. Maalouf, and B. Muckensturm, *Tetrahedron*, **29**, 2297 (1973); (b) R. Hanna, *Tetrahedron Lett.*, 3349 (1973).
(7) See A. T. Rowland, *J. Org. Chem.*, **27**, 1135 (1962), and references cited therein.
(8) L. F. Fieser and S. Rajagopalan, *J. Am. Chem. Soc.*, **71**, 3938 (1949).
(9) J. A. Donnelly, J. G. Hoey, and R. O'Donnell, *J. Chem. Soc., Perkin Trans. 1*, 1218 (1974).
(10) J. Kagan and J. T. Przybytek, *Tetrahedron*, 29, 1163 (1973).
(11) H. Reich, F. E. Walker, and R. W. Collins, *J. Org. Chem.*, **16**, 1753 (1951).
(12) R. G. Schultz, *J. Org. Chem.*, **24**, 1955 (1959).
(13) In comparison to the relative facility with which **2b** was isomerized to **2c**, the C-5 epimer[3] of bromo ketone **2e** was recovered unchanged after 186 h at room temperature when treated with an equal mass of LiBr in DMF. Further treatment of the same sample with a 2.4-fold excess of LiBr in DMF at room temperature for 92 h gave no reaction. The difficulty encountered in the epimerization in the 5β-hydroxy series may be ascribed to the unfavorable interactions of the C_5–OH, C=O, and C_7–Br dipoles in the resulting 7β-bromo compound.

Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Naturally Occurring Substances. 47. Cannabinoid Compounds[1]

Robert A. Archer* and Douglas W. Johnson

The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46206

Edward W. Hagaman, Louis N. Moreno, and Ernest Wenkert*

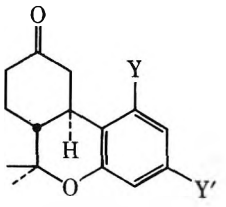
Department of Chemistry, Rice University, Houston, Texas 77001

Received July 19, 1976

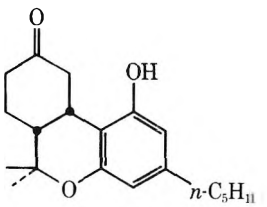
The ^{13}C NMR spectra of (−)-Δ⁹-THC, (−)-Δ⁸-THC, (±)-Δ⁸-*abn*-THC, (±)-*cis*-Δ⁹-THC, and four related ketones were recorded and their carbon shifts assigned. A ^{13}C NMR spectral diagnosis of the position of the double bond, location of the aromatic hydroxy and *n*-pentyl groups, and stereochemistry of the bridgeheads in THC derivatives is portrayed. A pyridine-induced shift procedure for the determination of phenol substitution patterns is introduced.

Several years have passed since the appearance of a ^{13}C NMR analysis of Δ⁸- and Δ⁹-tetrahydrocannabinol (THC) and some of their derivatives.[2,3] The carbon shift assignment had been based preponderantly on the correlation of the δ values among a small group of related compounds. In the light of present, better understanding of the chemical shift parameter as a function of bonding configuration, several shift correlations in the previous study are suspect. As a consequence a reinvestigation of Δ⁸- and Δ⁹-THC, with the use of additional ^{13}C NMR structure probes, was instituted, the goal of which being not only the proper shift assignment of the tetrahydrocannabinols but also the ^{13}C NMR differentiation of the natural products from their positional and stereochemical isomers. In the course of this work a technique for the recognition of the substitution pattern of phenols also came under study.

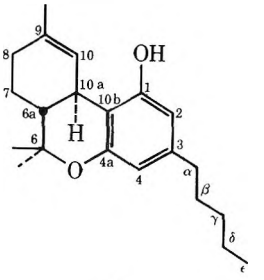
The analysis of eight substances—ketones **1a**,[5] **1b**, **1c**, and **2**,[5] (−)-Δ⁹-THC (**3**),[6,7] (−)-Δ⁸-THC (**4a**),[6,7] (±)-Δ⁸-*abn*-THC (**4b**), (±)-*cis*-Δ⁹-THC (**5**)[5]—was undertaken. The positional isomer **4b** of Δ⁸-THC and its ketone precursor **1c** were prepared in the following fashion. Treatment of the chromanone **6a**, prepared by the acid-induced condensation of olivetol and β-methylcrotonic acid,[5] with benzyl bromide and base and subsequent formylation of the resultant benzyl ether **6b**



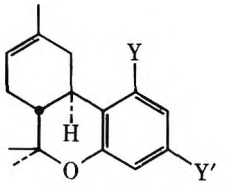
1a, Y = OH; Y′ = *n*-C_5H_{11}
b, Y = OCH_3; Y′ = *n*-C_5H_{11}
c, Y = *n*-C_5H_{11}; Y′ = *n*-OH



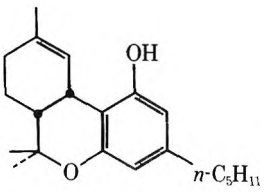
2



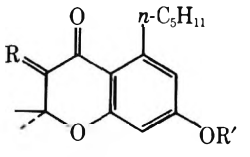
3



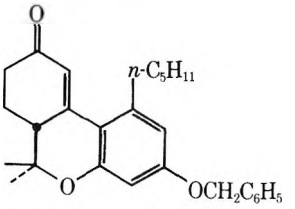
4a, Y = OH; Y′ = *n*-C_5H_{11}
b, Y = *n*-C_5H_{11}; Y = OH



5



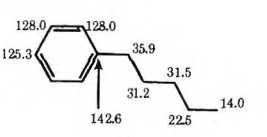
6a, R = H_2; R′ = H
b, R = H_2; R′ = $CH_2C_6H_5$
c, R = CHOH; R′ = $CH_2C_6H_5$



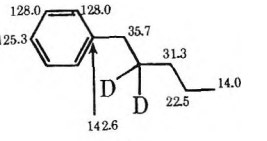
7

yielded the hydroxymethylene ketone **6c**. Base-catalyzed condensation of the latter with methyl vinyl ketone produced tricycle **7** whose reduction with lithium in ammonia afforded ketone **1c**. Exposure of the latter to methylmagnesium bromide and then to acid yielded Δ^8-*abn*-THC (**4b**), one of various THC isomers obtained by the acid-catalyzed condensation of olivetol with citral.[8]

The ^{13}C NMR analysis of the nonaromatic carbons of ketone **1a** proceeds in the following manner. Nonprotonated C(6) is a unique substitution site both in **1a** and all other cannabinoid compounds to be discussed and is insensitive to stereochemical changes at the nearby bridgehead centers. In view of C(10a) being benzylic the methines C(6a) and C(10a) of **1a** and the other substances can be distinguished by the difference of the magnitude of their residual coupling.[9,10] The methylenes of the *n*-pentyl side chain are distinguished from the ring methylenes by their shift equivalence with the methylenes of *n*-pentylbenzene (**8**). The side chain α carbon, a benzylic site, is recognized by its residual coupling, while the δ carbon is represented by a resonance characteristic of the second carbon from the end of a straight, long hydrocarbon chain.[9] The distinction of the β and γ carbons rests on the shift data of *n*-pentylbenzene (**8**) and its β,β-dideuterio derivative (**9**).[11] Surprisingly, the α and β carbons of the hydroxylated cannabinoid compounds are shielded (by ca. 0.5 ppm) with respect to like sites on *n*-pentylbenzene (**8**). Since the side chain carbon shifts of both the cannabinoid substances and model **8** are invariant over a 0.05–0.5 M concentration range, the effect cannot be the consequence of some molecular association and appears to be dipolar in nature. The field positions of the ketomethylenes of **1a** distinguish the latter from C(7), while their differentiation from each other is based on the similarity of the C(8) resonance to the ketomethylene shift of 4-*tert*-butylcyclohexanone[12] and the perturbation of the C(10) resonance of **1a** on methylation of the C(1) hydroxy group. In the methyl ether **1b** all tetrahedral carbons possess chemical shifts equivalent to those in **1a** except C(10), which is deshielded by 1.0 ppm. The sensitivity of the C(10) resonance to what is formally ϵ substitution suggests a strong steric compression of the C(1) substituent with H(10α). In the single-frequency off-resonance decoupled (sford) spectra of **1a–c** the C(10) resonance appears as a doublet of doublets revealing strong nonequivalence of the H(10α) and H(10β) resonances[10] whereas C(8) displays a triplet structure. The methyl groups of the dihydropyran ring differ from the side chain methyl unit by their exhibition of sharp quartets in the sford spectra due to the absence of vicinal hydrogens and second-order coupling. Owing to its nonbonded interactions with C(4a) and C(10a) the axial 6α-methyl group resonates ca. 9 ppm upfield of the 6β-methyl signal.



8



9

The aromatic carbon signals of **1a** are composed of a pair of upfield methines, a pair of downfield oxy carbons, and two nonprotonated centers. One occupies a high-field position as a consequence of shielding by two ortho oxygens. The differentiation of the oxy carbons from each other as well as the methines rests on a study of pyridine-induced shifts (vide infra). The large perturbation of the C(1) and C(2) resonances of **1b** by the *O*-methyl group allows the direct assignment of the aromatic carbons of this derivative.

The shift assignment of the nonaromatic carbons of ketone **1c** employs the same arguments as those used for the shift designation of like centers of **1a**. The dissimilarity of disposition of the aromatic methines and nonprotonated aromatic carbons to the oxy substituents permits their individual recognition. The aromatic oxy carbons are distinguished from each other by a pyridine-induced shift study (vide infra). Expectedly, the bridgehead methines and neighboring methylenes of the cis ketone are shielded with respect to like centers in **1a**.[13] Since the carbon–hydrogen coupling behavior of C(10) exhibited in **1a–c** (vide supra) is not duplicated in ketone **2**, the differentiation of the ketomethylenes of **2** relies on the assumed invariance of the C(8) shift despite configurational change of the ketones. The cis ring junction of **2** nullifies the large shift difference of the C(6) methyl groups. The carbon shifts of the four ketones **1a**, **1b**, **1c**, and **2** are listed in Table I.

The dramatic 4–5-ppm deshielding of the carbonyl resonance of **1a** with respect to **1b** and **1c** observed under identical conditions prompted a closer examination of the solvent and concentration dependence of this resonance in the ketone derivatives. The solvent dependence of the carbonyl resonance in aliphatic ketones has been previously characterized and interpreted in terms of dipolar and hydrogen bonding effects.[14,15]

In the presence of aprotic solvents, e.g., cyclohexane, ketonic carbonyl resonances experience increased shielding as the solute concentration is reduced while in protic solvents, e.g., chloroform, decreased shielding accompanies dilution. The former shifts presumably reflect the breakup of solute–solute interactions that are largely dipolar in nature and the down-

Table I. Carbon Shifts of Cannabinoid Compounds[a]

	1a[b]	1b[b,c]	1c[b]	2[b]	3	4a	4b	5
C(1)	155.3	158.1	143.0	155.6	154.4[f]	154.6[f]	143.3	153.4
C(2)	107.7	102.8	109.4	107.9	107.5	107.6	109.3	107.9
C(3)	143.4	143.0	155.2	143.1	142.5	142.4	154.4[f]	142.1
C(4)	108.7	109.9	102.0	108.8	109.8	109.8	102.0	109.5
C(4a)	154.2	153.9	154.3	153.9	154.1[f]	154.4[f]	154.2[f]	154.7
C(10b)	107.7	109.4	114.1	106.6	108.9	110.4	116.5	109.3
C(6)	76.4	76.3	76.1	75.8	77.1	76.3	76.1	76.1
C(6a)	47.3	47.4	48.9	40.0	45.7	44.8	46.4	40.0
C(7)	26.9	26.5	26.5	22.6	25.0	27.8	28.2	20.7
C(8)	40.7	40.7	40.3	41.4	31.1	119.1	119.7	29.7
C(9)	215.2[d]	210.6[e]	211.2	215.9	133.8	134.5	134.2	134.3
C(10)	44.7	45.8	48.4	38.7	123.7	35.9	38.6	122.0
C(10a)	34.7	34.7	35.8	31.1	33.6	31.5	33.2	31.4
6α-Me	18.8	18.6	18.2	24.7[f]	19.2	18.4	18.0	25.2[f]
6β-Me	27.7	27.8	27.5	26.3[f]	27.5	27.5	27.3	25.8[f]
9-Me					23.3	23.4	23.3	23.6
α-C	35.3	36.0	33.1	35.4	35.4	35.4	33.2	35.3
β-C	30.5	30.7	30.6	30.5	30.5	30.5	30.7	30.5
γ-C	31.6	31.6	31.6	31.5	31.4	31.5	31.8	31.5
δ-C	22.5	22.5	22.4	22.5	22.5	22.5	22.4	22.5
ε-C	14.0	13.9	13.9	14.0	14.0	14.0	14.0	14.0

[a] In parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b] Solute concentrations in $CDCl_3$ 0.5 M. [c] δ(OMe) 54.8 ppm. [d] This resonance appears at 213.5 ppm in 0.05 M $CDCl_3$ solution. [e] This resonance becomes 210.9 and 205.5 ppm in 0.05 M $CDCl_3$ and 0.5 M cyclohexane solution, respectively. [f] The signals in any vertical column may be reversed.

field shifts in protic solvents are the consequence of increased hydrogen bonding.[16] Dilution effects on ketone resonances are generally less than 2 ppm.

A tenfold reduction in the concentration of **1b** in deuteriochloroform solution (0.5 → 0.05 M) has an insignificant effect on the carbonyl resonance (210.6 → 210.9 ppm) while similar dilution of **1a** results in 1.7-ppm *shielding* of the carbonyl peak (see the legend of Table I). The latter shift, in contrast to that of simple monofunctional ketones,[15] most likely represents the net effect of decreased intermolecular hydrogen bonding between the carbonyl and phenolic hydroxyl functions (a shielding influence) and increased solvent–solute hydrogen bonding (a deshielding effect). The importance of the solvent–solute interaction in the absence of competition from a phenolic hydroxyl group is apparent from comparison of the carbonyl resonance of **1b** in deuteriochloroform (210.6 ppm) and in cyclohexane solution (205.5 ppm) at equal concentrations.

These trends suggest that the carbonyl group of **1a** (and **2**) is involved in a strong solute–solute intermolecular hydrogen bond in 0.5 M deuteriochloroform solution which is eliminated in the methyl ether derivative, **1b**, and strongly inhibited in **1c**, wherein the *n*-pentyl and hydroxyl functions on the aromatic ring are inverted from their natural positions. The carbonyl resonance of the latter two substances, 210.6 and 211.2 ppm, respectively, is similar to that of 4-*tert*-butylcyclohexanone (211.6 ppm) at equal concentration in deuteriochloroform.

The magnitude of the carbonyl shift in **1a** due to solute–solute hydrogen bonding, evaluated from 0.5 M deuteriochloroform solutions of **1a** and **1b**, is 4.6 ppm. In contrast, the carbonyl resonance of 0.5 M deuteriochloroform solution of 4-*tert*-butylcyclohexanone shifts downfield 2.9 ppm in the presence of 1 equiv of phenol. Thus, this system, designed to mimic the solution behavior of **1a**, substantially underestimates the carbonyl shift in the latter.

These correlations suggest that the 4-ppm difference in the carbonyl resonance of **1a** and **1c** is due to contributions from two sources. The five-carbon side chain of **1c** may assume an extended conformation which decreases the stability of solute–solute intermolecular hydrogen bonds. On the other hand, **1a** (and **2**) possesses a geometric configuration in which the carbonyl and hydroxyl functions radiate from the same side of the molecule. This arrangement is sterically compatible with the formation of two equivalent carbonyl–hydroxyl hydrogen bonds in a head-to-tail manner between two solute molecules. The increased stability of this system can account for the larger carbonyl shift contribution from hydroxylic sources in **1a** vs. the 4-*tert*-butylcylohexanone–phenol mixture.

The analysis of the methylcyclohexenic THC derivatives, **3**, **4**, and **5**, is similar to that of the ketones **1** and **2**. Specific decoupling of the downfield part of the allylic and benzylic hydrogen region sharpens two methylene signals in the sford spectra of Δ^9-THC (**3**), thereby distinguishing C(8) from C(7). The sford spectra of **3** exhibit three distinct multiplet patterns for the methyl groups, sharp quartets for those at C(6), a doublet of quartets for the 9-methyl function, and a complex second-order multiplet for the side chain terminal carbon. Under sford conditions of large olefinic carbon–hydrogen coupling the methyl group of the methylcyclohexene moiety of any of the THC derivatives shows a doublet of quartets which coalesces into a quartet upon direct olefinic hydrogen irradiation.

The allylic methylenes of Δ^8-THC (**4a**) may be differentiated by C(10) revealing a doublet of doublets in the sford spectra. This fact and the expected C(7) shift invariance distinguishes the two methylenes from each other in **4b**. In accord with the ca. 2.5 ppm and ca. 5 ppm shielding of allylic and homoallylic carbons of strain-free cyclohexenes,[17] respectively, by the double bond the difference of the C(7), C(6a), and C(10a) shifts between Δ^9-THC (**3**) and Δ^8-THC (**4a**) is 2.8, −0.9, and −2.1 ppm, respectively, hence close to the ideal 2.5, 0, and −2.5 ppm values. As in the stereochemical change of **1a** → **2** the conversion of Δ^9-THC (**3**) into *cis*-Δ^9-THC (**5**) shields the bridgehead methines and neighboring methylene and decreases dramatically the shift difference between the 6-methyl groups.

Neither chemical shift correlations nor coupling information are sufficient in distinguishing certain sets of aromatic carbon pairs among both the ketones (**1** and **2**) and THC derivatives (**3**, **4**, and **5**). Since all these substances are phenols, it was of interest to develop a ^{13}C NMR procedure of shift diagnosis useful for this class of compounds. In view of the

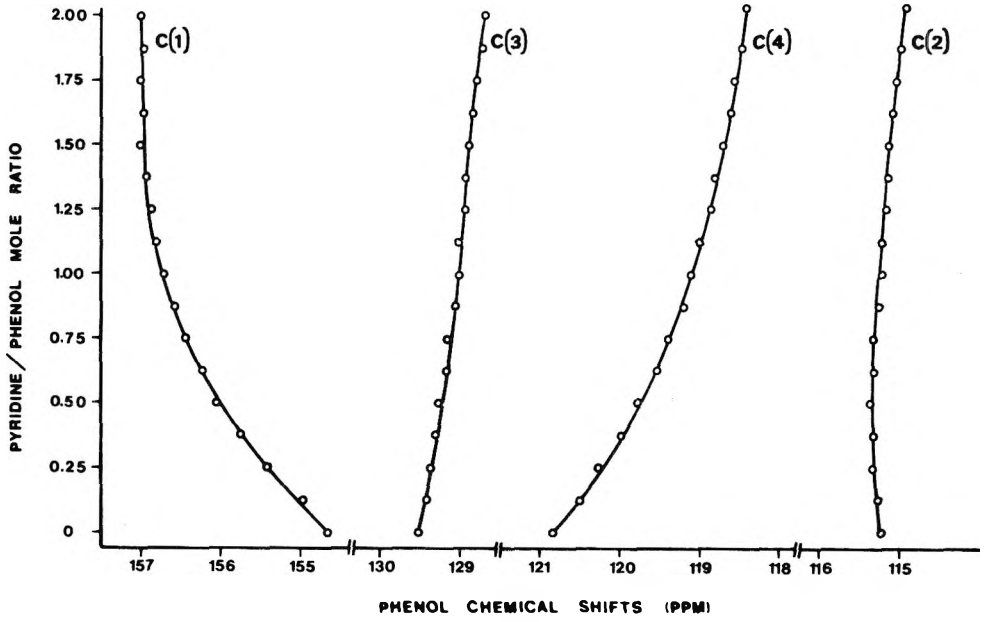


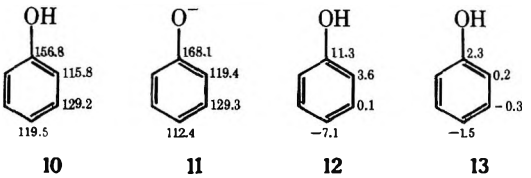
Figure 1.

Table II. Phenol Carbon Shifts and Pyridine-Induced Shift Differences

δ^a	14a	14b	14c[b]	14d	15a	15b	16a	16b	17a	17b	18
C(1)	154.6	153.2	153.9	145.1	154.6	156.3	152.5	149.2	151.8	153.6	159.3
C(2)	115.2	123.9	136.0	146.3	115.9	101.5	115.0	115.9	122.9	135.7	113.7
C(3)	129.5	130.8	126.8	110.6	139.6	160.3	129.8	114.8	128.3	124.7	129.2
C(4)	120.8	120.6	120.4	119.9	121.6	106.3	129.2	152.9	120.0	119.5	120.4
C(5)	129.5	126.8	126.8	121.1	129.2	130.0	129.8	114.8	128.3	124.7	129.2
C(6)	115.2	114.8	116.4	114.3	112.2	107.9	115.0	115.9	122.9	135.7	113.7
Me		15.6	29.5	55.5	21.1	55.1	20.2	55.6	15.6	30.3	54.8
$\Delta\delta^c$											
C(1)	2.3	1.9	2.0	1.0	2.0	1.7	1.9	1.6	1.2	−0.1	−0.2
C(2)	0.2	0.7	0.3	0.7	0.3	0.1	0.2	−0.2	0.7	0	−0.1
C(3)	−0.3	−0.1	−0.2	0.4	−0.5	0.3	−0.2	−0.6	−0.2	−0.2	−0.2
C(4)	−1.5	−1.3	−1.1	−0.7	−1.3	−1.4	−0.9	−0.6	−0.5	−0.2	−0.2
C(5)	−0.3	−0.3	−0.2	−0.3	−0.2	−0.4	−0.2	−0.6	−0.2	−0.2	−0.2
C(6)	0.2	0	0.1	0.7	0.3	−0.1	0.2	−0.2	0.7	0	−0.1

[a] The δ values in parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b] The quaternary carbon is at 34.4 ppm. [c] $\Delta\delta_{CDCl_3} = \delta_{CDCl_3}$ (1:1 phenol–pyridine) $- \delta_{CDCl_3}$ (phenol).

diagnostic value of pyridine-induced shifts in the ^1H NMR spectroscopy of phenols[18,19] a study of the effect of pyridine on their ^{13}C NMR spectra was undertaken. A simple, nondestructive procedure utilizing the acid properties of phenols is shown in Figure 1. The introduction of pyridine into a deuteriochloroform solution of phenol shields the para carbon and deshields the ipso center. While the complex behavior of the ortho and meta carbon resonances defy simple explanation, their shifts are small in comparison to those of the ipso and para carbons. The shift pattern is similar to the $\Delta\delta$ values depicted in formula **12**, derived from the shifts of phenol (**10**) and potassium phenoxide (**11**) in *tert*-butyl alcohol solution.[20] The $\Delta\delta$ values for 1:1 molar phenol–pyridine mixture in deuteriochloroform are shown on formula **13**. A comparison of the relative magnitude of shift differences (**12** vs. **13**) shows the pyridine-induced shifts to be the consequence of a natural



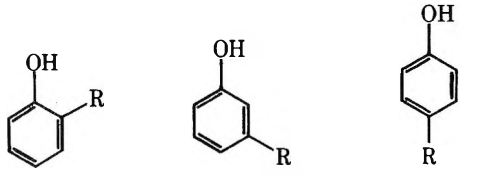
10 **11** **12** **13**

phenol response to base.[21] Since most of the pyridine-created shift is observed already at 1:1 molar ratio of substrate and pyridine and since at this pyridine concentration the aromatic spectral region is affected only minimally, it is convenient to record the pyridine shifts at this phenol–base ratio.

To test the generality of the pyridine-induced shift, the phenols **14–17** and anisole (**18**) were submitted to ^{13}C NMR study. The δ and $\Delta\delta$ values for the phenols are portrayed in Table II. The shift difference data reveal characteristics which are independent of the phenol substitution pattern, i.e., the downfield shift of the ipso carbon is always the largest perturbation. The ipso effect is constant with the notable exceptions of those in **14a, 14d, 17a,** and **17b.** Phenol (**14a**) displays somewhat larger shift differentials indicating that any alkoxy or alkyl ring substitution, independent of position, attenuates this parameter. Analogously, as the data for *p*-cresol (**16a**) and the monomethyl ether of hydroquinone (**16b**) show, the shielding $\Delta\delta$ value of the para carbon resonance, the next largest perturbation, is also subject to attenuation when the para carbon is substituted.

Comparison of the series—phenol (**14a**), 2,6-dimethylphenol (**17a**), and 2,6 di-*tert*-butylphenol (**17b**)—reveals that steric resistance to phenol hydrogen bond formation decreases

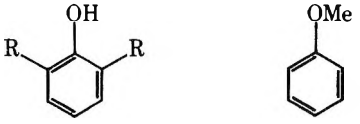
all pyridine-induced shifts of the ring carbons. The minimal shifts of the latter substance are experimentally indistinguishable from those observed in the absence of any ionizing phenolic hydroxy group, e.g., **18**, and indicate a limit to the successful application of this criterion for signal assessment. In the case of the intramolecularly hydrogen-bonded phenol, **14d**, the characteristic ipso and para effects are reduced to one-half of those observed for phenol itself. The shifts are consistent with the notion that guaiacol is stabilized by the intramolecular hydrogen bond and is less prone to complex with pyridine. The nearly superimposable $\Delta\delta$ values of **14d** and **17a** support this idea. The pyridine shift study permits the heretofore difficult shift assignment of the C(4) and C(5) carbon resonances of guaiacol (**14d**).



14a, R = H
b, R = Me
c, R = CMe_3
d, R = OMe

15a, R = Me
b, R = OMe

16a, R = Me
b, R = OMe



17a, R = Me
b, R = CMe_3

18

The aromatic methines in the THC derivatives **1a, 2, 3, 4a,** and **5**, containing the natural aromatic substitution pattern, possess similar chemical shifts due to their symmetrical disposition to the aromatic ring substituents. This symmetry also leads to similar δ values for the oxygenated aromatic centers in these substances. The aromatic oxy carbons of **1c** display chemical shifts identical with those in **1a** in spite of the inverted C(1)/C(3) substitution pattern. However, application of the pyridine-induced shift criterion to the ambiguous aromatic signals of these THC derivatives permits their assignment. Thus in Δ^8-THC (**4a**) the 107.6- and 109.8-ppm methine signals show $\Delta\delta$ values of 0 and −0.9 ppm, respectively, for a deuteriochloroform solution of an equimolar **4a**–pyridine mixture, indicating the latter signal to be that of the carbon para to the phenolic hydroxy group. Similarly, the 154.2- and 155.3-ppm oxy carbons of **1a** and the 154.3- and 155.2-ppm oxy carbons of 1c reveal $\Delta\delta$ values of +0.8 and −0.1 ppm and +1.3 and −0.1 ppm, respectively, allowing the assignment of the high-field resonance of each set to the carbon holding the phenolic hydroxy group.

In summary, the following comments indicate ^{13}C NMR spectroscopy to be useful in the structure analysis of THC derivatives. The determination of the cyclohexene double bond position, e.g., Δ^9-THC (**3**) vs. Δ^8-THC (**4a**), follows from inspection of sford spectra. The double bond isomers differ by their number of allylic methylenes, carbon types easily recognized by their one-bond, residual coupling behavior. In addition, Δ^8 systems which possess a trans ring junction reveal a unique C(10) coupling pattern as a consequence of the large, magnetic nonequivalence of the C(10) hydrogens. Stereochemical isomerism, e.g., **1a** vs. **2** and **3** vs. **5**, is indicated readily by the shift difference of the geminal 6-methyl groups. Positional isomerism, e.g., **1a** vs. **1c** and **4a** vs. **4b**, is reflected by the benzylic methylene shift, 35.4 ppm in its natural state and 33.2 ppm in the *abnormal* series, and by the difference of the aromatic methine shifts.[22]

Experimental Section

The ^{13}C NMR spectra were recorded on a Varian XL-100-15 spectrometer operating at 25.2 MHz in the Fourier transform mode. The compounds in Table II were examined as 3.3 M deuteriochloroform solutions, with eight successive additions of pyridine to reach a 1:1 pyridine–substrate molar ratio. Within these concentrations of pyridine the deuteriochloroform resonance shifts 5 ± 1 Hz downfield. The $\Delta\delta$ values in Table II have been corrected for this drift of the internal reference. The shifts on formulas 8 and **9** are in parts per million downfield from Me_4Si, $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm, while those of **10** and **11** are in parts per million downfield from internal Me_4Si.

7-Benzyloxy-2,2-dimethyl-5-*n*-pentyl-4-chromanone (6b). A mixture of 60.0 g of 2,2-dimethyl-5-*n*-pentyl-7-hydroxy-4-chromanone (**6a**),[5] 47.0 g of benzyl bromide, and 47.5 g of potassium carbonate in 500 ml of acetone was refluxed for 3 h. It then was filtered and the filtrate evaporated under reduced pressure. Chromatography of the residue on 1 kg of silica gel and elution with 10–20:1 hexane–ether yielded 78.1 g (97%) of colorless, oily ketone **6b**: ^1H NMR ($CDCl_3$) δ 0.88 (t, 3, J = 7 Hz, pentyl Me), 1.43 (s, 6, Me_2), 0.7–1.5 (m, 6, methylenes), 2.60 (s, 2, $COCH_2$), 3.00 (t, 2, J = 8 Hz, $ArCH_2$), 5.06 (s, 2, OCH_2), 6.35, 6.45 (d, 1 each, J = 3 Hz, aromatic H), 7.42 (m, 5, aromatic H of $C_6H_5CH_2O$).

Anal. Calcd for $C_{23}H_{28}O_3$: C, 78.38; H, 8.01. Found: C, 78.62; H, 7.80.

7-Benzyloxy-2,2-dimethyl-3-hydroxymethylene-5-*n*-pentyl-4-chromanone (6c). A solution of 33.7 g of ketone **6b** in 77 ml (71.0 g) of ethyl formate was added dropwise onto 23.1 g of sodium hydride. After the initial reaction had subsided, 100 ml of dry ether was added carefully and the mixture refluxed for 2 h. It then was poured onto ice and neutralized with 6 N hydrochloric acid. The aqueous phase was extracted exhaustively with ether and the combined organic phase and extracts were washed with water and saturated brine, dried over anhydrous sodium sulfate, and evaporated. Chromatography of the residue, 39.1 g, over 500 g of silica gel and elution with benzene yielded 13.6 g (37%) of pale yellow, oily ketone **6c**; m/e 380 (M^+); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3, J = 7 Hz, pentyl Me), 1.52 (s, 6, Me_2), 0.7–1.5 (m, 6, methylenes), 3.05 (t, 2, J = 8 Hz, $ArCH_2$), 5.04 (s, 2, OCH_2), 6.31, 6.46 (d, 1 each, J = 3 Hz, aromatic H), 7.36 (m, 5, aromatic H of $C_6H_5CH_2O$), 7.71 (d, 1, J = 8 Hz, OCH) (s after D_2O exchange), 15.6 (d, 1, J = 8 Hz, OH) (exchanges with D_2O).

Anal. Calcd for $C_{24}H_{28}O_4$: C, 75.76; H, 7.42; O, 16.82. Found: C, 76.06; H, 7.40; O, 17.06.

***trans*-6,6-Dimethyl-6,6a,7,8,10,10a-hexahydro-3-hydroxy-1-*n*-pentyl-9*H*-dibenzo[*b,d*]pyran-9-one (1c).** A solution of 13.6 g of ketone **6c**, 5.0 g of methyl vinyl ketone, and 2 ml of triethylamine in 75 ml of methanol was stirred at room temperature for 18 h. It then was extracted with ether and the extract washed with 10% sodium carbonate solution, water, and saturated brine solution, dried over anhydrous sodium sulfate, and evaporated. A solution of the residual oil, 16.9 g, and 175 ml of 2 N aqueous potassium hydroxide in 175 ml of ethanol was refluxed for 18 h. It was neutralized with 6 N hydrochloric acid and separated. The aqueous phase was extracted with ethyl acetate and the combined organic phase and extracts washed with water, dried over anhydrous sodium sulfate, and evaporated. Chromatography of the residue, 15.6 g, on 500 g of silica gel and elution with 10:1 hexane–ether yielded 6.8 g (47%) of 3-benzyloxy-6,6-dimethyl-1-*n*-pentyl-6,6a,7,8-tetrahydro-9*H*-dibenzo[*b,d*]pyran-9-one (**7**): m/e 404 (M^+); ^1H NMR ($CDCl_3$) δ 0.89 (t, 3, J = 7 Hz, pentyl Me), 1.15 (s, 3, 6α-Me), 1.46 (s, 3, 6β-Me), 0.8–2.7 (m, 13, methylenes and CH), 5.02 (s, 2, OCH_2), 6.40 (d, 1, J = 2 Hz, olefinic H), 6.34, 6.50 (d, 1 each, J = 3 Hz, aromatic H), 7.37 (m, 5, aromatic H of $C_6H_5CH_2O$).

A solution of 6.8 g of ketone **7** in 50 ml of tetrahydrofuran was added dropwise to 400 ml of a blue liquid ammonia solution of lithium at −33 °C. When the color began to fade, more lithium metal was dissolved before further addition of **7**. After complete addition of starting ketone the reaction was stirred for 15 min, solid ammonium chloride then was added, and the ammonia allowed to evaporate. The residue was dissolved in water and extracted with ethyl acetate. The extract was washed with water and saturated brine solution, dried over anhydrous sodium sulfate, and evaporated. Chromatography of the residue, 6.0 g, on 100 g of silica gel and elution with 50:1 benzene–ethyl acetate gave 3.48 g of a viscous oil whose crystallization from ether–petroleum ether yielded plates of ketone **1c**: mp 120–121 °C; m/e 316 (M^+); ^1H NMR ($CDCl_3$) δ 0.87 (t, 3, J = 7 Hz, pentyl Me), 1.06 (s, 3, 6α-Me) 1.44 (s, 3, 6β-Me), 2.53 (t, 2, J = 8 Hz, $ArCH_2$), 0.8–3.5 (m, 14, methylenes, methines), 5.27 (s, 1, OH) (exchanges with D_2O), 6.18, 6.30 (d, 1 each J = 3 Hz, aromatic H).

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92; O, 15.17. Found: C, 75.91; H, 8.74; O, 15.07.

(±)-*trans*-3-Hydroxy-1-*n*-pentyl-6,6,9-trimethyl-6a,7,10,10a-tetrahydrodibenzo[*b,d*]pyran (4b). A solution of 2.48 g of ketone **1c** in 50 ml of ether was added dropwise to a refluxing solution of 3.2 M methylmagnesium bromide in 50 ml of ether and the heating continued for 18 h. The mixture was poured onto ice and acidified with 0.5 N hydrochloric acid. The aqueous layer was extracted with ether and the combined organic phase and extracts washed with water and saturated brine solution, dried over anhydrous sodium sulfate, and evaporated. Crystallization of the residue from cyclohexane–acetone gave 980 mg of solid alcohol. Chromatography of the mother liquor, 1.6 g, on 40 g of Florisil and elution with 10:1 benzene–ether yielded an additional 380 mg of alcohol. A mixture of 380 mg of the latter and 120 mg of *p*-toluenesulfonic acid in 50 ml of benzene with the presence of a Dean-Stark water separator was refluxed for 2 h. It then was poured into a 5% sodium bicarbonate solution and separated. The aqueous layer was washed with ether and the combined organic solutions dried and evaporated. This gave 200 mg of 10:1 (±)-Δ^8-*abn*-THC (**4b**) and an isomer: *m/e* 314; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3, J = 8 Hz, pentyl Me), 1.04 (s, 3, 6α-Me), 1.34 (s, 3, 6β-Me), 1.66 (s, 3, 9-Me), 0.8–2.0 (m, 12, methylenes, methines), 5.45 (m, 1, olefinic H), 6.14, 6.27 (t, 1, J = 3 Hz, aromatic H); spectra identical with those of **4b** obtained by the condensation of citral with olivetol (vide infra).

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 79.97; H, 9.39.

A solution of 2.80 g of boron trifluoride etherate in 10 ml of dry benzene was added slowly with stirring to a solution of 3.60 g of olivetol (5-*n*-pentylresorcinol) and 3.60 g of citral in 20 ml of benzene and the mixture stirred at room temperature under nitrogen for 18 h. Upon the addition of water it was extracted with ether and the extract washed successively with 2 N sodium hydroxide and with water and dried over anhydrous sodium sulfate. Evaporation of the ether yielded 5.87 g of an orange oil whose GPC analysis revealed ten main peaks including one for unreacted citral. Chromatography of the oil on 250 g of Florisil and elution with 750 ml of hexane, 750 ml of 20:1 hexane–ether, and 1.8 l. of 9:1 hexane–ether led in the middle fractions of the last solvent pair to 480 mg (7% yield) of (±)-Δ^8-*abn*-THC (**4b**) of at least 73% purity (by GPC, the major impurity being (±)-*trans*-Δ^8-THC), spectra and GPC retention time identical with those of **4b** above.

Registry No.—**1a**, 52195-11-6; **1b**, 60761-08-2; **1c**, 60734-16-9; **2**, 60761-09-3; **3**, 1972-08-3; **4a**, 5957-75-5; **4b**, 41408-34-8; **5**, 6087-73-6; **6a**, 16849-52-8; **6b**, 60705-74-0; **6c**, 60705-75-1; **7**, 60705-76-2; **14a**, 108-95-2; **14b**, 95-48-7; **14c**, 88-18-6; **14d**, 90-05-1; **15a**, 108-39-4; **15b**, 150-19-6; **16a**, 106-44-5; **16b**, 150-76-5; **17a**, 576-26-1; **17b**, 128-39-2; **18**, 100-66-3; benzyl bromide, 100-39-0; ethyl formate, 109-94-4; methyl vinyl ketone, 78-94-4.

References and Notes

(1) For part 46 see L. Merlini, R. Mondelli, G. Nasini, F. W. Wehrli, E. W. Hagaman, and E. Wenkert, *Helv. Chim. Acta*, **59**, 2254 (1976).
(2) E. Wenkert, D. W. Cochran, F. M. Schell, R. A. Archer, and K. Matsumoto, *Experientia*, **28**, 250 (1972).
(3) A publication on the ^{13}C NMR analysis of solely Δ^8- and Δ^9-THC appeared in 1973[4] without reference to the previous work or new data.
(4) B. L. Hawkins and J. D. Roberts, *Proc. Natl. Acad. Sci. U.S.A.*, **70**, 1027 (1973).
(5) K. E. Fahrenholtz, M. Lurie, and R. W. Kierstead, *J. Am. Chem. Soc.*, **89**, 5934 (1967).
(6) R. Mechoulam, "Marijuana", Academic Press, New York, N.Y., 1973.
(7) The authors are indebted to Dr. R. Mechoulam for a sample of this substance.
(8) This compound had been assumed in the previous study[2] to be *cis*-Δ^8-THC.
(9) E. Wenkert, B. L. Buckwalter, I. R. Burfitt, M. J. Gasić, H. E. Gottlieb, E. W. Hagaman, F. M. Schell, and P. M. Wovkulich, "Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Naturally Occurring Substances", in G. C. Levy, "Topics in Carbon-13 NMR Spectroscopy", Vol. 2, Wiley-Interscience, New York, N.Y., 1976.
(10) E. W. Hagaman, *Org. Magn. Reson.*, **8**, 389 (1976).
(11) Prepared by carbonate-catalyzed deuteration of valerophenone, reduction of the dideuterio product with lithium aluminum hydride, mesylation of the resultant alcohol, and in situ reduction with lithium aluminum hydride.
(12) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972.
(13) D. K. Dalling and D. M. Grant, *J. Am. Chem. Soc.*, **96**, 1827 (1972).
(14) G. E. Maciel and G. C. Ruben, *J. Am. Chem. Soc.*, **85**, 3903 (1963).
(15) G. E. Maciel and J. J. Natterstad, *J. Chem. Phys.* **42**, 2752 (1965).
(16) T. T. Nakashima and G. E. Maciel, *Org. Magn. Reson.*, **4**, 321 (1972).
(17) E. Wenkert, D. W. Cochran, E. W. Hagaman, F. M. Schell, N. Neuss, A. S. Katner, P. Potier, C. Kan, M. Plat, M. Koch, H. Mehri, J. Poisson, N. Kunesch, and Y. Rolland, *J. Am. Chem. Soc.*, **95**, 4990 (1973).
(18) P. V. Demarco, E. Farkas, D. Doddrell, B. L. Mylari, and E. Wenkert, *J. Am. Chem. Soc.*, **90**, 548 (1968).
(19) Thus, for example, the H(2) and H(4) shifts of 6.17 and 6.30 ppm, respectively, for a deuteriochloroform solution of **4b** are altered to 6.72 and 6.80 ppm, respectively, in pentadeuteriopyridine solution. The perturbation of two hydrogen shifts is indicative of the presence of two methines ortho to the phenolic hydroxy group and thus distinguishes the structure pattern of **4b** from that of **4a**.
(20) The spectrum of the phenoxide ion determined in ethanol/sodium ethoxide solution has been reported previously.[21] The chemical shifts found in the present study show exact agreement for the ipso carbon resonance and minor deviations (≤1 ppm) for the ortho and meta carbon resonances. The para carbon resonance observed here appears 2.5 ppm upfield from that given in the earlier study.
(21) G. E. Maciel and R. V. James, *J. Am. Chem. Soc.*, **86**, 3893 (1964).
(22) A ^{1}H NMR spectroscopic method that distinguishes positional isomers utilizing aromatic solvent shifts (cf. ref 18 and 19) has appeared recently [A. Arnone, R. Bernardi, L. Merlini and S. Servi, *Gazz.Chim. Ital.*, **105**, 1127 (1975)].

(±)-Deoxyvernolepin. A Cytotoxic Vernolepin Prototype

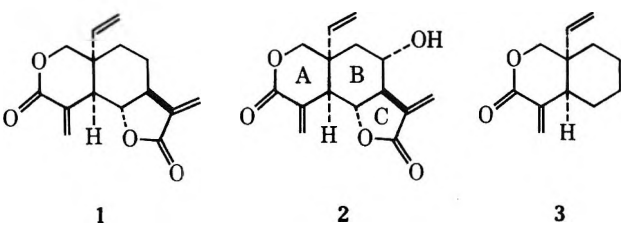
Paul A. Grieco,*[1] J. A. Noguez,[2] and Yukio Masaki

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Received July 7, 1976

The totally synthetic *trans*-decalone 4 possessing four chiral centers has been converted into (±)-deoxyvernolepin (1) via a sequence of transformations involving (a) cleavage of ring A, (b) introduction of the angular vinyl substituent by elimination of the o-nitrophenyl selenoxide derived from selenide 28, and (c) construction of the two α-methylene units via bis-α-hydroxymethylation of bisnordeoxyvernolepin followed by β-elimination. (±)-Deoxyvernolepin was tested as an inhibitor of the growth of CCRF-CEM human lymphoblastic leukemia cells in culture. Deoxyvernolepin was found to be at least an order of magnitude more potent than natural vernolepin.

We wish to disclose the details of the investigation which led to the total synthesis of deoxyvernolepin (1)[3] during the course of a program which had as its ultimate goal the total synthesis of vernolepin (2).[4] Deoxyvernolepin possesses both the ring A α-methylene-δ-valerolactone unit and the ring C α-methylene-γ-butyrolactone unit of vernolepin while lacking only the C-8 hydroxyl. The synthesis of deoxyvernolepin established the feasibility of bis-α-methylenation, indicating

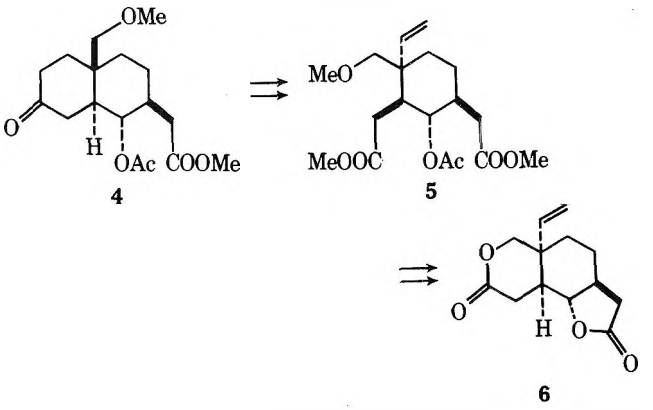


1 2 3

that such a process could be postponed until the final stages of a synthesis, and provided the needed synthetic methodology which set the stage for the successful completion of the total synthesis of vernolepin.[5] The key step in the synthetic route to 1 involves bis-α-hydroxymethylation of a dilactone enolate. In addition to the synthesis of 1 we report that the bifunctional α-methylene lactone system of deoxyvernolepin exhibits cytotoxicity against tumor cells in vitro. The studies revealed that *deoxyvernolepin is at least an order of magnitude more potent than natural vernolepin (vide infra).*

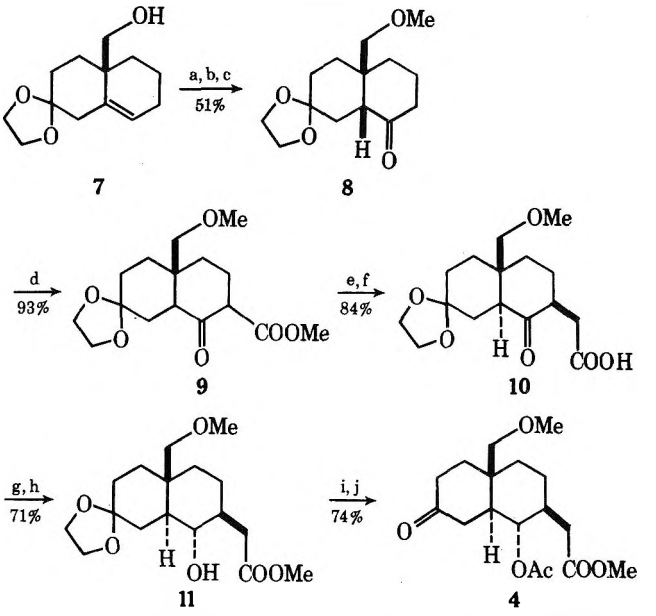
Our initial approach to deoxyvernolepin (Scheme I) centered around (a) construction of the *trans*-decalone **4** with all four chiral centers established, (b) cleavage of ring A with formation of the vinylcyclohexane derivative **5**, and (c) bislactonization of **5** to the tricyclic dilactone **6** (bisnordeoxyvernolepin) which would set the stage for bis-α-methylenation[6] employing the α-hydroxymethylation[7a] procedure introduced by us some years ago in conjunction with the synthesis of the vernolepin model **3**.[7b]

Scheme I

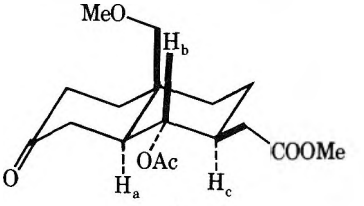


The preparation of decalone **4** (Scheme I) is outlined in Chart I. Hydroboration of the methyl ether of octalin **7** gave, in addition to the expected[8] β-oriented alcohol **12**, appreciable amounts (ca. 40%) of the tertiary alcohol[9] **12′** which upon treatment with 5% HCl in THF could be converted to octalone **13** and recycled. Collins oxidation[12] of the desired alcohol **12** proceeded smoothly in 96% yield to the *cis*-decalone **8**. That ketone **8** possessed the cis arrangement was demonstrated by its conversion to the thermodynamically more stable trans isomer **8′** via equilibration with sodium methoxide in refluxing methanol. At equilibrium the ratio of trans to cis was approximately 7:3. Introduction of the acetic acid side chain at C-7 (steroid numbering) in compound **8** was accomplished in a straightforward manner: (a) carbomethoxylation with formation of β-keto ester **9**, (b) alkylation of the sodium enolate of **9** with methyl bromoacetate, and (c) decarboxylation using barium hydroxide. A similar sequence of reactions for the introduction of an acetic acid unit adjacent to a carbonyl was recently employed in a total synthesis of (±)-isoalantolactone.[13] Reduction (sodium/2-propanol) and esterification of keto acid **10** generated the crystalline hydroxy ester **11**, mp 94–95 °C. During the course of the above chemical transformations equilibration at C-5 takes place (vide infra). Acetylation and deketalization of **11** produced the desired decalone **4**, mp 120 °C. The 250-MHz NMR spectrum of compound **4** exhibited a triplet centered at δ 4.75 for H_b with $J_{ab} = J_{bc} = 11$ Hz, indicating the required axial relationship between the three protons. Further support for the stereochemical assignment of structure **4** came from NOE measurements. Irradiation of the AB quartet centered at δ 3.53 ($-CH_2OMe$) resulted in a 14% enhancement of the H_b signal.

Chart I. Synthesis of the Key Intermediate *trans*-Decalone 4

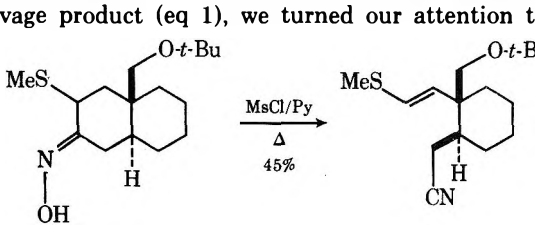


a, NaH, MeI, THF; b, BH_3·THF/OH^-, H_2O_2; c, CrO_3·2Py, CH_2Cl_2; d, NaH, $(MeO)_2CO$, dioxane; e, NaH, $BrCH_2COOMe$, dioxane; f, $Ba(OH)_2$·$8H_2O$, reflux; g, Na, *i*-PrOH; h, CH_2N_2, Et_2O; i, Ac_2O, Py; j, 5% HCl, THF



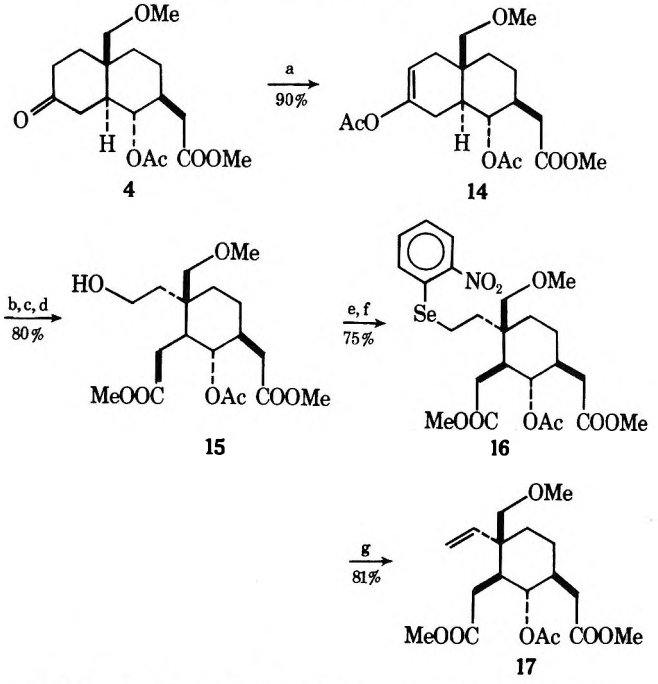
4

Having completed the synthesis of decalone **4**, which established the stereochemical requirements about the key asymmetric carbon atoms C-5, C-6, C-7, and C-10, attention was turned to the transformation of **4** to the tricyclic dilactone **6** (Scheme I). Specific cleavage of the C-2, C-3 carbon–carbon bond of the decalone derivative **4** with formation of an olefin between carbon atoms 1 and 2, and an ester moiety at C-3, so as to produce the highly functionalized cyclohexane derivative **5**, would upon bislactonization provide the desired tricyclic dilactone ring system. Having previously employed in the synthesis of **3**[7b] the second-order Beckman fragmentation of methylthio oximes[14] and obtained only moderate yields of cleavage product (eq 1), we turned our attention to the



(1)

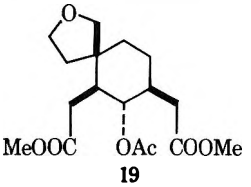
Chart II. Conversion of Decalone 4 to the Vinylcyclohexane Derivative 17



a, CH_2=C(OAc)CH_3, TsOH; b, O_3, MeOH–CH_2Cl_2 (2:3); c, BH_4^-, OH^-; d, CH_2N_2, Et_2O; e, MsCl, Py, 0°C; f, *o*-$O_2NC_6H_4SeCN$,[22] BH_4^-, DMF, room temperature; g, 50% H_2O_2, THF

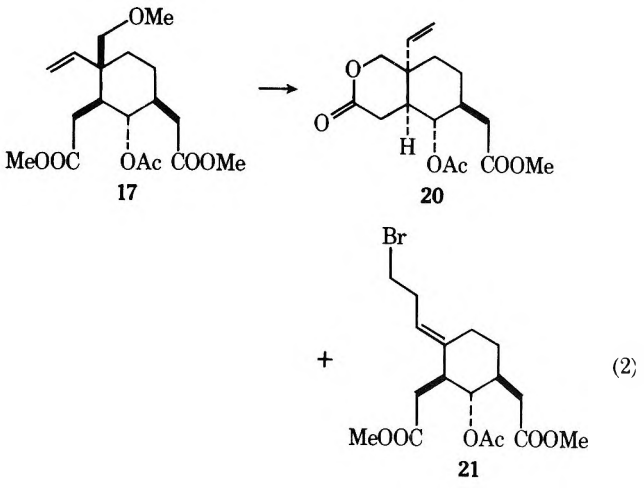
cleavage of the $\Delta^{2,3}$ enol acetate **14** derived from **4** (Chart II). Compound **4** upon enol acetylation with isopropenyl acetate under thermodynamically controlled conditions[15] resulted in exclusive formation of the crystalline $\Delta^{2,3}$ enol acetate **14**. It was to our advantage that none of the $\Delta^{3,4}$ isomer was formed.[16] it appears that the α-acetoxy function at C-6 interacts unfavorably with the C-4 proton of the $\Delta^{3,4}$ isomer. We have observed such effects with other α substituents at C-6.

Ozonolysis of **14** followed by a reductive workup and esterification resulted in an excellent yield of the cyclohexane derivative **15** possessing the all-trans arrangement of substituents. The hydroxyethyl side chain in compound **15** is potentially convertible into the required angular vinyl substituent employing the facile elimination of alkyl *o*-nitrophenylselenoxides recently introduced by Sharpless.[19] During the conversion of **15** to the o-nitrophenyl selenide **16** via the corresponding mesylate (**18**),[20-22] there was observed formation of the tetrahydrofuran derivative **19** in yields ranging from 0 to 11% (see Experimental Section). We believe that the

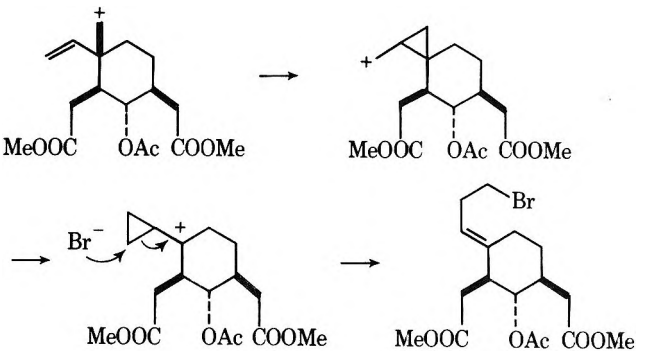


formation of **19** takes place via assisted displacement of the mesylate function followed by cleavage of the O–CH_3 bond by a nucleophile (presumably cyanide). Elimination of the corresponding o-nitrophenylselenoxide obtained by oxidation of selenide **16** established the angular vinyl group which was evident by NMR and IR analysis.

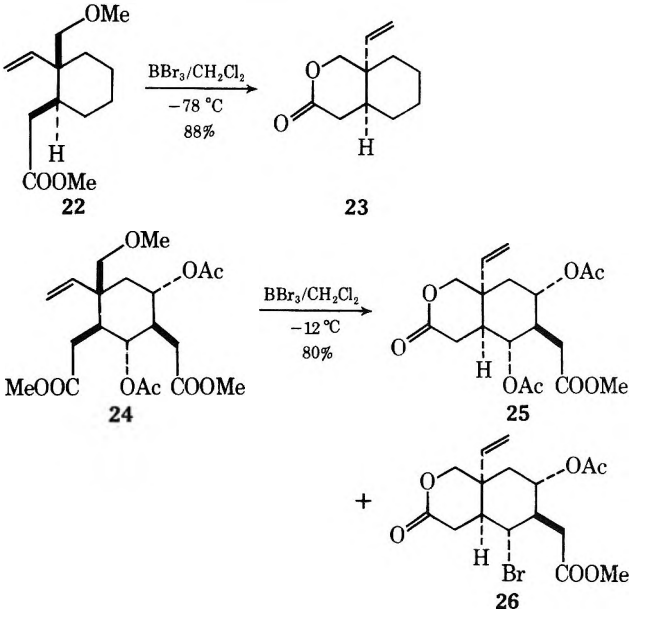
Attempted cleavage of the methyl ether **17** with boron tribromide (−78 °C) resulted in formation of lactone **20** in yields of 4–10%. The major product of the reaction (ca. 80%) was the homoallylic bromide **21** which apparently arises from cleavage of the "wrong" carbon–oxygen bond with formation of a homoallyl cation. A mechanism for the observed rearrangement



Scheme II

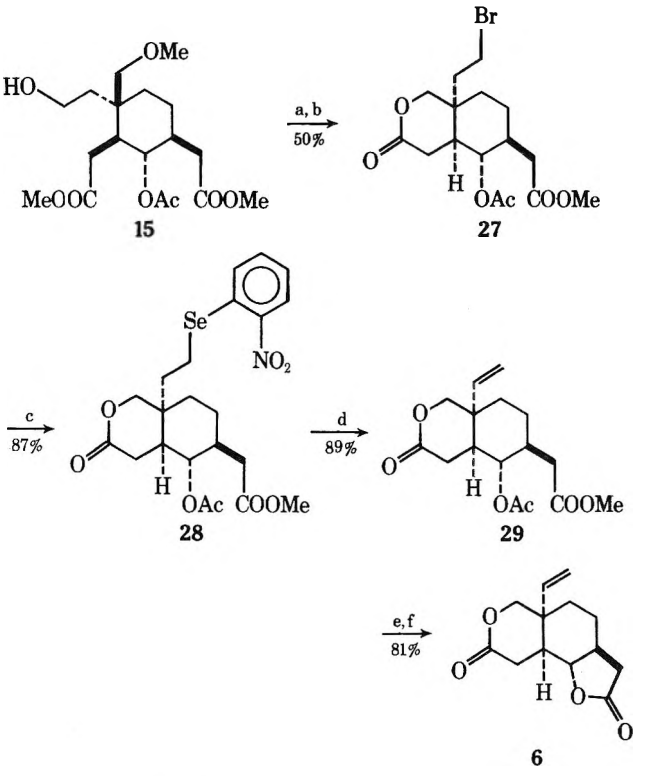


(**17** → **21**) is illustrated in Scheme II.[23] This result is surprising in view of previous work in our laboratory[17] in which we demonstrated that compound **22** undergoes smooth de-



methylation with boron tribromide providing in excellent yield the crystalline δ-lactone **23**. During the total synthesis of vernolepin we observed[5] that the more substituted methyl ether **24** similarly underwent smooth cleavage of the methyl ether with concomitant lactonization. No product derived from cleavage of the "wrong" carbon–oxygen bond was detected. It was indeed surprising in the case of **24** to find that the product was not exclusively the desired lactone **25**, but roughly an equal mixture of the desired compound **25** and a bromine-containing compound **26** in which the C-6 acetate function was replaced by a bromine atom with retention of

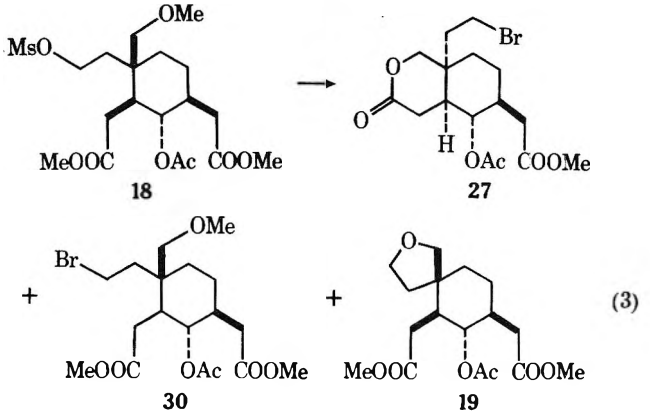
Chart III. Synthesis of Bisnordeoxyvernolepin (6)



a, MsCl, Py, 0°C; b, BBr_3, CH_2Cl_2, −78°C; c, *o*-$O_2NC_6H_4$-SeCN,[20,22] BH_4^-, DMF; d, 50% H_2O_2, THF; e, K_2CO_3, MeOH; f, TsOH, C_6H_6, reflux

configuration.[24] At present we have no reasonable explanation for the formation of the homoallylic bromide **21**.

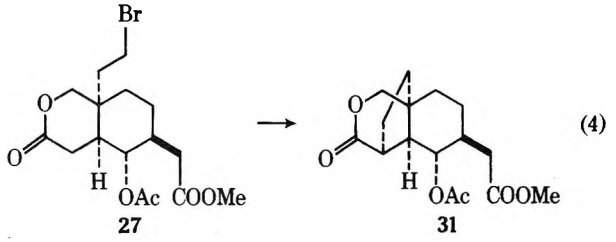
It therefore became apparent after many unsuccessful attempts at cleavage of the methyl ether **17** that any successful synthesis of deoxyvernolepin would require cleavage of the methyl ether prior to generation of the angular vinyl substituent (Chart III). Treatment of the mesylate **18** derived from the hydroxyethyl compound **15** with boron tribromide (eq 3)



(3)

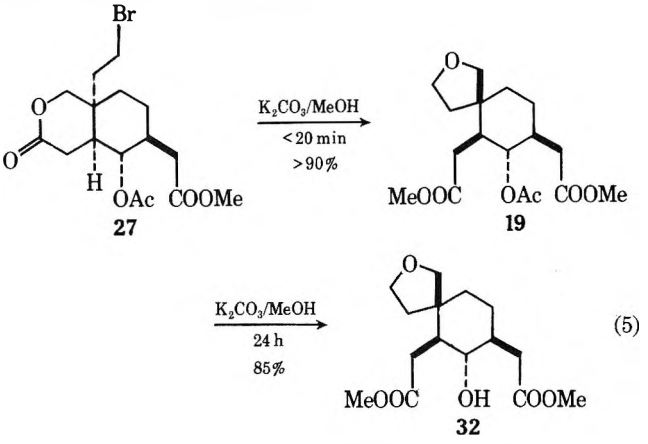
gave, in addition to the desired bromo lactone **27** (ca. 50%), the bromo ether **30** (13%) along with a trace of the tetrahydrofuran derivative **19**. In this particular reaction lactone closure competes with tetrahydrofuran ring formation.

Having thus succeeded in preparing a potential vinyl precursor we focused our attention on dehydrobromination of compound **27** with 1,5-diazabicyclo[5.4.0]undec-5-ene in benzene at room temperature. The reaction proceeded smoothly and in excellent yield, but not to the expected olefinic compound **29** (eq 4). There was obtained a tricyclic compound which has been tentatively assigned structure **31** on the basis of NMR, IR, and high-resolution mass spectra data (see Experimental Section).



(4)

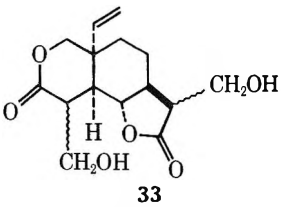
In an alternate approach to convert **27** to bisnordeoxyvernolepin (**6**), we attempted to first cleave the C-6 acetate function of **27** followed by γ-lactone formation. Treatment of compound **27** with anhydrous potassium carbonate in methanol under standard conditions for cleavage of an acetate resulted in a very facile reaction (eq 5) with formation of a new



(5)

compound which was less polar than the starting material. The compound was identified as the tetrahydrofuran derivative **19** on the basis of NMR, IR, MS, and TLC comparisons with a sample of **19** prepared earlier (eq 3). After prolonged treatment (20 h) with potassium carbonate in methanol, the hindered acetate function of **19** was cleaved.[26] In order to circumvent the problems associated with the above approaches (eq 4 and 5), we prepared the *o*-nitrophenyl selenide **28** from the bromo lactone **27** under conditions employed earlier for the preparation of **16**. Oxidation of **28** followed by elimination of the resultant selenoxide provided cleanly the olefinic compound **29** which was smoothly converted in the standard manner to the tricyclic dilactone **6**.

With bisnordeoxyvernolepin in hand, utilization and modification of the α-hydroxymethylation procedure[7a] paved the way for the completion of the total synthesis of deoxyvernolepin (**1**). Bis-α-hydroxymethylation of dilactone **6** in tetrahydrofuran containing 10% hexamethylphosphoramide gave the bis-α-hydroxymethylated adduct **33**. The use of hexamethylphosphoramide was essential in order to solubilize



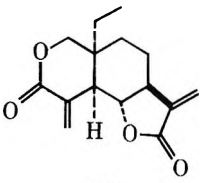
the dilactone enolate. In the absence of hexamethylphosphoramide only very poor yields of adduct **33** could be realized. Treatment of the mesylate derived from **33** with pyridine at elevated temperatures afforded crystalline deoxyvernolepin (**1**), mp 169–170 °C.

The synthetic deoxyvernolepin prepared above was tested,[27] along with natural vernolepin[28] and dihydrodeoxyvernolepin (**34**),[29] as inhibitors of the growth of CCRF-CEM human lymphoblastic leukemia cells in culture.[30] These cells have been characterized[31] as having an absolute nutritional

Table I. Growth Inhibition of CCRF-CEM Human Lymphoblastic Leukemia Cells in Culture by Unsaturated Lactones[27]

Compd	ID_{50}, μM
Dihydrodeoxyvernolepin (34)[29]	0.034
Deoxyvernolepin (1)	0.034
Vernolepin (2)[28]	0.43

requirement for exogenous L-cysteine. The use of CCRF-CEM cells to assay the growth-inhibitory properties of deoxyvernolepin and vernolepin was based on the expectation that these bis-α-methylene lactone systems would function as Michael acceptors[32] and thus scavenge cysteine.[33] The data in Table I indicate that deoxyvernolepin and dihydrodeoxyvernolepin are more active than vernolepin by at least one order of magnitude.



34

Experimental Section[34]

2,2-Ethylenedioxy-10-methoxymethyl-Δ⁸-octalin. To a suspension of 28.8 g (0.60 mol) of 50% sodium hydride (washed with hexane prior to use) in 650 ml of dry tetrahydrofuran at 0 °C was added dropwise a solution of 2,2-ethylendioxy-10-hydroxymethyl-Δ⁸-octalin (7,[35] 100 g, 0.45 mol) in 220 ml of dry tetrahydrofuran. The reaction mixture was warmed to room temperature and stirring was continued for 1 h after which time the reaction mixture was cooled to 0 °C. Methyl iodide (170 g, 1.2 mol) was added dropwise and stirring was continued after addition was complete for 16 h (room temperature). The solvent was removed under reduced pressure on a rotary evaporator and the resulting residue was treated with water and the product isolated by ether extraction.[36] The crude product (102 g, 95%) was homogeneous by TLC analysis on silica gel (benzene/ethyl acetate, 4:1; R_f 0.67) and was used directly in the next reaction. An analytical sample was obtained by column chromatography on silica gel (hexane/ether, 7:3) followed by distillation: bp 95 °C (bath temperature) (0.45 mm); IR (film) 1660 cm^{-1} (C=C); NMR (60 MHz) (CCl_4) δ 5.35 (bs, 1 H, C=CH), 3.80 (s, 4 H, $-OCH_2CH_2O-$), 3.25 (bs, 5 H, $-CH_2OCH_3$).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.34; H, 9.20.

***cis*-2,2-Ethylenedioxy-10-methoxymethyl-8-decalone (8).** To a solution of 34.0 g (0.14 mol) of 2,2-ethylenedioxy-10-methoxymethyl-Δ⁸-octalin in 600 ml of dry tetrahydrofuran cooled to 0 °C was added dropwise 149.6 ml (0.15 mol) of a 1.02 M tetrahydrofuran solution of borane under an atmosphere of nitrogen. The reaction mixture was stirred for 6 h at room temperature, cooled to 0 °C, and then treated with 4.6 ml of water, followed by 56 ml of 3 N aqueous sodium hydroxide and 56 ml of 30% hydrogen peroxide. After stirring for an additional 6 h at room temperature, the tetrahydrofuran was removed under reduced pressure on a rotary evaporator. The product was isolated from the resulting heterogeneous mixture by extraction with ether.[36] The residue amounted to 38.0 g of an oil which was chromatographed on 1000 g of silica gel. Elution with hexane/ethyl acetate (2:1) gave 15.8 g (43%) of the tertiary alcohol 12′ [R_f 0.73 (hexane/ethyl acetate, 1:1). Elution with ethyl acetate gave 20.3 g (56%) of *cis*-2,2-ethylenedioxy-10β-methoxymethyl-8β-decalol (12) [R_f 0.38 (hexane/ethyl acetate, 1:1)] as an oil: IR (film) 3450 cm^{-1}; NMR (60 MHz) ($CDCl_3$) δ 3.98 (m, 5 H, $-OCH_2CH_2O-$, CHOH), 3.38 (bs, 5 H, $-CH_2OCH_3$).

Collins oxidation of this alcohol (17.0 g, 0.066 mol) in 95 ml of dry methylene chloride was carried out in the following manner. To a flask equipped with a mechanical stirrer containing dry methylene chloride (715 ml) and dry pyridine (62.8 g, 0.79 mol) cooled to 0 °C under nitrogen was carefully added portionwise 39.7 g (0.39 mol) of chromium trioxide. After 15 min, the reaction mixture was warmed to room temperature and stirring was continued for 45 min. The methylene chloride solution of the alcohol was added, all at once, to the vigorously stirred reaction mixture. After 20 min, the organic layer was decanted and the remaining black tar was washed with 2 × 100 ml of ether. The remaining residue was dissolved in 600 ml of 5% aqueous sodium hydroxide and washed with 4 × 200 ml of ether. The combined organic layers were washed with 5% aqueous sodium hydroxide until the solution was light yellow followed by washing with water and brine. The organic layer was dried over anhydrous magnesium sulfate. Evaporation of the solvent in vacuo gave 16.1 g (96%) of 8 which was homogeneous by TLC analysis [silica gel (hexane/ethyl acetate, 3:1)], R_f 0.61: IR (film) 2950, 2875, 2825, 2800, 1705, 1481, 1458, 1431, 1390, 1360, 1310, 1290, 1230, 1200, 1170, 1100, 1030 cm^{-1}; NMR (60 MHz) (CCl_4) δ 3.88 (s, 4 H, $-OCH_2CH_2O-$), 3.30 (s, 3 H, OCH_3), 3.10 (AB q, 2 H, CH_2O). An analytical sample was prepared by distillation [110 °C (bath temperature) (0.15 mm)]. On standing, the sample crystallized, mp 59–61 °C.

Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 65.98; H, 8.81.

Carbomethoxylation of Ketone 8. A solution of 2.66 g (10.5 mmol) of ketone 8 in 4.0 ml of dry dioxane was added dropwise over 45 min to a stirred suspension of 1.05 g (20.9 mmol) of 50% sodium hydride (washed with hexane prior to use) and 4.64 g (51.6 mmol) of dimethyl carbonate in 9.0 ml of dry dioxane heated to 80–85 °C under nitrogen. After addition of the ketone, the reaction mixture was stirred at 80–85 °C for an additional 4 h followed by cooling to room temperature (6 h). The reaction mixture was cooled to 0 °C and acidified with a slight excess of 50% aqueous acetic acid, and the solvent was evaporated under reduced pressure. The residue was diluted with water and the product isolated by ether extraction.[36] The crude product (3.45 g) was purified on 40 g of silica gel. Elution with hexane/ethyl acetate (7:3) gave 3.02 g (93%) of ketone 9 as a mixture of isomers which was used directly in the next reaction: IR (film) 1740 (m), 1705 (m), 1650 (s), 1610 cm^{-1} (s); NMR (60 MHz) (CCl_4) δ 3.85 (s, 4 H, $-OCH_2CH_2O-$), 3.70 (s, 3 H, $COOCH_3$), 3.25 (s, 3 H, OCH_3), 3.10 (AB q, 2 H, $-CH_2O-$).

***trans*-2,2-Ethylenedioxy-10β-methoxymethyl-8-oxo-7β-decalylacetic Acid (10).** To a suspension of 233 mg (4.85 mmol) of a 50% sodium hydride dispersion (washed with pentane prior to use) in 5.0 ml of dry dioxane was added dropwise 1.01 g (3.23 mmol) of keto ester 9 in 5 ml of dry dioxane. After ca. 15 min, methyl bromoacetate (1.09 g, 7.1 mmol) was added and the reaction mixture was heated at 65 °C for ca. 45 min.

The reaction mixture was cooled in an ice water bath and acidified with 50% aqueous acetic acid. The solvent was concentrated in vacuo and the product was isolated by ether extraction.[36] There was obtained 1.07 g (86%) of alkylated material which was used directly in the next reaction.

To a solution of the above keto ester (726 mg, 1.89 mmol) in 8 ml of ethanol was added a solution of $Ba(OH)_2 \cdot 8H_2O$ (2.98 g, 9.46 mmol) in 20 ml of water. The reaction mixture was refluxed for 24 h. The solvent was removed under reduced pressure. The resulting residue was diluted with water and acidified with 5% hydrochloric acid. The product was isolated by ether extraction.[36] There was obtained after removal of the solvent in vacuo 575 mg (98%) of crystalline keto acid 10: IR ($CHCl_3$) 3700–2200, 1700 cm^{-1}; NMR (60 MHz) δ ($CDCl_3$) 9.86 (s, 1 H), 3.96 (s, 4 H), 3.21 (s, 5 H). Recrystallization from ether/hexane gave analytically pure β-keto acid, mp 143–144 °C.

Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.52; H, 7.74. Found: C, 61.46; H, 7.66.

Methyl *trans*-2,2-Ethylenedioxy-10β-methoxymethyl-8α-hydroxy-7β-decalylacetate (11). Sodium (36 g) in small portions was added over a 1.5-h period to a refluxing solution of keto acid 10 (4.88 g, 15.6 mmol) in 340 ml of 2-propanol. After refluxing for 4 h, 50 ml of 2-propanol was added to react with the remaining sodium metal (ca. 2 h). After cooling (0 °C), the mixture was neutralized with aqueous acetic acid and the solution was concentrated in vacuo. The residue was dissolved in ether and extracted with 5% aqueous potassium carbonate solution. The aqueous layer was neutralized with acetic acid. Isolation of the product by ether extraction[36] gave 5.2 g of crude acid. An analytical sample was obtained by crystallization from acetone, mp 178–179 °C.

Anal. Calcd for $C_{16}H_{26}O_6$: C, 61.13; H, 8.34. Found: C, 60.90; H, 8.18.

Esterification of the above carboxylic acid (5.2 g) with diazomethane gave, after crystallization from carbon tetrachloride/hexane, 3.1 g of pure hydroxy ester 11, mp 92–93 °C. Chromatography of the mother liquors on 10 g of silica gel [elution with hexane–ethyl acetate (7:3)] gave an additional 542 mg of pure product (total yield 71%): IR ($CHCl_3$) 3450, 2915. 2860, 2800, 1725, 1440, 1435, 1355, 1270, 1182, 1160, 1085, 1058, 1025, 990, 968, 940, 918, 880, 848, 808 cm^{-1}; NMR (60 MHz) (CCl_4) δ 3.88 (bs, 5 H, $-OCH_2CH_2O-$, CHO), 3.62 (s, 3 H,

$-COOCH_3$), 3.30 (bs, 5 H, $-CH_2OCH_3$). Recrystallization from carbon tetrachloride/hexane provided an analytically pure sample of decalol **11**, mp 94–95 °C.

Anal. Calcd for $C_{17}H_{28}O_6$: C, 62.18; H, 8.59. Found: C, 62.01; H, 8.62.

Methyl *trans*-10β-Methoxymethyl-2-oxo-8α-acetoxy-7β-decalylacetate (4). A solution of alcohol **11** (1.5 g, 4.57 mmol) in 12 ml of dry pyridine was treated with 12 ml of acetic anhydride at room temperature. After 18 h, the solvent was removed under reduced pressure. After isolation by ether extraction,[36] the product [1.6 g (98%), IR (film) 2920, 2870, 2700, 1730, 1441, 1435, 1362, 1238, 1182, 1141, 1091, 1055, 1010, 970, 960, 925, 800, 750 cm^{-1}; NMR (250 MHz) ($CDCl_3$) δ 4.76 (t, 1 H, J = 12.5 Hz), 3.97 (s, 4 H), 3.70 (s, 3 H), 3.51 (AB q, 2 H, J = 10 Hz, $\Delta\nu_{AB}$ = 13.7 Hz), 3.38 (s, 3 H), 2.14 (s, 3 H)] was deketalized in 18 ml of a 2:1 mixture of tetrahydrofuran/5% hydrochloric acid. After ca. 19 h at room temperature, the product was isolated by extraction[36] with ethyl acetate which gave 1.41 g of the crude decalone **4**. Crystallization from carbon tetrachloride/hexane gave 1.05 g (74%) of pure crystalline **4**: mp 120 °C; IR ($CHCl_3$) 3010, 2950, 2925, 2815, 1730, 1710, 1485, 1455, 1435, 1375, 1240, 1205, 1108, 1025, 975, 940 cm^{-1}; NMR (250 MHz) ($CDCl_3$) δ 4.75 (t, 1 H, J = 11 Hz), 3.59 (s, 3 H), 3.53 (AB q, 2 H, J = 9 Hz, $\Delta\nu_{AB}$ = 15.6 Hz), 3.34 (s, 3 H), 2.00 (s, 3 H).

Anal. Calcd for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03. Found: C, 62.31; H, 8.24.

Enolacetylation of Decalone 4. A mixture of decalone **4** (696 mg, 2.14 mmol) and 22 ml of isopropenyl acetate containing 130 mg of *p*-toluenesulfonic acid was refluxed (bath temperature, 96 °C) for 9 h. Upon cooling the reaction mixture, solid sodium bicrabonate was added to neutralize the acid present. The solvent was evaporated in vacuo on a rotary evaporator and the remaining residue was taken up in ether and washed with brine. The organic layer was dried (sodium sulfate) and the solvent evaporated leaving 1.07 g of crude product which crystallized on standing (780 mg, 98%). Recrystallization from ethyl acetate/hexane provided pure enol acetate, mp 120 °C: IR ($CHCl_3$) 2924, 2880, 2810, 1730, 1690, 1480, 1435, 1368, 1311, 1230, 1150, 1120, 1100, 1055, 1020, 970, 936, 905, 851 cm^{-1}; NMR (60 MHz) δ (CCl_4) 5.20 (m, 1 H), 4.80 (m, 1 H), 3.60 (s, 3 H), 3.40 (s, 2 H), 3.30 (s, 3 H), 2.03 (s, 3 H), 1.98 (s, 3 H).

Anal. Calcd for $C_{19}H_{28}O_7$: C, 61.94; H, 7.66. Found: C, 62.13; H, 7.69.

Ozonolysis of Enol Acetate 14. A solution of enol acetate **14** (459 mg, 1.25 mmol) in 150 ml of methylene chloride cooled to −78 °C was treated with 1 equiv of ozone. After addition of ozone, 100 ml of absolute methanol was added at −78 °C. Stirring was continued at that temperature for 15 min followed by addition of 47.4 mg (1.25 mmol) of sodium borohydride. After 15-min intervals for ca. 1 h, an equal amount of sodium borohydride was added (−78 °C). The reaction mixture was warmed to room temperature (ca. 45 min) and 2.2 ml of 1 N aqueous sodium hydroxide was added. After an additional 30 min, the solvent was removed under reduced pressure and the residue was taken up in water and washed with ether. The aqueous layer was cooled (0 °C), acidified carefully with 37% hydrochloric acid, and extracted exhaustively with ethyl acetate. The combined organic layers were evaporated to leave a solid (414 mg) which was dissolved in ether and treated (0 °C) with an ethereal solution of diazomethane. There was obtained 395 mg of crude diester which was purified on 7.0 g of silica gel. Elution with hexanes/ethyl acetate (3:2) followed by ethyl acetate gave 372 mg (80%) of pure **15**: IR ($CHCl_3$) 3450, 1730 cm^{-1}; NMR (250 MHz) δ ($CDCl_3$) 4.94 (t, 1 H, J = 10 Hz), 3.76 (m, 2 H), 3.71 (s, 6 H), 3.40 (s, 3 H), 3.38 (AB q, 2 H, J = 9 Hz, $\Delta\nu_{AB}$ = 49.2 Hz), 2.05 (s, 3 H).

Anal. Calcd for $C_{18}H_{30}O_8$: C, 57.74; H, 8.08. Found: C, 57.63; H, 8.07.

Preparation of *o*-Nitrophenyl Selenide 16. Methanesulfonyl chloride (156 mg, 1.36 mmol) was added to a solution of alcohol **15** (430 mg, 1.14 mmol) in 6.2 ml of dry pyridine cooled to 0 °C. After 30 min at 0 °C, the reaction temperature was warmed to 25 °C where stirring was continued for an additional 30 min. The solvent was removed under high vacuum and the residue was taken up in ether and washed with water. The combined ether extracts were dried over anhydrous magnesium sulfate. Filtration followed by removal of the solvent in vacuo gave 484 mg (94%) of crude mesylate: IR (film) 1725, 1340, 1165 cm^{-1}; NMR (60 MHz) δ ($CDCl_3$) 4.80 (m, 1 H, CHOAc), 4.32 (t, 2 H, $MsOCH_2$), 3.61 (s, 6 H), 3.25 (bs, 5 H, CH_2OCH_3), 2.99 (s, 3 H, CH_3SO_2), 1.95 (s, 3 H, OAc).

The above crude mesylate (484 mg) in 5.0 ml of dry dimethylformamide was added dropwise to a solution of *o*-nitrophenylselenium anion prepared by addition of sodium borohydride (108 mg) to *o*-nitrophenyl selenocyanate[22] (340 mg, 1.50 mmol) in 7.5 ml of dry dimethylformamide cooled to 15 °C. After 20 h, the reaction mixture was taken up in ether and washed with water. The aqueous layer was further extracted with ether. The combined organic washes were dried (anhydrous magnesium sulfate) and evaporated in vacuo, leaving 742 mg of crude selenide. Purification on 120 g of silica gel using hexane/ether (2:1) gave in order of elution 17 mg (5%) of the tetrahydrofuran derivative **19** (identical in all respects with a sample prepared below) and 482 mg of pure *o*-nitrophenyl selenide **16** (75% overall yield from alcohol **15**): IR ($CHCl_3$) 1730, 1590, 1565, 1518, 1336 cm^{-1}; NMR (60 MHz) ($CDCl_3$) δ 8.20 (d, 1 H), 7.40 (m, 3 H), 4.81 (m, 1 H), 3.60 (s, 6 H), 3.35 (s, 3 H), 3.25 (bs, 2 H), 2.78 (m, 2 H), 1.92 (s, 3 H).

Anal. Calcd for $C_{24}H_{33}NO_9Se$: C, 51.61; H, 5.96. Found: C, 51.54; H, 5.90.

***trans*-2-Acetoxy-*trans*-4-vinyl-*cis*-4-methoxymethyl-*cis*, *cis*-1,3-cyclohexanediacetic Acid Dimethyl Ester (17).** A solution of 720 mg (1.29 mmol) of *o*-nitrophenyl selenide (**16**) in 17 ml of tetrahydrofuran cooled to 0 °C was treated dropwise with 0.35 ml of 50% hydrogen peroxide. After addition was complete, the reaction mixture was warmed to room temperature and stirring was continued for 20 h. The reaction mixture was concentrated in vacuo and the residue was dissolved in ether and washed with water. The aqueous layer was extracted exhaustively with ether. The combined ether extracts were dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. There was obtained 505 mg of crude olefin. Purification on silica gel [elution with hexane/ethyl acetate (10:1)] gave 370 mg (81%) of crystalline compound. Recrystallization from ether/hexane gave pure olefin **17**, mp 69–71 °C: IR ($CHCl_3$) 3080, 1735, 1638 cm^{-1}; NMR (250 MHz) δ (CCl_4) 5.06–5.75 (typical vinyl eight-line pattern, 3 H), 4.90 (t, 1 H, CHOAc), 3.55 (s, 6 H), 3.45 (AB q, 2 H, J = 10 Hz, $\Delta\nu_{AB}$ = 33.5 Hz), 3.30 (s, 3 H, OCH_3), 1.88 (s, 3 H, OAc).

Anal. Calcd for $C_{18}H_{28}O_7$: C, 60.66; H, 7.92. Found: C, 60.54; H, 7.89.

Methyl *cis*-10α-(β-Bromomethyl)-2-oxo-3-oxa-8α-acetoxy-7β-decalylacetate (27). Methanesulfonyl chloride (100 μl, 1.3 mmol) was added to a solution of alcohol **15** (400 mg, 1.07 mmol) in 6.0 ml of anhydrous pyridine cooled to 0 °C. The reaction mixture was stirred for 30 min at room temperature and was then taken up in ether and washed with cold 5% aqueous hydrochloric acid, water, and brine. The ether layer was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure, providing 475 mg (98%) of crude mesylate which was used immediately in the next reaction.

To a solution of 370 mg (0.818 mmol) of crude mesylate in 30 ml of dry methylene chloride cooled to −78 °C was added dropwise with stirring 1.5 ml of boron tribromide. The reaction mixture was gradually warmed to 0 °C over a period of ca. 1 h. Stirring was continued for an additional 2 h at 0 °C followed by quenching with 12 ml of ether. After 10 min, 12 ml of water was added and stirring was continued at 0 °C for 10 min. The reaction mixture was taken up in ethyl acetate and washed with brine. After drying over anhydrous magnesium sulfate and evaporation of the solvent in vacuo, there was obtained 330 mg of material. Chromatography (ether/hexane, 2:3) of the crude product gave in order of elution 46 mg (13%) of bromo compound **30** [homogeneous on TLC analysis (silica gel, ether, R_f 0.80)] [IR ($CHCl_3$) 3010, 2950, 2930, 2860, 2810, 1732, 1438, 1379, 1210, 1160, 1110, 1020, 975 cm^{-1}; NMR (60 MHz) (CCl_4) δ 4.85 (bt, 1 H), 3.65 (s, 3 H), 3.60 (s, 3 H), 3.35 (s, 3 H), 3.2–3.6 (m, 5 H, $-CH_2Br$, $-CH_2OMe$), 1.95 (s, 3 H)]; a trace of the tetrahydrofuran derivative **19** [R_f 0.57 (ether)] (identical in all respects with a sample prepared below); and 160 mg (50%) of pure crystalline bromo lactone **27** [homogeneous on TLC (silica gel, ether, R_f 0.38)]. Recrystallization from ether/hexane (1:1) gave analytically pure bromo lactone **27**, mp 98–99 °C: IR ($CHCl_3$) 3010, 2950, 2930, 2860, 1730, 1438, 1375, 1209, 1175, 1070, 1020 cm^{-1}; NMR (250 MHz) ($CDCl_3$) δ 4.89 (t, 1 H, J = 11 Hz, CHOAc), 4.24 (AB q, 2 H, J = 12 Hz, $\Delta\nu_{AB}$ = 119.4 Hz), 3.69 (s, 3 H, OCH_3), 3.42 (m, 2 H, CH_2Br), 2.12 (s, 3 H, CH_3CO).

Anal. Calcd for $C_{16}H_{23}BrO_6$: C, 49.11; H, 5.92. Found: C, 49.28; H, 6.02.

***o*-Nitrophenyl Selenide 28.** To a solution of 190 mg (0.84 mmol) of *o*-nitrophenyl selenocyanate[22] in 17.0 ml of dry dimethylformamide at 0 °C was added 42 mg (1.1 mmol) of sodium borohydride. After 10 min, a solution of bromo lactone **27** (220 mg, 0.56 mmol) in 4.0 ml of dry DMF was added dropwise at 0 °C to the deep blood red reaction mixture. Stirring was continued for ca. 20 h at room temperature. Isolation by ether extraction[36] provided 403 mg of crude product. Washing with ether gave 250 mg (87%) of crystalline selenide, mp 154–155 °C: IR ($CHCl_3$) 3000, 2935, 1730, 1590, 1562, 1510, 1438, 1370, 1330, 1300, 1205, 1095, 1070, 1022, 910, 885, 850 cm^{-1}; NMR (250 MHz) ($CDCl_3$) δ 8.24 (d, 1 H, J = 8 Hz), 7.54 (t, 1 H, J = 8 Hz), 7.43

(d, 1 H, J = 8 Hz), 7.30 (t, 1 H, J = 8 Hz), 4.88 (t, 1 H, J = 11 Hz), 4.26 (AB q, 2 H, J = 12 Hz, $\Delta\nu_{AB}$ = 101.3 Hz), 3.64 (s, 3 H), 2.08 (s, 3 H). Recrystallization from benzene/ether (1:1) gave analyically pure selenide **28**, mp 156–157 °C.

Anal. Calcd for $C_{22}H_{27}NO_8Se$: C, 51.57; H, 5.31. Found: C, 51.73; H, 5.19.

Methyl *cis*-10α-Vinyl-2-oxo-3-oxa-8α-acetoxy-7β-decalylacetate (29). A solution of selenide **28** (240 mg, 0.46 mmol) in 12.0 ml of tetrahydrofuran cooled to 0 °C was treated dropwise with 50% hydrogen peroxide (165 μl). After addition was complete, the reaction mixture was stirred at room temperature for 18 h. The solvent was concentrated in vacuo and the product isolated by ether extraction.[36] Purification of the crude product on silica gel (ether/hexane, 3:2) gave 130 mg (89%) of crystalline **29**. Recrystallization from ether/hexane (1:1) provided analytically pure lactone **29**, mp 96–98 °C: IR ($CHCl_3$) 3080, 3020, 2950, 2930, 2850, 1730, 1638, 1490, 1439, 1400, 1370, 1205, 1121, 1000, 980, 930 cm^{-1}; NMR (250 MHz) ($CDCl_3$) δ 5.8–5.2 (typical vinyl pattern, 8 lines, 3 H), 4.92 (t, 1 H, J = 11 Hz), 4.43 (AB q, 2 H, J = 13 Hz, $\Delta\nu_{AB}$ = 66.7 Hz), 3.68 (s, 3 H), 2.10 (s, 3 H).

Anal. Calcd for $C_{16}H_{22}O_6$: C, 69.04; H, 7.97. Found: C, 68.97; H, 7.95.

Bisnordeoxyvernolepin (6). To a solution of 130 mg (0.42 mmol) of acetoxy lactone **29** in 8.0 ml of anhydrous methanol was added 116 mg (0.84 mmol) of anhydrous potassium carbonate. After 2.5 h at room temperature, the reaction was quenched with 10% aqueous hydrochloric acid and the mixture was evaporated in vacuo. The crude product (117 mg), isolated by ethyl acetate extraction,[36] was dissolved in 20 ml of benzene containing 40 mg of *p*-toluenesulfonic acid and was refluxed for 1.25 h. Isolation by ethyl acetate extraction[36] gave 108 mg of crude crystalline product. Washing of the crude product with ether gave 70 mg of pure **6**. Chromatography (silica gel, ether/hexane, 3:1) of the mother liquor gave an additional 10 mg of pure bisnordeoxyvernolepin (total yield, 81%). Recrystallization from benzene/hexane (1:1) gave analytically pure bisnordeoxyvernolepin, mp 112–113 °C: IR ($CHCl_3$) 3080, 3020, 2925, 2850, 1787, 1735, 1640, 1490, 1460, 1450, 1430, 1401, 1360, 1302, 1285, 1260, 1203, 1160, 1150, 1120, 1085, 1055, 1002, 938, 875, 850, 815 cm^{-1}; NMR (250 MHz) ($CDCl_3$) δ 5.8–5.3 (typical vinyl pattern, 3 H), 4.35 (AB q, J = 12 Hz, 2 H, $\Delta\nu_{AB}$ = 42.3 Hz), 4.02 (t, 1 H, J = 11 Hz).

Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 65.96; H, 6.77.

Deoxyvernolepin (1). A solution of dry diisopropylamine (77 μl, 0.55 mmol) in dry tetrahydrofuran (1.0 ml) cooled to 0 °C was treated dropwise with *n*-butyllithium (0.30 ml of a 1.58 M solution in hexane). After 15 min, the resultant solution of lithium diisopropylamide was cooled to −78 °C and treated dropwise over 30 min via a syringe pump with a solution of bisnordeoxyvernolepin **6** (50 mg, 0.21 mmol) in 2.0 ml of dry tetrahydrofuran containing 0.3 ml of dry hexamethylphosphoramide. After addition was complete, stirring was continued at −78 °C for 10 min, followed by warming to −20 °C. Formaldehyde [generated by depolymerization of paraformaldehyde (200 mg) at 150 °C (bath temperature)] was passed into the cooled (−20 °C) reaction vessel with the aid of a stream of nitrogen. After complete depolymerization (ca. 20 min) the reaction mixture was stirred for an additional 30 min (−20 °C). The reaction was quenched by the addition of 2.0 ml of 5% hydrochloric acid. Isolation of the product by ethyl acetate extraction left 572 mg of very crude product still containing hexamethylphosphoramide. The crude mixture of diols from above (572 mg) was diluted with 0.3 ml of dry pyridine and treated at 0–5 °C with methanesulfonyl chloride (58 mg, 2.4 equiv). Stirring at 5 °C was continued for 8 h. After isolation of the product by ethyl acetate extraction, there was obtained 81 mg of crude dimesylate which was used directly in the next reaction.

The mixture of crude dimesylate (81 mg) was dissolved in 4.0 ml of dry pyridine and refluxed for 17 h. After cooling to room temperature the reaction mixture was diluted with 30 ml of ethyl acetate and washed with water, 5% hydrochloric acid, saturated sodium bicarbonate, and brine. The organic layer was dried ($MgSO_4$) and the solvent was evaporated in vacuo, leaving 42 mg of crude material. Chromatography on 700 mg of silica gel [elution with ethyl acetate/hexane (2:3)] gave 21 mg of pure, crystalline deoxyvernolepin, mp 169–170 °C. The overall yield was 38%. Deoxyvernolepin exhibited the following spectral characteristics: IR ($CHCl_3$) 3015, 2940, 2910, 2850, 1770, 1720, 1670, 1620, 1405, 1340, 1305, 1287, 1250, 1210, 1160, 1130, 1080, 1065, 1010, 990, 950 cm^{-1}; NMR (250 MHz) ($CDCl_3$) δ 6.71 (s, 1 H), 6.17 (d, J = 2.5 Hz, 1 H), 5.91 (s, 1 H), 5.50 (d, J = 2.5 Hz, 1 H), 5.3–5.8 (typical vinyl pattern, 8 lines, 3 H), 4.40 (AB q, 2 H, J = 12 Hz, $\Delta\nu_{AB}$ = 81.2 Hz), 3.97 (t, 1 H, J = 11 Hz), 3.00 (d, 1 H, J = 11 Hz).

Anal. Calcd for $C_{15}H_{16}O_4$: 260.0949. Found: 260.0955.

Reaction of Compound 27 with Potassium Carbonate in Methanol. A suspension of anhydrous potassium carbonate (6 mg, 0.04 mmol) in methanol (0.9 ml) containing bromo lactone **27** (21 mg, 0.05 mmol) was stirred at room temperature for 20 min. Neutralization of the reaction mixture with 10% hydrochloric acid and isolation of the product by ethyl acetate extraction[36] gave 18 mg (99%) of **19**: IR ($CHCl_3$) 3030, 2960, 2940, 2855, 1735, 1440, 1379, 1348, 1245, 1212, 1165, 1120, 1100, 1080, 1050, 1025, 980 cm^{-1}; NMR (250 MHz) (CCl_4) δ 4.43 (t, 1 H, J = 11 Hz), 3.70 (m, 2 H), 3.63 (s, 3 H), 3.60 (s, 3 H), 3.48 (AB q, 2 H, J = 9 Hz, $\Delta\nu_{AB}$ = 53.2 Hz), 1.89 (s, 3 H).

Anal. Calcd for $C_{17}H_{26}O_7$: C, 59.64; H, 7.65. Found: C, 59.50; H, 7.61.

Reaction of Compound 27 with DBU. A mixture of bromo lactone **27** (21 mg, 0.05 mmol) in 2.1 ml of dry benzene containing 75 mg of 1,5-diazabicyclo[5.4.0]undec-5-ene was stirred at room temperature for 72 h. The reaction mixture was diluted with ethyl acetate and washed with 5% hydrochloric acid, and the product isolated by extraction with ethyl acetate.[36] There was obtained 11 mg of crude product. Purification on silica gel [elution with ethyl acetate/hexane (5:2)] gave 7 mg of pure, crystalline **31**, mp 139–140 °C: IR ($CHCl_3$) 1735 cm^{-1}; NMR (250 MHz) ($CDCl_3$) δ 4.88 (t, 1 H, J = 11 Hz), 4.22 (AB q, 2 H, J = 12 Hz, $\Delta\nu_{AB}$ = 109.3 Hz), 3.68 (s, 3 H), 2.82 (bs, 1 H), 2.08 (s, 3 H).

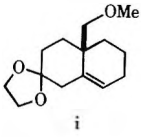
Anal. Calcd for $C_{16}H_{22}O_6$: *m/e* 310.1416. Found: *m/e* 310.1424.

Acknowledgment. This investigation was supported by Public Health Service Research Grant CA 13689-04 from the National Cancer Institute. We are deeply indebted to Drs. A. Rosowsky and H. Lazarus for the biological data. We also thank Dr. S. Morris Kupchan for a sample of natural vernolepin. We are deeply indebted to Chester S. Pogonowski and Dena Boxler for the experimental assistance during the course of this work.

Registry No.—**1**, 60872-71-1; **2**, 18542-37-5; **4**, 60872-72-2; **6**, 60872-73-3; **7**, 60815-97-6; **7** methyl ether, 60815-98-7; **8**, 60815-99-8; **9**, 60816-00-4; **10**, 60872-74-4; **11**, 60872-75-5; **11** free acid, 60816-01-5; **11** acetate, 60816-02-6; **12**, 60816-03-7; **12′**, 60816-04-8; **14**, 60872-76-6; **15**, 60872-77-7; **15** mesylate, 60816-05-9; **16**, 60816-06-0; **11**, 60816-07-1; **19**, 60816-08-2; **27**, 60872-78-8; **28**, 60872-79-9; **29**, 60816-09-3; **30**, 60816-10-6; **31**, 60840-35-9; **34**, 60816-11-7; o-nitrophenyl selenocyanate, 51694-22-5.

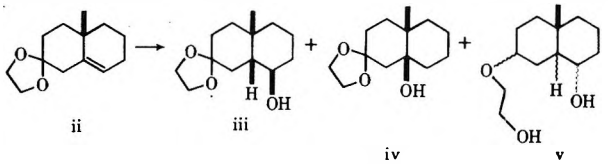
References and Notes

(1) Fellow of the Alfred P. Sloan Foundation, 1974–1976.
(2) Postdoctoral fellow supported by a fellowship from the Universidad Nacional Autonoma de Mexico and the Banco de Mexico, S. A.
(3) For a preliminary account of this work see P. A. Grieco, J. A. Noguez, and Y. Masaki, *Tetrahedron Lett.*, 4213 (1975).
(4) S. M. Kupchan, R. J. Hemingway, D. Werner, A. Karim, A. T. McPhail, and G. A. Sim, *J. Am. Chem. Soc.*, **90**, 3596 (1968); S. M. Kupchan, R. J. Hemingway, D. Werner, and A. Karim, *J. Org. Chem.*, **34**, 3903 (1969).
(5) P. A. Grieco, M. Nishizawa, S. D. Burke, and N. Marinovic, *J. Am. Chem. Soc.*, **98**, 1612 (1976).
(6) For a review of α-methylenation of lactones, see P. A. Grieco, *Synthesis*, 67 (1975).
(7) (a) P. A. Grieco and K. Hiroi, *J. Chem. Soc., Chem. Commun.*, 1317 (1972); (b) P. A. Grieco and K. Hiroi, *Tetrahedron Lett.*, 1831 (1973).
(8) We expected the cis-fused β-decalol **12** to predominate owing to the axial oxygen of the ketal moiety in compound i which effectively blocks the α face of the double bond [cf. M. Nussim, T. Mazur, and F. Sondheimer, *J. Org. Chem.*, **29**, 1120 (1964)].



i

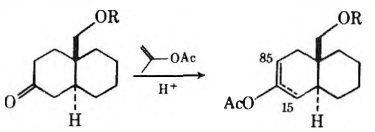
(9) Marshall,[10] during the hydroboration of olefin ii, observed, in addition, the expected product iii (50%), the anti-Markownikoff product iv (10%), and the ketal cleavage products v (40%). We observed no evidence of products derived from cleavage of the ketal.[11] We speculate that the large percentage of anti-Markownikoff product **12′** obtained from i is due to directed hydroboration by the β-methoxymethyl function in the angular position.



ii iii iv v

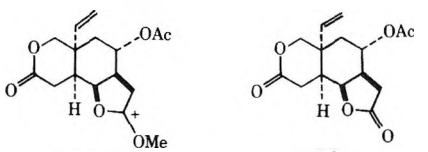
(10) J. A. Marshall, M. T. Pike, and R. D. Carroll, *J. Org. Chem.*, **31**, 2933 (1966).

(11) Cf. C. H. Heathcock and R. Ratcliffe, *J. Am. Chem. Soc.*, **93**, 1746 (1971).
(12) R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970).
(13) R. B. Miller and R. D. Nash, *Tetrahedron*, **30**, 2961 (1974).
(14) R. K. Hill, *J. Org. Chem.*, *27*, 29 (1962); R. L. Autrey and P. W. Scullard, *J. Am. Chem. Soc.*, **90**, 4924 (1968).
(15) R. Villotti, H. J. Ringold, and C. Djerassi, *J. Am. Chem. Soc.*, **82**, 5693 (1960).
(16) We found previously[17] that decalone vi gave ca. 15% of the $\Delta^{3,4}$ isomer vii. Heathcock[18] has made a similar observation with decalone viii.



vi, R = Me
viii, R = Ac
vii, R = Me
ix, R = Ac

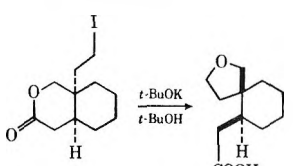
(17) P. A. Grieco, J. J. Reap,and J. A. Noguez, *Synth. Commun.*, **5**, 155 (1975); P. A. Grieco, K. Hiroi, J. J. Reap, and J. A. Noguez, *J. Org. Chem.*, **40**, 1450 (1975).
(18) R. D. Clark and C. H. Heathcock, *J. Org. Chem.*, **41**, 1396 (1976).
(19) K. B. Sharpless and M. W. Young, *J. Org. Chem.*, **40**, 947 (1975). For application of the *o*-nitrophenyl selenoxide elimination to natural product synthesis (moenocinol) see P. A. Grieco, Y. Masaki, and D. Boxler, *J. Am. Chem. Soc.*, **97**, 1597 (1975).
(20) The *o*-nitrophenylselenium anion is generated by treatment of *o*-nitrophenyl selenocyanate[21,22] with sodium borohydride in dimethylformamide.[3] For a facile one step conversion of alcohols to alkyl aryl selenides, see P. A. Grieco, S. Gilman, and M. Nishizawa, *J. Org. Chem.*, **41**, 1485 (1976).
(21) H. Bauer, *Ber.*, **46**, 92 (1913); also see ref 19.
(22) Previous reports[19,21] have reported *o*-nitrophenyl selenocyanate as light brown crystals, mp 139–141[19] and 142 °C.[21] We have found that the crude crystalline material obtained from the procedure of Bauer[21] can be sublimed at 100 °C (0.2 mmHg) providing yellow crystals of *o*-nitrophenyl selenocyanate, mp 144 °C.
(23) For similar rearrangements see J. Tadanier, *J. Org. Chem.*, 31, 3204 (1966); J. J. Bonet, H. Wehrli, and K. Schaffner, *Helv. Chim. Acta*, **45**, 2615 (1962); M. Kojima, M. Maeda, H. Ogawa, K. Nitta, and T. Ito, *J. Chem. Soc., Chem. Commun.*, 47 (1975).
(24) We speculate that compound **26** is formed via the intermediacy of species x which arises through displacement of the C-6 acetate by the neighboring ester function followed by attack of bromide ion. We were unable to detect any of the cis-fused tricyclic dilactone xi which would have arisen from displacement at methyl instead of C-6. Complete details, including proof of structure for compound **26**, will be reported in due course.



x

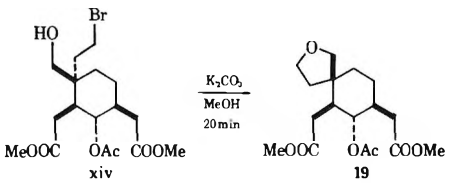
xi

(25) Heathcock[18] has observed a similar transformation on the iodoethyl lactone xii. Treatment of xii with *t*-BuOK/*t*-BuOH gave in excellent yield the spirotetrahydrofuran derivative xiii which presumably arises from a ketene intermediate.



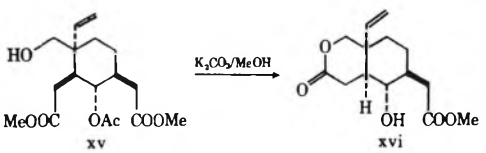
xii xiii

(26) Apparently compound **27** upon initial treatment with potassium carbonate in anhydrous methanol results in formation of the hydroxy ester xiv which spontaneously cyclizes to the spirotetrahydrofuran derivative **19**. In the



xiv 19

conversion of **29** to bisnordeoxyvernolepin (**6**) the initially formed hydroxy ester xv relactonizes upon workup providing hydroxy ester xvi.



xv xvi

(27) We are indebted to Drs. Andre Rosowsky and Herbert Lazarus (Sidney Farber Cancer Center and Departments of Biological Chemistry and Pathology, Harvard Medical School) for carrying out these tests.
(28) We are indebted to Dr. S. Morris Kupchan (University of Virginia) for a sample of natural vernolepin.
(29) For the synthesis and biological evaluation of dihydrodeoxyvernolepin and a variety of mono- and bifunctional α-methylene lactone derivatives, see P. A. Grieco, J. A. Noguez, Y. Masaki, K. Hiroi, M. Nishizawa, A. Rosowsky, S. Oppenheim, and H. Lazarus, *J. Med. Chem.*, in press.
(30) G. E. Foley and H. Lazarus, *Biochem. Pharmacol.*, **16**, 659 (1967).
(31) G. E. Foley, E. F. Bareli, R. A. Adams, and H. Lazarus, *Exp. Cell Res.*, **57**, 129 (1969).
(32) S. M. Kupchan, D. C. Fessler, M. A. Eakin, and T. A. Giacobbe, *Science*, **168**, 376 (1970); R. L. Hanson, H. A. Lardy, and S. M. Kupchan, *ibid.*, **168**, 378 (1970); S. M. Kupchan, T. J. Giacobbe, I. S. Krull, A. M. Thomas, M. A. Eakin, and D. C. Fessler, *J. Org. Chem.*, **35**, 3539 (1970).
(33) A. Rosowsky, N. Papathanasopoulos, H. Lazarus, G. E. Foley, and E. J. Modest, *J. Med. Chem.*, **17**, 672 (1974).
(34) Melting points were determined on a Fisher-Johns hot stage melting point apparatus. All melting points and boiling points are uncorrected. Infrared (IR) spectra were determined on a Perkin-Elmer 247 grating infrared spectrometer and nuclear magnetic resonance (NMR) spectra were recorded at either 60 MHz (Varian A-60A or T-60 spectrometer) or at 250 MHz as indicated. Chemical shifts are reported in part per million (δ) relative to Me_4Si (δ_{Me_4Si} 0.0 ppm) as an internal standard. Low-resolution mass were recorded on an LKB-9000 spectrometer. High-resolution spectra were recorded on a Varian MAT CH-5DF instrument. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Reactions were run under an atmosphere of nitrogen. "Dry" solvents were dried immediately before use. Tetrahydrofuran and dimethoxyethane were distilled from lithium aluminum hydride; dimethylformamide (DMF), hexamethylphosphoramide (HMPA), dimethyl sulfoxide (DMSO), and pyridine were distilled from calcium hydride. Diethyl ether and dioxane were distilled from sodium. Methylene chloride was passed through a column of alumina prior to use.
(35) L. S. Minckler, A. S. Hussey, and R. H. Baker, *J. Am. Chem. Soc.*, **78**, 1009 (1956).
(36) The products were isolated by extraction of the aqueous layer with several portions of the indicated solvent. The combined organic extracts were washed with water followed by saturated brine. The organic layer was usually dried with either anhydrous sodium sulfate or anhydrous magnesium sulfate. Filtration followed by removal of the solvent in vacuo (water aspirator) employing a rotary evaporator provided the products.

Photoisomerization of Triquinacene Congeners

Leo A. Paquette,* James D. Kramer,[1a] Paul B. Lavrik,[1b] and Matthew J. Wyvratt[1c]

Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

Received July 28, 1976

The triplet-sensitized photochemical rearrangements of 2,3-dihydrotriquinacene (**2**), nortriquinacene (**7**), and benzotriquinacene (**13**) are described. These molecules, which comprise rigid structures having fixed parallel double bonds, undergo formal [$_\pi$2 + $_\pi$2] cycloaddition by a process believed to be stepwise. The initial bonding scheme is identical with that which is utilized in the di-π-methane rearrangement, but ultimate vinylcyclopropane formation is not realized, probably because of structural reasons. The synthesis of **13** was achieved by a convenient benzoannulation sequence starting with 2,3-dihydrotriquinacen-2-one (**9**).

The last decade has witnessed extensive exploration of the so-called di-π-methane rearrangement,[2] that process by which the excited state of a 1,4-diene transmutes by 1,2-vinyl migration and ring closure to a vinylcyclopropane. These

studies have played an important role in the development of our understanding of structural and substituent effects on excited-state multiplicity, control of regiospecificity, and preferred rearrangement stereochemistry. Of particular interest to us have been those photoisomerizations where the customary course of the di-π-methane rearrangement is rerouted at some intermediate stage for one of several reasons. As an example, it is entirely plausible that many rigid dienes may be of such geometry that the requisite molecular distortion or steric strain required to arrive at their vinylcyclopropane photoisomers would prove inimical to this process and cause conversion instead to a structurally rather different product. Suggestive evidence has been provided particularly by Hart,[3] and less directly by Gorman,[4] Kaupp,[5] Freeman,[6] and Linstrumelle[7] that bicyclo[3.3.0]octa-2,7-diene and bicyclo[3.2.0]hepta-2,6-diene ring systems incorporate folded molecular geometries with atomic distances and orbital dihedral angles highly unfavorable to direct [$_\pi$2 + $_\pi$2] cycloaddition. Nevertheless, the prevailing proximity effects are now such that operation of the normal di-π-methane rearrangement could be diverted without formation of a discrete vinylcyclopropane intermediate.

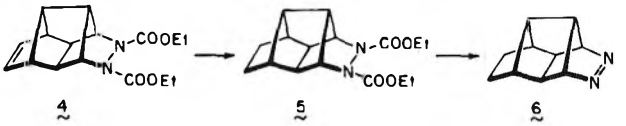
For these reasons, an examination of the photochemistry of several highly cup-shaped molecules of the triquinacene family was undertaken. An ancillary goal was to gain access to strained molecules of rather unusual structure for utilization in other research programs.

Results

2,3-Dihydrotriquinacene (**2**), the first example studied, was prepared in 85% yield by conversion of alcohol **1a**[8] to its mesylate followed by reduction of **1b** with lithium aluminum hydride. Irradiation of **2** in benzene solution containing 5%

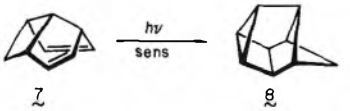
acetone as sensitizer with Corex filtered light (Hanovia 450-W) for 85 h afforded a single volatile photoproduct in 40% yield. Even at such long reaction times, 10% of **2** remained unchanged. Separation of the two components was achieved by elution of the concentrated photolysate through silver nitrate (5%) impregnated silica gel with pentane. The mass spectrum and elemental composition of the pure photoproduct indicated it to be isomeric with **2**. The absence of trigonal carbons was apparent from the lack of olefinic protons in its ^{1}H NMR spectrum. On this basis and the appearance in its ^{13}C spectrum of only six lines, **3** was assigned the symmetrical structure indicated.

An unequivocal synthesis of **3** was accomplished by catalytic hydrogenation of **4**,[9] hydrolysis–oxidation of the resulting dihydro derivative (**5**) to give azo compound **6**, and nitrogen extrusion from **6** by irradiation through Pyrex at 3500 Å in



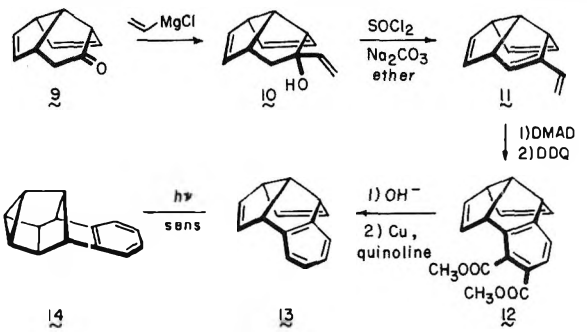
pentane solution. *Under these conditions, there* was produced 37–40% of **2**, 50–55% of **3**, and two minor unidentified products. As in the case of a structurally related azo compound,[9] formation of the principal photoproducts can be rationalized in terms of an intermediate 1,3 biradical which either closes to form a bicyclo[2.1.0]pentane moiety or experiences central bond cleavage to generate a pair of olefinic bonds.

The fate of nortriquinacene (**7**)[10] proved to be entirely comparable. Its irradiation under the predescribed conditions for 65 h caused almost complete conversion to a single volatile product (14%) with simultaneous polymer formation. Structural assignment to **8** follows from the combined spectral ev-



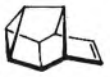
idence. While its proton magnetic resonance spectrum is characterized by six groups of upfield signals (see Experimental Section) bearing many close similarities to those which characterize **3**, its ^{13}C spectrum features uniquely those six peaks required by the molecular symmetry.[11]

At this point, attention was turned to benzotriquinacene (**13**). To elaborate this structure, use was made of the ketone benzoannulation scheme developed earlier in this laboratory.[14] The action of vinylmagnesium chloride converted ketone **9**[8,15]



into vinyl alcohol **10** whose dehydration afforded vinyltriquinacene (**11**). Addition of dimethyl acetylenedicarboxylate to **11** followed by dehydrogenation with DDQ led to adduct **12** which underwent ready saponification and copper-catalyzed decarboxylation to give **13**. The triquinacene nature of this hydrocarbon is readily apparent from the rather simple ^{1}H NMR spectrum ($CDCl_3$) which consists of two singlets at δ 7.12 (4 H, aromatic) and 5.67 (4 H, vinylic) in addition to a four-proton multiplet (4.47–3.73) arising from the bridgehead protons. With the exception of the anisotropic effects introduced by the benzene ring, close agreement exists with the values reported in the literature for the parent ring system.[16]

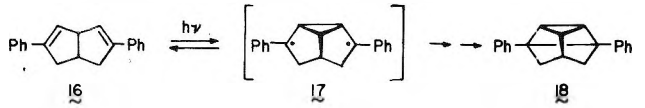
Despite the fact that **13** is intrinsically capable of excited state benzo–vinyl as well as vinyl–vinyl bonding, no evidence was found for the first pathway under the sensitized conditions required for photoisomerization. This behavior is in line with the structure–multiplicity relationships generally adhered to in di-π-methane rearrangements.[2] When the progress of reaction was monitored by VPC, disappearance of the majority (96%) of **13** and formation of **14** as the only volatile product in low (8.5%) yield was observed after 90 h of irradiation. Separation of **14** from polymer was achieved by sequential column and gas chromatography. The ^{1}H NMR spectrum ($CDCl_3$) of this stable, oily hydrocarbon shows the expected downfield aromatic singlet (δ 7.01, 4 H) in addition to multiplets at 3.32 (3 H), 2.32–2.26 (4 H), and 1.70–1.47 (1 H) attributable to (a) the benzylic and apical protons, (b) cyclobutyl hydrogens, and (c) remaining cyclopropyl proton, respectively. In its upfield region, this spectrum is highly reminiscent of that exhibited by **15**.[9] The paired ^{13}C signals of **14** likewise accord with the C_s symmetry of the molecule.



15

Discussion

The photoisomerizations of **2**, **7**, and **13** proceed exceptionally slowly in the absence of sensitization with production of polymers. The efficiency of their sensitized reactions suggests that triplet excited states intervene. Direct [$_\pi$2 + $_\pi$2] ring closures seem highly unlikely in these examples because of the large distance separating the central sp^2-hybridized carbons and the poor dihedral angle relationships of their pπ orbitals. Rather, the initial step is preferably viewed as proceeding by bonding of the proximal olefinic centers in a fashion analogous to that which triggers di-π-methane rearrangements, since a minimum of geometric change is involved (Scheme I). If such biradicals do intervene, there would be obvious reason to expect enhancement of reaction efficiency upon phenyl substitution as in **16**. In this regard, Kaup and

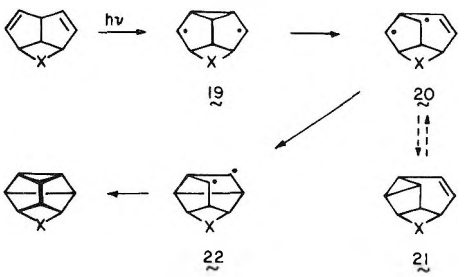


16 **17** **18**

Krieger have found convincing evidence for generation of **17** as the short-lived electronic intermediate which ultimately leads to **18**.[5] Primarily due to the residual large separation of the radical centers in **17** and **19**, there exists a greater likelihood for cleavage of the three-membered ring to give **20** than of formation of a tetracyclic framework.

Subsequent collapse of the biradical centers in **20** would deliver the normal di-π-methane products **21**. However, no evidence was obtained for generation of compounds of this type. If such molecules had been formed as discrete intermediates in those examples where X = CH_2 or $-CH_2CH_2-$, no

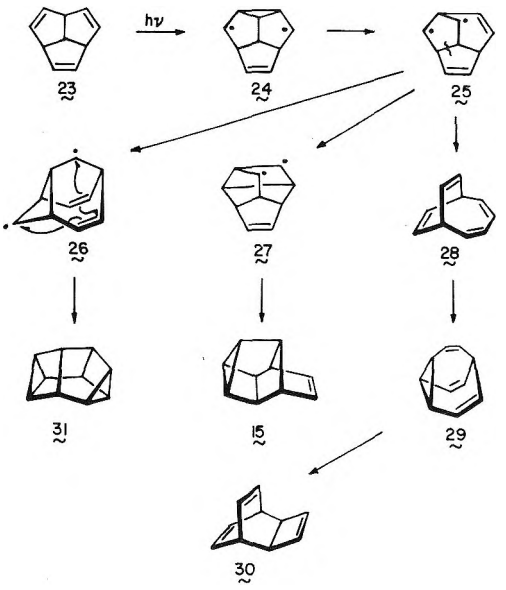
Scheme I



precedent exists for their photolability under the reaction conditions. This route to the observed products, clearly a two-photon pathway, is both difficult to dismiss and to substantiate without access to the hydrocarbons **21**.

At this point, it is appropriate to discuss the photochemistry of triquinacene (**23**). Under the conditions employed in this study, **23** underwent polymerization exclusively. At the appearance of Bosse and de Meijere's paper,[17] further work was discontinued in our laboratory. The Göttingen group observed that direct irradiation of **23** for 30–50 h in pentane solution at −40 °C in a falling film apparatus gave a mixture of eight products with **15** and **28–31** predominating (Scheme II). We

Scheme II

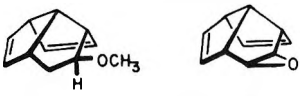


suggest that a comparable pair of biradicals (**24** and **25**) intervene. Because of the additional available double bond in **25**, redirection of the customary electronic reorganization occurs as the direct result of internal σ bond cleavage. Once access is gained to **28** (9%), its photoequilibration with bullvalene (**29**, 5%) and tricyclodecatriene **30** (6%) can be fully anticipated.[18] Perhaps as the direct result of singlet state reactivity, **25** is further capable of 1,2-alkyl shift to generate **26**, the likely precursor to **31** (49% relative yield).

The formation of **15** (26%) is the only common link to the present work. If these reactions are stepwise as depicted, the altered geometry of **20** (Scheme I) and **25** (Scheme II) brings the radical centers and the π bond into proximity adequate for conjoining of the two central carbons. The structural features of **22** and **27** are conducive to formation of the final bicyclopentane bond.

The weight of evidence which is presently available suggests, but does not of course prove, that a multistep mechanism occurs in those intramolecular [$_\pi$2 + $_\pi$2] cycloadditions involving rigid molecules having fixed parallel double bonds. Our experience with such reactions is that they lack

generality, particularly when polar substituents are present elsewhere in the molecule. For example, alcohol **1a**, ether **32**,



32 **33**

and epoxide **33** gave no volatile products, but only polymerized when subjected to sensitized irradiation.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 467 spectrophotometer. The ^1H NMR spectra were determined with Varian A-60A and HA-100, as well as Bruker HX-90, instruments, and apparent splittings are given in all cases. The ^{13}C spectra were also run on the Bruker spectrometer. Mass spectra were measured on an AEI-MS9 spectrometer at an ionizing energy of 70 eV. Preparative scale VPC separations were performed on a Varian Aerograph Model A-90-P3 instrument equipped with thermal conductivity detectors. Microanalytical determinations were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

2,3-Dihydrotriquinacene (2). To an ice-cold solution of **1a**[8] (2.00 g, 13.5 mmol) in purified dichloromethane (20 ml) was added 2.4 ml (17.6 mmol) of triethylamine. Methanesulfonyl chloride (1.7 g, 14.9 mmol) dissolved in 4 ml of dichloromethane was introduced dropwise at 0 °C. After 20 min at this temperature, water (20 ml) was added and the organic layer was washed with 10% hydrochloric acid (2 × 25 ml), saturated sodium bicarbonate solution (2 × 25 ml), and brine prior to drying and evaporation. The crude mesylate (2.85 g, 93%) was dissolved in anhydrous ether (50 ml) and this solution was added dropwise to a slurry of lithium aluminum hydride (700 mg, 18.4 mmol) in ether (50 ml). The slightly exothermic reaction was completed by stirring overnight at 25 °C followed by 6 h at the reflux temperature. The excess hydride was quenched by sequential addition of water (0.7 ml), 15% sodium hydroxide solution (0.7 ml), and water (2.1 ml). The precipitated white solid was removed by filtration and washed well. The combined filtrates were dried and carefully evaporated. The concentrate was dissolved in pentane, filtered through a 1.5 × 0.75 in. plug of neutral alumina, and the solvent was removed by careful distillation through an 8-in. Vigreux column. There remained 1.5 g (85%) of **2** whose ^1H NMR spectrum was identical with that reported earlier.[19]

Photoisomerization of 2. A solution of **2** (600 mg) in 5% acetone–benzene (600 ml) was deoxygenated with nitrogen for 30 min. Irradiation for 85 h with a 450-W medium-pressure Hanovia lamp through Corex optics yielded a yellow solution containing suspended solid. VPC analysis (10 ft × 0.125 in. 15% Carbowax 20M on Chromosorb P, 100 °C) revealed that 10% of **2** remained and that a single photoproduct had been formed in 40% yield. The photolysate was filtered and the clear yellow solution was carefully concentrated to a volume of 20 ml by distillation through a 45-cm Vigreux column. Pentane (10 ml) was added and the solution passed through a column of 5% silver nitrate on silica gel (40 g) with pentane elution. The colorless eluate, which contained no **2** (VPC analysis), was concentrated to a volume of 2 ml by spinning band distillation. Preparative VPC purification (4 ft × 0.25 in. 10% SF-96 on Chromosorb P, 80 °C) afforded 140 mg (23%) of **3** as a colorless, volatile liquid: δ_{Me_4Si} ($CDCl_3$) (100 MHz) 2.45–2.27 (m, 1), 2.27–2.14 (m, 2), 2.15 (s, 2), 2.03–1.96 (m, 2), 1.74–1.54 (m, 1), 1.54–1.26 (m, 2), and 1.02–0.26 (m, 2); ^{13}C NMR ($CDCl_3$) 53.79, 47.80, 42.73, 28.38, 25.14, and 22.44 ppm.

Anal. Calcd for $C_{10}H_{12}$: C, 90.85; H, 9.15. Found: C, 90.64; H, 9.26.

Diethyl Octahydro-3,4,7-metheno-1*H*-pentaleno[2,1-*c*]pyrazole-1,2(3*H*)-dicarboxylate (5). A solution of **4** (1.05 g, 3.47 mmol)[9] in 10 ml of absolute ethanol containing 32 mg of 5% palladium on carbon catalyst was hydrogenated at an initial pressure of 50 psi of hydrogen. After 2 h, the mixture was filtered through a Celite pad and the filtrate was concentrated to yield a clear oil which solidified (1.04 g, 98%). Recrystallization from ether/pentane afforded **5** as white crystals: mp 66.5–68 °C; ν_{max} (CCl_4) 1744, 1702, and 1315 cm^{-1}; δ_{Me_4Si} ($CDCl_3$) 4.38 (br s, 2), 4.18 (q, J = 7 Hz, 4), 2.31 (m, 3), 2.08 (m, 3), 1.57 (br s, 4), and 1.28 (t, J = 7 Hz, 6).

Anal. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.72; H, 7.24; N, 9.14. Found: C, 62.46; H, 7.25; N, 9.19.

3a,3b,4,5,6,6a,7,7a-Octahydro-3,4,7-metheno-3*H*-pentaleno-[2,1-c]pyrazole (6). A solution of **5** (0.631 g, 2.062 mmol) and potassium hydroxide (1.349 g, 20.8 mmol) in 80 ml of 2-propanol was heated at reflux under nitrogen for 2 h. The heterogeneous mixture was acidified at 0 °C to a pH of 2 with 3 N hydrochloric acid. After warming to room temperature, the acidic mixture was neutralized with aqueous 3 N ammonium hydroxide solution, and to this heterogeneous mixture was added 1.90 g (0.0206 mol) of manganese dioxide. After being stirred at room temperature for 2.5 h, the mixture was diluted with 100 ml of dichloromethane and filtered, and the filtrate was treated with 500 ml of water. After separation of the layers, the aqueous phase was extracted with dichloromethane (5 × 75 ml) and the combined organic layers were washed with water (3 × 125 ml) and brine before drying. The solvent was removed at atmospheric pressure to yield a reddish oil (387 mg) which was either recrystallized from pentane or chromatographed on silica gel (30% ether/petroleum ether) prior to sublimation at 80 °C (35 mm). There was obtained 250 mg (76%) of **6** as white plates: mp 44.5–45.5 °C; ν_{max} (CCl_4) 2865, 1500, and 1252 cm^{-1}; δ_{Me_4Si} ($CDCl_3$) 5.08 (d, J = 3 Hz, 2), 2.60 (br s, 2), 2.47 (m, 1), 2.02 (m, 1), and 1.56 (br s, 6); *m/e* calcd 160.1000, obsd 160.1003.

Anal. Calcd for $C_{10}H_{12}N_2$: C, 74.96; H, 7.55. Found: C, 74.57; H, 7.51.

Photolysis of 6. A stirred, degassed solution of **6** (304 mg, 1.90 mmol) in 125 ml of purified pentane contained in a Pyrex tube was irradiated under nitrogen in a Rayonet reactor equipped with 3500 Å lamps for 23 h. The pentane solution was concentrated through a vacuum-jacketed Vigreux column at atmospheric pressure. VPC analysis of the concentrate (10 ft × 0.125 in. Carbowax 20M on Chromosorb P, 80 °C) showed 37–40% of dihydrotriquinacene (**2**), 50–55% of **3**, together with 3–4% and 7–8% of two minor, unidentified products which had been formed.

The crude mixture was chromatographed on a silica gel column (16 × 2.5 cm). Pentane elution achieved partial separation of **2** from **3**. Preparative VPC (10 ft × 0.25 in. 10% Carbowax 20M on Chromosorb G, 110 °C) afforded the pure hydrocarbons, the spectra of which were superimposable on those of the original samples.

Photoisomerization of Tricyclo[4.2.1.0^{3,9}]nona-4,7-diene (Nortriquinacene, 7). A solution of 236 mg (2.0 mmol) of **7**[10] dissolved in 200 ml of 5% acetone in benzene was flushed free of oxygen by bubbling nitrogen through the solution for 30 min. The stirred solution was irradiated through a Corex filter with a 450-W Hanovia medium-pressure lamp. The progress of the reaction was monitored by VPC (10 ft × 0.125 in. 15% Carbowax 20M on Chromosorb P, 90 °C). After 65 h, 5% unreacted starting material remained and 14% of a single volatile photoproduct had been formed. The solvent was removed by careful distillation through a 24-in. Vigreux column until 3 ml of solution remained. The concentrate was chromatographed through a small Florisil column using pentane as the eluent. The resulting colorless solution was again concentrated to a 3-ml volume by fractional distillation at room atmosphere and photoproduct **8** was isolated by preparative VPC (6 ft × 0.25 in. 10% OV-11 on Chromosorb W, 95 °C): ν_{max} (neat) 3050, 2980, 2880, 1280, 1265, 1235, 1210, 1190, 1145, 935, 795, 765, and 725 cm^{-1}; δ_{Me_4Si} ($CDCl_3$) 2.74 (br s, 3), 2.45 (br s, 2), 2.22 (br d, 2), 1.75 (m, 1), 1.45 (m, 1), 0.85 (d, J = 8.0 Hz, 1); ^{13}C NMR ($CDCl_3$) 54.1, 53.2, 41.8, 31.0, 29.8, 28.1 ppm; *m/e* calcd 117.0704, obsd 117.0707.

Anal. Calcd for C_9H_{10}: C, 91.47; H, 8.53. Found: C, 91.61; H, 8.60.

2-Vinyl-2,3-dihydrotriquinacen-2-ol (10). A solution of 1.0 g (6.8 mmol) of 2,3-dihydrotriquinacen-2-one (**9**)[8,15] in 10 ml of dry tetrahydrofuran was added dropwise to a solution of vinylmagnesium chloride freshly prepared from 333 mg (13.7 mg-atoms) of finely cut magnesium and excess vinyl chloride in 20 ml of dry tetrahydrofuran.[20] The reaction mixture was heated briefly to the reflux temperature and stirred at room temperature for 3 h. Excess Grignard reagent was destroyed by careful addition of water and the resulting solution was evaporated. The residues were partitioned between ether (50 ml) and water (50 ml) and the emulsion was broken by dropwise addition of 10% hydrochloric acid. The aqueous layer was separated and extracted with additional ether (2 × 50 ml). The combined ether solutions were washed with saturated sodium bicarbonate solution, dried, and evaporated to give 1.5 g of yellow oil. Its chromatographic purification on 20 g of silica gel (elution with 25% ether in pentane) afforded 1.0 g (85%) of pure **10**. VPC analysis (10 ft × 0.125 in. 10% SF-96 on Chromosorb P, 125 °C) indicated the alcohol to be essentially pure endo isomer (>98%): ν_{max} (neat) 3400, 3050, 2955, 2890, 1640, 990, 920, 848, 733, and 715 cm^{-1}; δ_{Me_4Si} ($CDCl_3$) 6.4–4.9 (m, 7, characteristic terminal vinyl pattern superimposed on 4 H multiplet), 4.0–3.8 (br m, 1), 3.8–2.9 (m, 3), 2.3–1.6 (m, 3, the OH proton superimposed upon a symmetrical five-line multiplet).

Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.38; H, 8.31.

2-Vinyltriquinacene (11). To a solution of **10** (100 mg, 0.57 mmol) in 5 ml of anhydrous ether was added 1.0 g of solid sodium carbonate

and 150 μl (250 mg, 2.1 mmol) of thionyl chloride. The mixture was stirred under a nitrogen atmosphere for 36 h at room temperature and filtred. The filtrate was washed with water and saturated sodium bicarbonate solution, dried, and evaporated to yield 80 mg of yellow oil. Chromatography on 1.0 g of silica gel with pentane elution afforded 60 mg (90%) of **11**. Alternatively, the hydrocarbon could be purified by VPC on a 6 ft × 0.25 in. 5% SE-30 on Chromosorb P column at 125 °C: ν_{max} (neat) 3012, 2849, 2770, 1639, 1590, 990, 901, 738, and 713 cm^{-1}; δ_{Me_4Si} ($CDCl_3$) 6.7–6.1 (4 lines, H_X), 5.9–5.5 (m, 5), 5.5–4.9 (8 lines, H_A and H_B, J_{AX} = 10, J_{BX} = 18, J_{AB} = 1.5 Hz), 4.1–3.5 (br m, 4).

Dicarbomethoxybenzotriquinacene (12). A mixture of 5.4 g (34.6 mmol) of **11** and 10 g (0.0735 mol) of dimethyl acetylenedicarboxylate was heated at 90 °C under a nitrogen atmosphere for 15 h. The unreacted dimethyl acetylenedicarboxylate was removed from the reaction mixture by distillation at 2 mm pressure (bp 60–65 °C). The resulting viscous liquid was dissolved in 10 ml of 30% ether in pentane to allow crystallization of the adduct. This solid was washed with pentane and dried to yield 9.2 g (89%) of product: δ_{Me_4Si} ($CDCl_3$) 5.83–5.40 (m, 4), 5.40–5.16 (m, 1), 3.94–3.44 (m, 4), 3.80 (s, 3), 3.71 (s, 3), and 2.95 (br s, 3).

A solution of the adduct in 150 ml of dry benzene was treated with 14.0 g of dichlorodicyano-*o*-benzoquinone. After 10 min, the initial deep red solution turned orange and a solid began to deposit. After being stirred at 25 °C for 20 h, the reaction mixture was evaporated and the solid residue was chromatographed on alumina. Elution with ether gave 5.7 g (64%) of **12** which crystallized as colorless needles: mp 88.5–89.5 °C from ethyl ether; ν_{max} (KBr) 2910, 2850, 1720, 1430, 1275, and 1135 cm^{-1}; δ_{Me_4Si} ($CDCl_3$) 7.72–7.10 (AB m, J_{AB} = 8.0 Hz, 2), 5.62 (s, 4), 4.58–4.10 (m, 2), 4.10–3.58 (m, 2), 3.87 (s, 3), and 3.79 (s, 3).

Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.79; H, 5.58.

Benzotriquinacene (13). Diester **12** (4.0 g, 13.5 mmol) was added to an aqueous solution containing 4 equiv of sodium hydroxide and the suspension was stirred at 40 °C until a homogeneous solution was obtained. Subsequent acidification with 10% hydrochloric acid deposited a white solid which was collected by filtration and dried under vacuum at room temperature. The diacid, which amounted to 3.40 g (94%), was recrystallized from 10% dichloromethan in ether to give white crystals: mp 176–178 °C dec; δ_{max} (KBr) 3600–2300, 1700, 1580, 1480, 1420, 1280, 1180, and 1140 cm^{-1}; δ_{Me_4Si} (CD_3COCD_3) 8.72 (br s, 2), 7.75–7.35 (AB m, J_{AB} = 8.0 Hz, 2), 5.70 (s, 4), and 4.72–3.67 (m, 4).

The dicarboxylic acid (2.0 g, 7.46 mmol) was dissolved in 100 ml of freshly distilled quinoline and placed in a 250-ml three-necked flask equipped with nitrogen gas inlet, condenser, and mechanical stirrer. To the solution was added 4.74 g (74.6 mg-atoms) of copper powder and the mixture was refluxed for 24 h under a nitrogen atmosphere.[21] After this time, the reaction mixture, which had gradually turned black, was cooled to room temperature, diluted with 300 ml of pentane, and decanted from the solid copper residue into a separatory funnel. The pentane solution was thoroughly washed with 2 N hydrochloric acid, water, and saturated sodium bicarbonate solution, before drying and evaporation of solvent. The dark residue was chromatographed on acidic alumina (pentane elution) to give 0.72 g (54%) of **13** as a colorless oil: ν_{max} (neat) 3050, 2980, 1480, 1455, 910, 900, 865, 805, and 725 cm^{-1}; δ_{Me_4Si} ($CDCl_3$) 7.12 (s, 4), 5.67 (s, 4), and 4.47–3.73 (m, 4); *m/e* calcd 180.0938, obsd 180.0942.

Anal. Calcd for $C_{14}H_{12}$: C, 93.29; H, 6.71. Found: C, 93.14; H, 6.77.

Photoisomerization of Benzotriquinacene (13). A solution of **13** (0.241 g, 1.34 mmol) in 300 ml of 5% acetone in benzene was irradiated through Corex as predescribed. Progress of the reaction was monitored by VPC (10 ft × 0.125 in. 5% SE-30 on Chromosorb W, 155 °C). After 90 h, 4% of unreacted starting material remained and 8.5% of a single volatile photoproduct had been formed. The solvent was removed by evaporation and the residue was chromatographed through a Florisil column using pentane as the eluent. After concentration of the resulting clear solution, photoproduct **14** was isolated by preparative VPC (12 ft × 0.25 in. 15% SE-30 on Chromosorb G, 160 °C): ν_{max} (neat) 3050, 2960, 1465, 1245, 1085, 945, and 740 cm^{-1}; δ_{Me_4Si} ($CDCl_3$) 7.01 (s, 4 H), 3.32 (br s, 3), 2.32–2.26 (m, 4), and 1.70–1.47 (m, 1); ^{13}C NMR ($CDCl_3$) 142.2, 126.0, 121.6, 65.0, 60.1, 42.7, 29.4, and 24.3 ppm; *m/e* calcd 180.0939, obsd 180.0942.

Anal. Calcd for $C_{14}H_{12}$: C, 93.29; H, 6.71. Found: C, 93.16; H, 6.68.

Acknowledgment. The authors are indebted to the National Science Foundation for partial financial support.

Registry No.—**2**, 31678-74-7; **3**, 60803-88-5; **4**, 54107-02-7; **5**, 60803-89-6; **6**, 60803-90-9; **7**, 58913-91-0; **8**, 60803-91-0; **9**, 60828-34-4; **10**, 60803-92-1; **11**, 60803-93-2; **12**, 60803-94-3; **12** dihydro derivative, 60803-95-4; **12** free acid, 60803-96-5; **13**, 60803-97-6; **14**, 60840-54-2; vinyl chloride, 75-01-4; dimethyl acetylenedicarboxylate, 762-42-5.

References and Notes

(1) (a) National Institutes of Health Postdoctoral Fellow, 1974–1975; (b) National Institutes of Health Postdoctoral Fellow, 1975–1976; (c) National Science Foundation Graduate Fellow, 1972–1975.
(2) S. S. Hixson, P. S. Mariano, and H. E. Zimmerman, *Chem. Rev.*, **73**, 531 (1973).
(3) H. Hart and M. Kuzuya, *J. Am. Chem. Soc.*, **96**, 3709 (1974); **97**, 2450, 2459 (1975).
(4) A. A. Gorman and J. B. Sheridan, *Tetrahedron Lett.*, 2569 (1969); A. R. Brember, A. A. Gorman, and J. B. Sheridan, *ibid.*, 481 (1973).
(5) G. Kaupp and K. Krieger, *Angew. Chem.*, **84**, 719 (1972); *Angew. Chem., Int. Ed. Engl.*, **11**, 719 (1972).
(6) P. K. Freeman and T. D. Ziebarth, *J. Org. Chem.*, **38**, 3635 (1973).
(7) G. Linstrumelle, *Tetrahedron Lett.*, 85 (1970).
(8) L. A. Paquette, W. B. Farnham, and S. V. Ley, *J. Am. Chem. Soc.*, **97**, 7273 (1975).
(9) M. J. Wyvratt and L. A. Paquette, *Tetrahedron Lett.*, 2433 (1974).
(10) L. A. Paquette, H. C. Berk, C. R. Degenhardt, and G. D. Ewing, to be submitted.
(11) When **8** is redrawn as ii, the molecule is seen to be closely related structurally to cuneane (i)[12] and norsnoutane (iii).[13] To circumvent potential

problems with such trivial nomenclature, we offer at this time the suggestion that only **8** and not its isomer iii be referred to as "homocuneane".
(12) L. Cassar, P. E. Eaton, and J. Halpern, *J. Am. Chem. Soc.*, **92**, 6366 (1970).
(13) L. A. Paquette and J. C. Stowell, *J. Am. Chem. Soc.*, **92**, 2584 (1970); **93**, 2459 (1971); L. A. Paquette, R. A. Boggs, and J. S. Ward, *ibid.*, **97**, 1118 (1975).
(14) L. A. Paquette, W. P. Melega, and J. D. Kramer, *Tetrahedron Lett.*, 4033 (1976).
(15) R. C. Kelly, Ph.D. Thesis, Harvard University, 1965; L. A. Paquette, G. V. Meehan, and S. J. Marshall, *J. Am. Chem. Soc.*, **91**, 6779 (1969); R. Russo, Y. Lambert, and P. Deslongchamps, *Can. J. Chem.*, **49**, 531 (1971); L. A. Paquette, I. Itoh, and W. B. Farnham, *J. Am. Chem. Soc.*, **97**, 7280 (1975).
(16) R. B. Woodward, T. Fukunaga, and R. C. Kelly, *J. Am. Chem. Soc.*, **86**, 3164 (1964).
(17) D. Bosse and A. de Meijere, *Angew. Chem.*, **86**, 706 (1974); *Angew. Chem., Int. Ed. Engl.*, **13**, 663 (1974).
(18) L. T. Scott and M. Jones, Jr., *Chem. Rev.*, **72**, 181 (1972).
(19) R. Srinivasan, *J. Am. Chem. Soc.*, **92**, 7542 (1970).
(20) S. D. Rosenberg, J. J. Walburn, T. D. Stankovich, A. E. Balint, and H. E. Ramsden, *J. Org. Chem.*, **22**, 1200 (1957).
(21) J. H. Dopper and H. Wynberg, *J. Org. Chem.*, **40**, 1957 (1975).

Photooxidative Transformations of Anthrone, Bianthronyl, and Bianthrone in Acid Solution

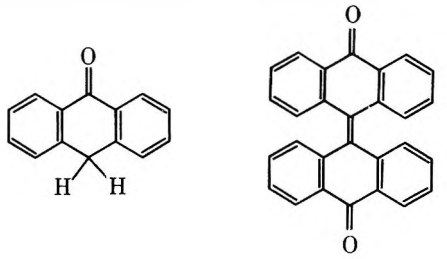
Nicolae Filipescu,* Eliza Avram,[1] and Katherine D. Welk

Department of Chemistry, The George Washington University, Washington, D.C. 20052

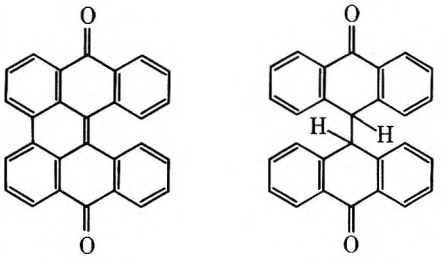
Received August 6, 1976

Time-lapse spectrometry and preparative-scale analytical data have shown that the hydroxylcarbocation of anthrone, when irradiated with visible or near-ultraviolet light, undergoes a three-step photooxidative transformation. The first is a photodehydrodimerization to protonated bianthronyl which in the next less efficient step is converted to the hydroxycarbocation of anthraquinone. As the irradiation time is extended, the protonated anthraquinone is further photooxidized to the sulfuric ester of 2-hydroxyanthraquinone. There is no evidence for the formation of bianthrone or naphthobianthrone, the "natural" photooxidative products of anthrone and bianthronyl in neutral solvents. In separate experiments, bianthrone was smoothly converted to *meso*-naphthobianthrone by photolysis is sulfuric acid.

The photochemistry of anthrone (**1**), $\Delta^{10,10'}$-bianthrone (**2**), dibenzo[*a*,*o*]perylene-7,16-dione ("helianthrone") (**3**), and



1 **2**

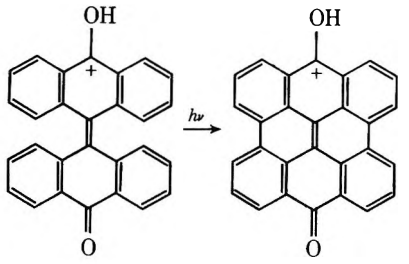


3 **4**

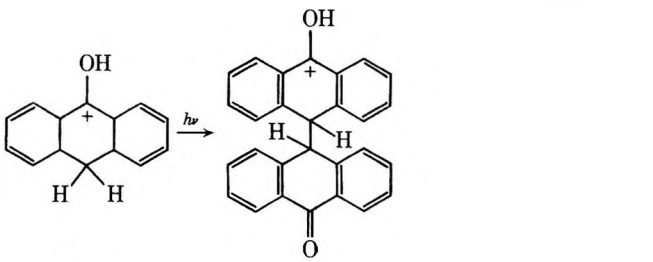
their derivatives in neutral organic solvents has been investigated[2-7] not only because of their own synthetic and mechanistic significance but also because these molecular systems offer a suitable structural model for photodehydrocyclization, a general reaction of considerable theoretical and bichemical importance.[8]

As a natural extension of our own interest in photocyclization[9] and in the photochemistry and molecular spectroscopy of representative carbonyl compounds in strongly acidic media.[10-12] we have investigated the light-induced reactions of anthrone **1**, bianthrone **2**, and bianthronyl **4** in concentrated sulfuric acid. In this paper, we present spectroscopic and preparative-analytical evidence for a sequential three-step photooxidative transformation of anthrone. In the first step protonated anthrone **5** undergoes photodehydrodimerization to the hydroxycarbocation derived from bianthronyl **6**. In the second slower step, bianthronyl **6** is converted to protonated anthraquinone **7**, which, in turn, is changed photochemically in the last step to anthraquinone 2-sulfate **8**.

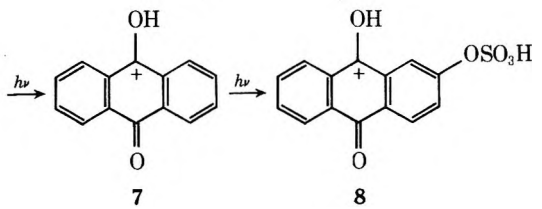
We also show that bianthrone **9**, when irradiated in concentrated sulfuric acid, undergoes double photodehydrocyclization to protonated phenanthro[1,10,9,8-*opqra*]perylene-7,14-dione (*meso*-naphthiobianthrone, **10**).



9 **10**



5 **6**



7 **8**

Results

Anthrone dissolved readily in concentrated sulfuric acid to form stable yellow solutions with ultraviolet absorption maxima at 352, 282, 273 (sh), 247, 240 (sh), and 210 nm, as shown in Figure 1, curve 1. Since the electronic absorption spectrum is completely different from that of anthrone in neutral organic solvents, it is reasonable to assume[10] that, in sulfuric acid, **1** is completely protonated to **5**.

Solutions of **5** (10^{-4}–10^{-5} M) displayed no significant spectral changes over extended periods of time (weeks) while stored in the dark at ambient temperature under nitrogen. That no irreversible chemical transformations take place either on dissolving or on storage in the dark for weeks in closed containers was also shown by recovery experiments in which more concentrated (10^{-1} M) solutions of anthrone in acid were hydrolyzed weeks after preparation, and extracted with methylene chloride: virtually quantitative amounts of unchanged anthrone were recuperated.

Dark Reactions of Anthrone. In the presence of dissolved oxygen, protonated anthrone undergoes a slow dark reaction to anthraquinone. This transformation was conveniently followed by time-lapse UV–visible spectrometry.[13] The absorption spectra of dilute acid solutions of **1** in closed and open cells with initial oxygen saturation or with continuous O_2

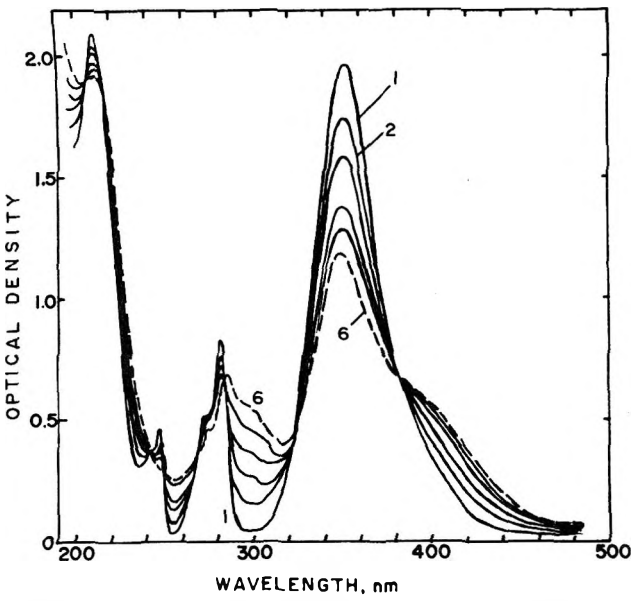


Figure 1. Changes in the UV–visible absorption spectrum of a 7×10^{-5} M solution of anthrone in sulfuric acid on irradiation with a 9-W long-wave UV hand lamp. 1: before irradiation. 2–6: after 0.5, 1, 2, 3, and 4 h total irradiation, respectively.

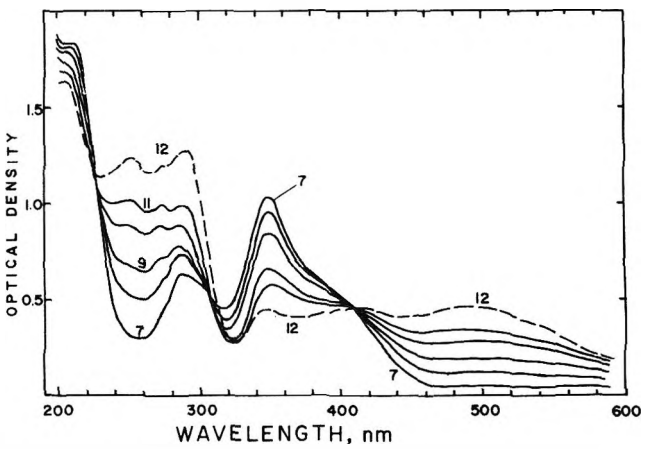


Figure 2. Photolysis of anthrone in acid, continuation. 7–12: after 19, 65, 134, 206, 254, and 376 h total irradiation, respectively.

passage were intermittently monitored over periods of weeks.

The progressive changes in the spectra of these solutions stored in the absence of light at room temperature clearly showed that **5** reacts slowly with available oxygen to form only one product, protonated anthraquinone. The corresponding intermediate spectra could be reproduced with equivalent solutions prepared from anthrone and anthraquinone. If no additional oxygen was provided, the reaction mixture remained stable indefinitely after consumption of dissolved oxygen. Under continuous oxygen bubbling, however, the transformation continued to completion. Ultimately, a typical protonated anthraquinone spectrum[12] with λ_{max} at 270, 310, and 410 nm was obtained.

It should be pointed out that the reaction of protonated anthrone **5** with residual oxygen in sealed cells, with or without prior deoxygenation, is too slow to interfere significantly with the photochemical reactions described below.

The other aromatic ketones in this study were found to be stable indefinitely in concentrated sulfuric acid. The UV–visible absorption spectra of dilute acid solutions of bianthrone, bianthronyl, anthraquinone, and naphthobianthrone remained unchanged after many weeks of storage in the dark in capped cells.

Time-Lapse Spectrometry. A. Anthrone and Bianthronyl. Figure 1 shows the successive changes taking place in the UV–visible absorption spectrum of a 7×10^{-5} M solution of anthrone **1** in sulfuric acid over an initial period of 5 h on continuous irradiation in a 1-cm cell with 9-W long-wave hand lamp. The consecutive spectral recordings formed seven clearly defined isosbestic points at 381, 321, 285, 270, 249, 241, 216, and 205 nm. The presence of these points of equivalent absorbance indicate that the photoreaction taking place throughout this irradiation period is quite free of significant side reactions.

The spectral changes observed in the same solution on further continuous irradiation beyond the initial 5 h are shown in Figure 2. Since the total photolysis time represented in this second diagram extends from 5 to more than 350 h, it is quite evident that the monitored photoreaction is much slower. Close inspection of Figure 2 reveals the presence of three "nearly isosbestic" points around 225, 305, and 415 nm. The slight departure from "isosbesticity" around 305 nm is easily understood in terms of the still-present tail end of the original phototransformation depicted in Figure 1 and of two other slow consecutive photochemical reactions which became evident in the preparative-scale irradiations described below.

During the continuous-irradiation experiments, the initial yellow anthrone solution changed to a deep brown-purple color consistent with the attendant increase in absorbance in the visible region.

The time-lapse spectrometry of *bianthronyl* in sulfuric acid will not be shown in a separate diagram because it would represent a duplication. The UV-visible absorption of bianthronyl in acid was virtually identical with that shown in Figure 2, scan 7, with maxima at 286 and 347 nm. The changes in this absorption on irradiation with near-ultraviolet light closely paralleled those shown in Figure 2 for the photolysis of anthrone in excess of the first 5 h.

The virtual identity of bianthronyl absorption in acid and curve 7 in Figure 2 and their subsequent changes under irradiation strongly suggested that bianthronyl is the first photoproduct formed during photolysis of anthrone in acid. This was confirmed by the preparative-scale photoreactions described below. The identity of the final photoproduct from either **1** or **4**, anthraquinone 2-sulfate **8**, however, cannot be easily inferred from the TLS experiments.

The progress of the photochemical reaction of anthrone or bianthronyl in acid was also followed conveniently by monitoring the fluorescence spectrum of dilute ($\sim 10^{-5}$ M) solutions undergoing photolysis. Protonated anthrone **4** exhibited broad-band blue-green fluorescence centered at 472 nm in good mirror-image relationship with its excitation maximum at 352 nm. As the phototransformation proceeded, the fluorescence of protonated bianthronyl centered at 508 nm became detectable and increased in intensity with extent of irradiation. The excitation spectrum of this emission was concordant with the absorption spectrum of bianthronyl in sulfuric acid. Finally, after prolonged irradition (~2 weeks, 9-W lamp) the orange fluorescence of anthraquinone 2-sulfate **8** with λ_{max} at 583 nm became readily detectable.

Comparison of these emission spectra with those of authentic samples of bianthronyl and 2-hydroxyanthraquinone[14,15] in acid confirmed their origin. Both the emission and excitation spectra of **5**, **6**, and **8** are sufficiently different to allow sensible interpretation of the emission from mixed solutions. Besides, since the photodehydrodimerization of **5** takes place much more rapidly than the subsequent photooxidation of **6** to **8**, one essentially determines only emission from binary mixtures of either **5** and **6** or **6** and **8**. In separate experiments with both anthrone and bianthronyl, it was found that the electronic absorption spectra of solutions undergoing

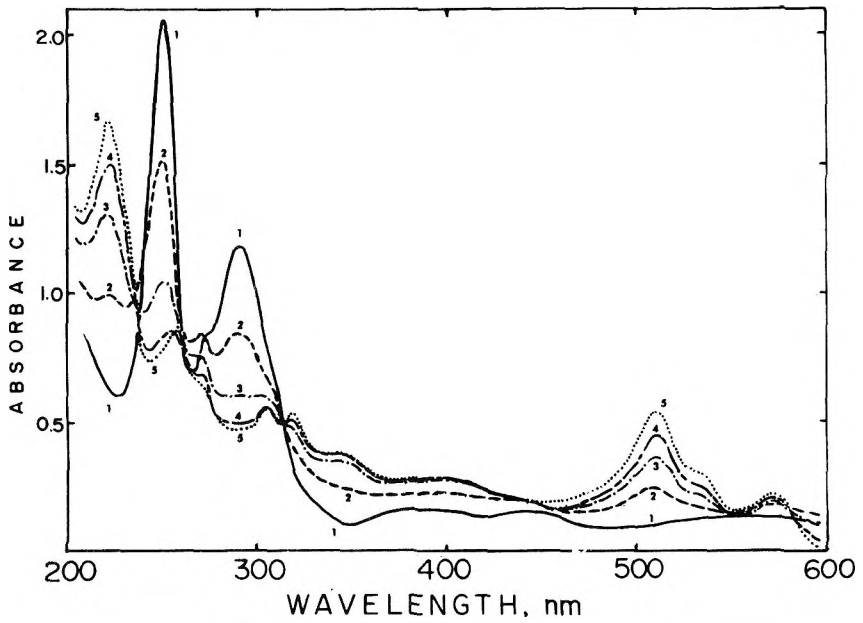


Figure 3. Photolysis of bianthrone in acid. 1: 4×10^{-4} M bianthrone in sulfuric acid, before irradiation. 2–5: after 15, 30, and 45, and 70 min total photolysis, respectively.

photolysis did not change at all when the irradiation was interrupted and the cells stored in the dark. This was true at any stage throughout the photolysis. The lack of spectral change testifies that the reactions illustrated in Figures 1 and 2 are indeed photochemically initiated with no significant contribution from slow parallel dark transformations.

B. Bianthrone. The absorption spectrum of dilute 2 in concentrated acid is shown in Figure 3, scan 1. Consecutive irradiations in the UV or visible range caused progressive decrease in bianthrone maxima and appearence and increase in new peaks characteristic of *meso*-naphthobianthrone in acid.

The naphthobianthrone was separately prepared from bianthrone by photolysis if *p*-xylene.[14] Its UV–visible absorption spectrum in pure sulfuric acid resembled closely that of an acid solution of bianthrone after prolonged near-UV or visible irradiation. Although the scans in Figure 3 pass through an isosbestic point at 315 nm, the isosbestic behavior is not preserved in the visible and in the short-ultraviolet regions of the spectrum. The significance of these observations will be discussed below.

Preparative-Scale Photoreactions. A. Anthrone. Relatively concentrated sulfuric acid solutions of anthrone (10^{-2}–10^{-1} M) were irradiated in the Hanovia immersion well with a 450-W medium-pressure Hg arc lamp under inert atmosphere for 25–35 h. At the end of this interval, the acid solution was poured over ice and extracted with methylene chloride. From the extract, bianthronyl was isolated in amounts equivalent to 50–65% of initial anthrone used. The identity of the bianthronyl photoproduct was established not only by elemental analysis, molecular weight, and melting point but also by comparison of IR, NMR, and UV spectra with those of an authentic sample. Unreacted anthrone (25–40%) was also recovered from the hydrolyzed photolysate.

B. Bianthronyl. Acid solutions of bianthronyl (10^{-2}–10^{-1} M) were exposed in separated reaction tubes under nitrogen to near-ultraviolet and/or visible light for periods extending from a few days to several weeks. The UV–visible spectra of acid-diluted aliquots were examined periodically. The reaction tubes were removed from exposure at various intervals during photolysis and their content quenched in sodium bicarbonate aqueous solutions or on ice and extracted with ether, benzene, or methylene chloride. The products were separated using silica gel thin layer and column chromatography and analyzed by UV–visible and IR spectrometry and comparison with authentic samples. Four components were identified: unreacted bianthronyl, anthraquinone, 2-hydroxyanthraquinone, and anthrone. The last two were found only in trace amounts even after lengthy irradiation. It is important to point out that at no time throughout several weeks of photolysis of bianthronyl in acid were we able to detect the presence of any other intermediates or products. This was true for both the diluted aliquots and the quenched preparative samples. The bianthronyl concentration decreased slowly with extent of irradiation while anthraquinone content increased proportionally. The 2-hydroxyanthraquinone accumulated only to a minor extent toward the end of the exposure while anthrone was present only in minute amounts. The UV–visible spectrum of a diluted acid aliquot did not differ significantly from that of a quenched sample, extracted, evaporated, and redissolved in acid. Such an absorption spectrum could be reproduced closely with fresh bianthronyl, anthraquinone, and 2-hydroxyanthraquinone dissolved in sulfuric acid in appropriate concentrations.

C. Bianthrone. Irradiation of 10^{-2} M solutions of bianthrone in sulfuric acid for 1 to 2 weeks with a 275-W sun lamp followed by quenching on ice, extraction with benzene, evaporation, and analysis showed variable conversion to *meso*-naphthobianthrone. Attempts to isolate helianthrone in significant amounts were unsuccessful. The identity of naphthobianthrone product was readily established by comparison of its IR spectrum with that of an authentic sample.

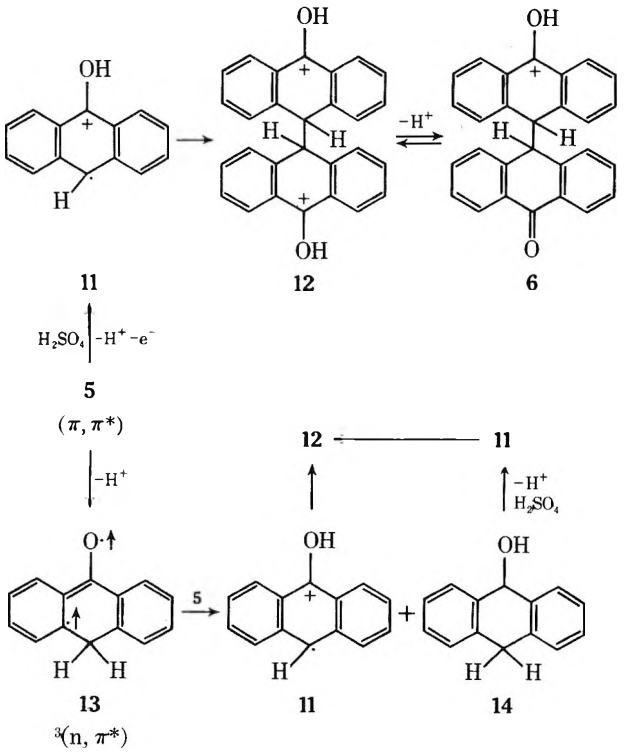
Discussion

The initial clean photochemical reaction of dilute anthrone in acid during the first 5 h of irradiation corresponds to a nearly quantitative conversion to protonated bianthronyl **6**. The identity of **6** was established not only by the ability to reproduce the spectral changes illustrated in Figure 1 with equivalent nonirradiated acid solutions of anthrone and bianthronyl, but also by isolation of bianthronyl in better than 50% yield from preparative-scale reactions in which the irradiation was interrupted before the next slower photoconversion became significant.

Close examination of the last curve in Figure 1 reveals that there was very little residual anthrone at the end of 5 h of photolysis. This is shown by comparing the absorbance at 420 nm, where only photoproduct **6** exhibits absorption, with that around 348 nm, where both **5** and **6** have significant absorption. For instance, a pure solution of bianthronyl in sulfuric acid with an absorbance of 0.25 OD units at 420 nm has a corresponding 1.1 units absorbance at 340 nm. If significant amounts of residual anthrone were present in the solution irradiated for 4 h (curve 6, Figure 1), the absorbance at 348 nm would certainly exceed the observed 1.1 OD units.

The formation of the first photoproduct, protonated bianthronyl **6**, seems to require bimolecular coupling of radical ion **11** (see Scheme I). This assumption is not based only on

Scheme I



analogy with the photodimerizations of acridines,[16-19] acridinium salts,[16,20,21] and 9-bromoanthrones[22] but also on the lack of other reasonable alternatives. For example, radical addition to the 9 position, a path which had to be ruled out in the case of acridine photooxidative dimerization,[17-19] is not available for the Dneaction of protonated anthrone **4.**

Although the coupling of two cationic radicals postulated above seems to be an electrostatically unfKvorable event, such reactions are well documented both in ground-state[23] and in photochemical[24] reactions.

The generation of **11** can be visualized to occur in two ways as depicted in Scheme I. The first would involve interaction of the π,π^* excited state of **5** with the solvent and direct formation of **11** presumably by hydrogen-atom transfer. The other alternative would require deprotonation of the π,π^* state followed by radiationless transition to a lower lying n, π^* triplet **13** which in turn would abstract a hydrogen atom from a ground-state **5** molecule with formation of a radical cation **11** and a neutral radical **14.** This latter species would then react with the solvent to generate another molecule of **11.** However, the second process seems much less probable in view of estimated rate constants for the individual steps and the need for a bimolecular reaction between excited **13** and **5** at low solute concentrations (10^{-5}).

Both redox reactions involving the solvent and either the π,π^* excited **5** or radical **14** are possible. For example, Deno et al.[25] have shown that concentrated sulfuric acid readily converted xanthene to xanthyl cation. If the acid concentration was 85% or higher, this hydride transfer reaction to the solvent was instantaneous.[25]

Since no intermediates in the **5** → **6** reaction were detected spectroscopically and no products other than bianthronyl could be identified, it is difficult to differentiate between the two mechanistic possibilities outlined in Scheme I. The fact that protonated anthrone **5** emits strong $\pi^* \rightarrow \pi$ fluorescence shows that the radiative deactivation of its π,π^* singlet successfully competes with both reaction with oxidizing solvent and deprotonation.

The subsequent steps in the photochemical reactions of anthrone in acid, namely the conversion of bianthronyl to anthrquininone and then to 2-hydroxyanthraquinone sulfate, are much less efficient than the initial **5** → **6** step. It has been shown that in neutral solvents the photooxidative transformations of bianthronyl lead first to bianthrone **2** and then to *meso*-naphthobianthrone.[2] In sulfuric acid, however, there is no evidence of formation of either one of these two dehydrocyclization products. This behavior in strong acid seems to be a natural consequence of the ground state protonation of bianthronyl. The **12** ⇄ **6** equilibrium is probably displaced greatly toward the double protonated species **12.** This seems reasonable in view of the lack of conjugation between the two "anthrone" halves of bianthronyl and their nearly perpendicular relative orientation.[26] Furthermore, this hypothesis is even more acceptable in view of the demonstrated diprotonation of both carbonyl groups of conjugated aromatic diketones and quinones in concentrated sulfuric acid.[27]

Protonation at both carbonyl groups in **12** eliminates the n,π^* set of levels on direct excitation. Consequently, the π,π^* excited singlet formed on photon absorption has more favorable deactivation paths available than deprotonation and intersystem crossing to an n,π^* triplet which is suspected to be responsible for H abstraction from another bianthronyl molecule in neutral solvents.[2] Furthermore, such a hydrogen abstraction in the case of **12** would involve a collision between a divalent and a monovalent cation, an electrostatically unfavorable event. It is probable that the other options accessible to π,π^* excited **12,** namely, fluorescence, dissociation to two radical cations **11,** and radiationless deactivation, are able to completely suppress photooxidation to bianthrone. The formation of anthraquinone on very long exposure to light in acid is most probably a consequence of the side reaction of cation radicals **11** with the oxidizing solvent. The last step in this sequence of photoreactions, the formation of 2-hydroxyanthraquinone from anthraquinone, has been studied separately and reported elsewhere.[12]

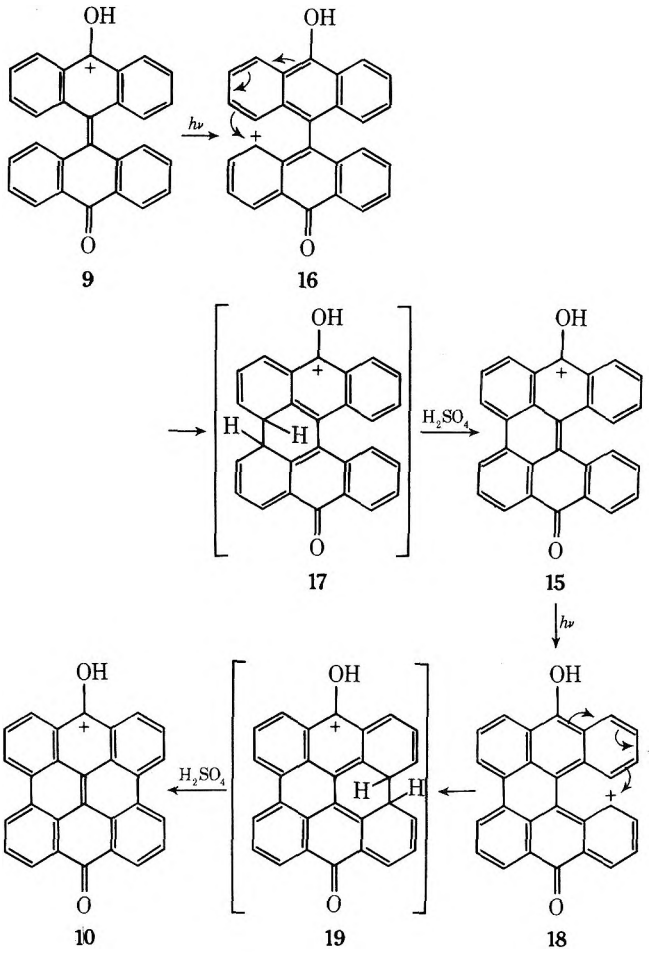
There is little doubt that the irradiation of protonated bianthrone **9** leads eventually to nearly complete conversion to naphthobianthrone **10.** However, the transformation is not a direct **9** → **10** reaction. This is demonstrated by the family of scans in the time-lapse spectrometry diagram shown in Figure 3. In spite of the apparent isosbestic point at 315 nm, there are clear departures from "isosbesticity" in the 230–280-nm and 500–700-nm regions. In addition, there are small peaks detectable in the intermediate scans at 272, 346, and 402 nm which cannot be accounted for by the absorption of either **9** or **10.** In fact these peaks are at the same wavelengths as the maxima reported for the absorption of helianthrone in sulfuric acid.[15] Furthermore, the isosbestic point at 315 nm in Figure 3 coincides with the wavelength of equiabsorptivity of **9, 10,** and **15.** This not only reinforces the suggested **9** → **15** → **10** photoxidative mechanism but also explains the fortuitous occurrence of an isosbestic point at 315 nm. The existence of this point also testifies to the absence of side reactions, since any intermediate or product other than **9, 15,** or **10** would either add its own absorbance at 315 nm or depress the total

optical density at this wavelength of its absorbs less than its precursor.

The photodehydrocyclizations of bianthrone **2** and helianthrone **3** in nonacidic solvents have been studied by Brockmann and Muhlmann.[4] They clearly established the fate of the hydrogen atoms lost by the reacting molecules. There is no formation of gaseous hydrogen. In the presence of dissolved oxygen in nonoxidizing solvents hydrogen peroxide was detected.[4] On the other hand, in the absence of oxygen and in solvents unable to accept the hydrogen atoms, an exact disproportionation was noted with the molecules undergoing dehydrocyclization being equal to those being converted from diketones to diphenols.

There is little doubt that the hydrogen atoms lost by bianthrone and helianthrone during photolysis in sulfuric acid are readily accepted by the oxidizing solvent. The probable overall mechanism is shown in Scheme II.

Scheme II



The photooxidative cyclization of bianthrone in sulfuric acid is a very efficient reaction. The quantum yield determined from disappearance of reactant at less than 20% conversion was over 0.9. This efficiency may be explained by the high probability of cyclization in protonated excited ketones **18** and **21** and the ability of the solvent to accept hydrogen atoms of intermediates **19** and **22**. The excited states of **9** and **15** were arbitrarily represented by the valence-bond structures **16** and **18**, respectively, which exhibit the difference in electronic density in the carbon atoms involved in cyclization.

The sum of the free valence numbers in the first excited electronic state ΣF_r^* of the atoms involved in the cyclization step was estimated by an MO-SCF-CI calculation with appropriate corrections for the oxygen atoms.[28-31] The π delocalization included both oxygen atoms in bianthrone but extended[10] only over the carbonyl oxygen in its respective hydroxycarbocation **9**. The ΣF_r^* values for bianthrone were 0.879 in the ground state and 0.898 in the first excited singlet or triplet state. For its cation **9**, the ΣF_r^* values in the S_1, T_1, and T_2 states were 0.925, 0.912, and 1.003, respectively. These results are only moderately consistent with the observed more facile photocyclization in the protonated species.[28]

Experimental Section

Fluorometric grade pure sulfuric acid (Matheson) was used for all time-lapse spectrometry determinations. Reagent-grade acid (Fisher, 96%) was adequate for preparative-scale reactions, after verifying that TLS in this acid was the same as in the 100% fluorometric grade. UV-visible absorption spectra were recorded on a Cary Model 15 spectrophotometer in double-beam mode. Infrared spectra were taken on a Perkin-Elmer 221 spectrometer. Emission spectra were recorded on a Hitachi Perkin-Elmer SPF spectrophotometer. Ultraviolet Products 9-W UV hand lamps were used for most TLS experiments. A GE 275-W sun lamp or the Hanovia 450-W Hg lamp were used for preparative-scale photolysis.

Recovery of Anthrone from Acid. Anthrone (1.013 g, 5.2 mmol) was dissolved in 50 ml of 96% sulfuric acid. The yellow solution was kept in a closed flask for 1 week. A diluted aliquot showed an unchanged UV-visible spectrum. The acid solution was added dropwise to 350 g of ice when a white precipitate formed. Extraction with CH_2Cl_2, washing of the organic phase with 5% aqueous $NaHCO_3$, drying over anhydrous $MgSO_4$, and vacuum evaporation of solvent yielded 0.94 g (93%) of an off-white crystalline material, mp 152–156 °C. The IR spectrum and melting point of an ether–benzene recrystallized sample (155 °C) showed it to be unchanged anthrone.

Photolysis of Anthrone. Anthrone (1.17 g, 5 mmol) in 350 ml of 96% sulfuric acid was photolyzed with a 450-W medium-pressure Hg arc lamp in the Hanovia immersion well for 30 h while N_2 was bubbled continuously and cooling water was circulated through the well mantle. The progress of the reaction was followed by recording UV-visible spectra of diluted aliquots. The final solution was added dropwise to crushed ice, extracted with CH_2Cl_2, and worked up as above, obtaining 0.9 g (86%) of a crystalline product. Thin layer and column chromatography on silica gel afforded separations into two components, identified by IR, UV, NMR spectra, and melting point to be unreacted anthrone and bianthronyl in 42 and 58% yield, respectively.

Photolysis of Bianthronyl. Bianthronyl (0.2 g) was dissolved in 5 ml of 96% sulfuric acid under constant magnetic stirring. The deep yellow solution was placed in three different 0.5-cm quartz tubes and irradiated with a GE 275-W sun lamp while bubbling O_2-free nitrogen through capillary tubes immersed in the acid solutions and having the outside of the tubes cooled with running water. The tubes were photolyzed for 200, 500, and 800 h, respectively. Aliquots were taken at different intervals, volumetrically diluted, and the UV-visible spectra recorded. At the end of the photolysis the green content of the tube was poured dropwise with constant stirrings into saturated aqueous $NaHCO_3$ (or ice), extracted repeatedly with ether (or methylene chloride), washed with distilled water, dried over anhydrous $MgSO_4$, filtered, and rotary evaporated. The greenish impure crystals were dissolved in a small amount of $CHCl_3$ and chromatographed on a silica gel column by eluting with petroleum ether, chloroform, and ethyl acetate. Evaporation of fractions and (1) comparison with the thin layer pattern, (2) IR, UV-visible, and emission spectrometry, and (3) comparison with authentic samples confirmed the presence of unreacted bianthronyl, anthraquinone, 2-hydroxyanthraquinone, and anthrone. The last two were found only in trace amounts in all three tubes. The amount of anthraquinone increased at the expense of bianthronyl as the time of photolysis was extended.

Photolysis of Bianthrone. Bianthrone (0.2 g) was dissolved in 10 ml of 96% sulfuric acid and irradiated under N_2 with water cooling for 2 weeks with the GE 275-W sunlamp. Hydrolysis on ice, extraction with benzene, and evaporation yielded 0.11 g of crude *meso*-naphthobianthrone, identified by comparison of IR, UV-visible, and NMR spectra with those of an authentic sample prepared from bianthrone by photolysis in xylene.[14]

Acknowledgment. This work was supported by the Energy Research and Development Administration on Contract E-(40-1)-3797.

Registry No.—**1**, 90-44-8; **2**, 434-85-5; **4**, 434-84-4.

References and Notes

(1) Postdoctoral Research Associate on leave from the Research Institute for Organic Chemistry, Bucharest, Romania, 1973–1974.
(2) W. Koch, T. Saito, and Z. Yoshida, *Nippon Kagaku Zasshi*, **88**, 684 (1967).
(3) G. Lober, *Z. Phys. Chem. (Frankfurt am Main)*, **54**, 73 (1957).
(4) H. Brockmann and R. Muhlmann, *Chem. Ber.*, **82**, 348 (1949).
(5) H. Brockmann, R. Neef, and R. Muhlmann, *Chem. Ber.*, **83**, 467 (1950).
(6) H. Brockmann and H. Eggers, *Angew. Chem.*, **67**, 706 (1955).
(7) E. D. Bergamann and H. J. E. Loewenthal, *Bull. Res. Counc. Isr. Sect. A*, **3**, 72 (1953).
(8) R. F. Stermitz in "Organic Photochemistry", Vol. 1, O. L. Chapman, Ed., Macrel Dekker, New York, N.Y., 1967.
(9) T. D. Doyle, N. Filipescu, W. R. Benson, and D. Barnes, *J. Am. Chem. Soc.*, **92**, 6371 (1970).
(10) N. Filipescu, S. K. Chakrabarti, and P. G. Tarassoff, *J. Phys. Chem.*, **77**, 2276 (1973).
(11) P. G. Tarassoff and N. Filipescu, *J. Chem. Soc., Chem. Commun.*, 208 (1975).
(12) G. G. Mihai, P. G. Tarassoff, and N. Filipescu, *J. Chem. Soc., Perkin Trans. 1, 000* (1975).
(13) N. Filipescu, F. L. Minn, and J. W. Pavlik, *Anal. Chem.*, **43**, 83 (1971).
(14) H. Meyer, R. Bondy, and A. Eckert, *Monatsh. Chem.*, **33**, 1447 (1912).
(15) R. A. Heber, M. B. Goren, and A. A. Vernon, *J. Am. Chem. Soc.*, **74**, 5779 (1952).
(16) F. Mader and V. Zanker, *Chem. Ber.*, **97**, 2418 (1964).
(17) A. Kellmann, *J. Chim. Phys. Phys.-Chim. Biol.*, **63**, 936 (1966).
(18) S. Kato, S. Minagawa, and M. Koizumi, *Bull. Chem. Soc. Jpn.*, **34**, 1026 (1961).
(19) A. Kellmann, *J. Chim. Phys. Phys.-Chim. Biol.*, **57**, 1 (1960).
(20) H. Goth, P. Cerutti, and H. Schmid, *Helv. Chim. Acta*, **48**, 1395 (1965).
(21) V. Zanker, E. Erhardt, F. Mader, and J. Thies, *Z. Naturforsch. B*, **21**, 102 (1966).
(22) W. Koch, T. Saito, and Z. Yoshidam, *Nippon Kagaku Zasshi*, **88**, 684 (1967).
(23) E. T. Seo, R. F. Nelson, J. M. Fritsch, L. S. Marcoux, D. W. Leedy, and R. N. Adams, *J. Am. Chem. Soc.*, **88**, 3498 (1966).
(24) C. K. Bradsher, L. E. Beavers, and J. H. Jones, *J. Org. Chem.*, **22**, 1740 (1957).
(25) N. Deno, G. Saines, and M. Spangler, *J. Am. Chem. Soc.*, **84**, 3295 (1962).
(26) D. Cohen and I. T. Millar, *J. Chem. Soc. C*, 793 (1968).
(27) M. Liler in "Reaction Mechanism in Sulphuric Acid", Academic Press, New York, N.Y., 1971, p 127.
(28) M. Scholz, M. Muhlstadt, and F. Dietz, *Tetrahedron Lett.*, 665 (1967).
(29) W. H. Laarhoven, T. J. H. M. Cuppen, and R. J. F. Nivard, *Recl. Trav. Chim. Pays-Bas*, **87**, 687 (1968); *Tetrahedron*, **26**, 1069 (1970).
(30) E. V. Blackburn and C. J. Timmons, *J. Chem. Soc. C*, 172 (1970).
(31) G. C. Marx and E. D. Bergman, *J. Org. Chem.*, **37**, 1807 (1972).

Catecholborane (1,3,2-Benzodioxaborole). A Versatile Reducing Agent[1]

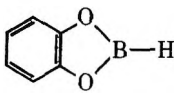
George W. Kabalka,* John D. Baker, Jr., and Gary W. Neal

Department of Chemistry, University of Tennessee, Knoxville, Tennessee 37916

Received May 25, 1976

The reaction of 1,3,2-benzodioxaborole [catecholborane (CB)] with representative functional groups was studied to determine the utility of CB as a selective reducing agent. The approximate rates, stoichiometry, and products of the reductions were determined under standard conditions ($CHCl_3$, 25 °C). The results indicate that CB is unique compared to other substituted boranes. The reduction rates appear to be solvent independent with the exception of alkenes. Primary alkenes react very sluggishly, whereas secondary alkenes are unreactive at room temperature; as a result, many selective reductions can be performed in the presence of alkenes.

In the important area of selective reductions, we wish to report on the useful applications of catecholborane (1,3,2-benzodioxaborole, 1). Although borane complexes[2,3] and



1

substituted boranes[4,5,6] have been employed as selective reducing agents, catecholborane (CB) has certain unique properties which merit attention. Recently, a review article on some of the chemistry of CB has appeared.[7]

CB has some practical advantages over other, commonly used reducing agents: (1) It is a liquid at room temperature and may be used without solvent.[8] (2) CB is soluble and stable in all common, aprotic solvents (e.g., benzene, toluene, chloroform, ether, hexane, etc.). (3) CB is stable in dry air and reacts only slowly with moist air. (4) CB may be stored unchanged for over a year at 0 °C, in contrast to certain other substituted boranes.[9,10]

Results and Discussion

Since this study was carried out to determine the relative reactivity of CB toward various functional groups, a standard set of conditions was selected. The reactions were conducted at room temperature, generally in $CHCl_3$, with stoichiometric amounts of hydride and substrate (with the initial concentration of substrate at approximately 0.5 M). Faster reaction can be achieved by using excess hydride, raising the temperature, or increasing the concentration of the substrate. The rates of reduction were usually independent of the solvent utilized, although the hydroboration of alkenes was, in fact, solvent dependent[11] (Table I).

The reactivity exhibited by the various functional groups toward CB in $CHCl_3$ can be classified for convenience into three broad categories:

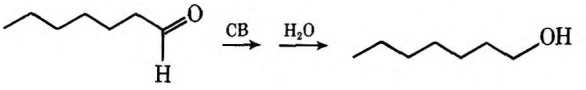
(1) Fast—those functionalities that react in 24 h or less (Table II).

(2) Slow—those functionalities whose reaction times exceed 24 h (Table III).

(3) Inert—those functionalities that exhibit no reactivity toward CB (Table IV).

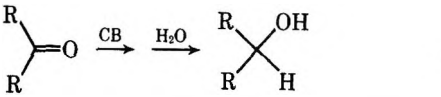
The data in the tables demonstrate that there is a wide range of reactivity within each category.

Aldehydes, Ketones, and Derivatives. Heptanal and benzaldehyde were investigated as representatives of aliphatic and aromatic aldehydes. Heptanal is rapidly and quantitatively reduced to the corresponding alcohol (eq 1).[12] Likewise, benzaldehyde is reduced rapidly to benzyl alcohol.



(1)

Cyclic and acyclic aliphatic ketones were reduced in high yields (eq 2).[12] 2-Octanone was slowly reduced with 1 or 2



(2)

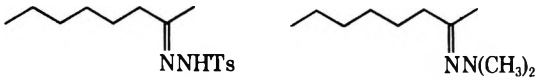
equiv of hydride. On the other hand, cyclopentanone and cyclohexanone exhibited varying degrees of reactivity,[13] as shown in the tables.

Table I. Representative Examples of Reduction Rates in Various Solvents[a]

Substrate	Solvent	Redn time, h	% redn[b]
$C_6H_{13}CH{=}CH_2$	$CHCl_3$	43.2	5
$C_6H_{13}CH{=}CH_2$	THF	46.5	25
Cyclohexene	$CHCl_3$	46	0[c]
Cyclohexene	THF	46	0[c]
Cyclopentanene	$CHCl_3$	72	68
Cyclopentanone	THF	72	71
Cyclohexanone	$CHCl_3$	24.6	84[c]
Cyclohexanone	Tolune	21	96[c]
$C_6H_{13}CHO$	$CHCl_3$	3	94
$C_6H_{13}CHO$	THF	3	87
$C_6H_{13}CHO$	THF	3.5	97

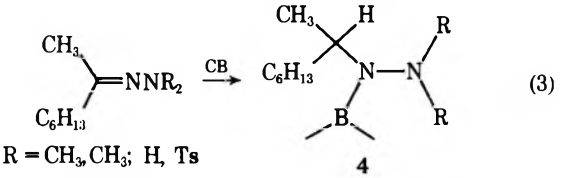
[a] Reductions were carried out using equimolar amounts of substrate and CB (concentration of reactants: ~0.5 M) at room temperature. [b] Reduction followed by GLC. [c] Reduction followed by NMR.

Two imine derivatives, 2-octanone *p*-toluenesulfonylhydrazone (**2**) and 2-octanone *N,N*-dimethylhydrazone (**3**), were



2 **3**

prepared and reduced. These compounds were very reactive with CB and produced the corresponding hydrazinoborane derivatives, **4**, in nearly quantitative yields (eq 3).

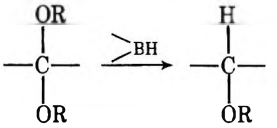


(3)

R = CH_3, CH_3; H, Ts

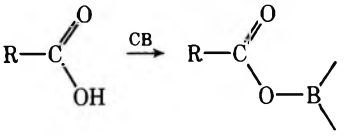
4

The reduction of acetals and ketals was examined since they are commonly utilized as protecting groups for ketones and aldehydes. CB reacted with the diethyl ketal of cyclohexanone and the diethyl acetal of heptanal to give the corresponding ethers (eq 4). This cleavage with CB is analogous to results with BH_3.[14]



(4)

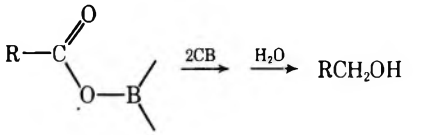
Carboxylic Acids and Derivatives. Propionic and benzoic acids reacted rapidly and quantitatively with 1 equiv of CB, liberating hydrogen gas, to form the corresponding acyloxyborane,[2,15] **5** (eq 5). The acyloxyborane, **5**, reacted further with



(5)

5

2 additional equiv of CB to give a quantitative yield of the corresponding alcohols (eq 6). Attempts were made, by



(6)

varying reaction conditions to produce the corresponding aldehyde from the acid precursor. However, only trace amounts of aldehyde were detected indicating that reduction of the acyloxyborane, **5**, is slow in comparison to reduction of the aldehyde formed during the reduction.

Propionic acid reacted at a moderate rate whereas benzoic acid was reduced much slower, presumably owing to the weaker Lewis basicity of the carbonyl group in the latter compound.

The sodium salt of stearic acid was reduced rapidly over the period of 6.5 h at room temperature in THF. This is a surprising result when compared to the fact that borane is inert toward the sodium salt of an acid.[16]

Butyric anhydride required 4 equiv of CB for complete reduction. Presumably, the first equivalent of hydride produces the corresponding aldehyde and an acyloxyborane (eq 7). The

Table II. Reduction of Fast Reacting Groups with Catecholborane[a]

Functionality	Substrate	Registry no.	Ratio of H/substrate	Time for 50% redn, min	% overall redn (time, h)[b]
Aldehyde	$C_6H_{13}CHO$	111-71-7	1:1	20	93[c] (4)
	C_6H_5CHO	100-52-7	1:1	35	85 (2)
	C_6H_5CHO		2:1	11	92 (1.5)
Ketone	Cyclohexanone	108-94-1	1:1	75	84 (24.7)
Hydrazone	$C_6H_{13}C(CH_3){=}NNHTs$	54798-76-4	1:1	19	100 (0.92)
	$C_6H_{13}C(CH_3){=}NN(CH_3)_2$	60676-12-2	1:1	16	93 (1)
Acid salt	$C_{17}H_{35}CO_2Na$	822-16-2	3:1[d]		100 (6.5)
Sulfoxide	$(CH_3)_2SO$	67-68-5	2:1	27	93 (23.8)
Amine oxide	$(CH_3)_3NO$	1184-78-7	2:1	3	94 (8.5)
Anhydride	$(C_3H_7CO)_2O$	106-31-0	4:1	30	86 (24)
Epoxide	Propylene oxide	75-56-9	1:1[e]	165	99[c] (27)
	Propylene oxide		2:1[f]	10	100 (1)
	Styrene oxide	96-09-3	1:1[e]		100 (.25)
RC≡CH	$C_4H_9C{\equiv}CH$	693-02-7	1:1	738	79 (25.3)
Acetal	$C_6H_{13}CH(OC_2H_5)_2$	688-82-4	1:1		20 (24)
Ketal	1,1-Diethoxycyclohexane	1670-47-9	1:1		100 (1)

[a] Reactions were carried out using an initial substrate concentration of 0.5 M in $CHCl_3$ at room temperature. [b] Reduction followed by NMR. [c] Reduction followed by GLC. [d] Sodium stearate was reduced in THF because of solubility problems in $CHCl_3$. [e] The epoxides react with 1 equiv of CB to give a mixture of products. [f] Propylene oxide reacts with 2 equiv of CB to give i (79%) and ii (21%).

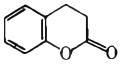
i ii

Table III. Reduction of Slow Reacting Groups with Catecholborane[a]

Functionality	Substrate	Registry no.	Ratio of H/substrate	Time for 50% redn, h	% overall redn (time, h)[b]
RCOR	Cyclopentanone	120-12-3	1:1	28	68[c] (72)
	$C_6H_{13}COCH_3$	111-13-7	1:1	40	70 (163)
	$C_6H_{13}COCH_3$		2:1	7.3	91 (71.8)
RCOCl	CH_3COCl[d]	75-36-5	2:1		20 (72)
$RCM{=}CH_2$	$C_6H_{13}CH{=}CH_2$	111-66-0	1:1		5 (44)
$RC{\equiv}N$	$C_2H_5C{\equiv}N$	107-12-0	2:1	48.6	54 (63)
RCO_2H	$C_6H_5CO_2H$	65-85-0	3:1		28[e] (20)
	p-$NO_2C_6H_4CO_2H$	62-23-7	3:1		87 (90)
$RCONR_2$	$CH_3CON(CH_3)_2$	125-19-5	2:1		40 (96)

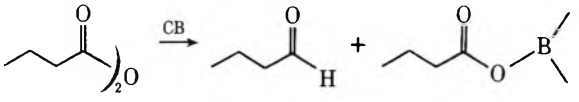
[a] Reductions were carried out using an initial substrate concentration of 0.5 M in $CHCl_3$ at room temperature. [b] Reduction followed by NMR. [c] Reduction followed by GLC. [d] Initial concentration was 1.66 M. [e] This reduction goes to 85% completion in 152 h in refluxing $CHCl_3$.

Table IV. Groups Exhibiting No Reactivity toward Catecholborane[a]

Functionality	Substrate	Registry no.	Ratio of H^-/substrate	Rxn time, h	% redn[b]
RCO_2R	$C_3H_7CO_2C_2H_5$	105-54-4	1	81	0[c]
RSR	$(CH_3S)_2$	624-92-0	1	42.7	0
RNO_2	CH_3NO_2	75-52-5	1	168	0
RSO_2R	Tetramethylenesulfone	126-33-0	1	94	0
RCH=CHR	Cyclohexene	110-83-8	1	46	0
RCO_2R		119-84-6	1	96	0
$(RCO)_2O$	$(CF_3CO)_2O$	407-25-0	4	21	0
	Maleic anhydride	108-31-6	4	50	0
RBr	n-$C_8H_{17}Br$	111-83-1	1	48	0
RI	n-$C_5H_{11}I$	628-17-1	1	48	0

[a] Reductions were carried out using an initial substrate concentration of 0.5 M in $CHCl_3$ at room temperature. [b] Reduction followed by NMR. [c] Reduction followed by GLC.

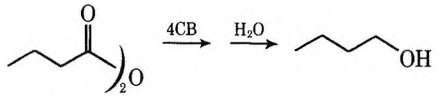
proposed initial step prompted us to investigate the possibility of aldehyde production under varying reaction conditions.



(7)

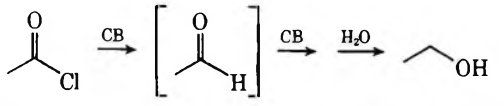
Only trace amounts of aldehyde were detected in all cases. It is apparent that the reduction of the anhydride by CB is slow compared to the reduction of the aldehyde produced from the initial addition of CB to the anhydride.

The reduction of butyric anhydride was fairly rapid; after 20 h an 86% yield of butanol was obtained (eq 8). Trifluoroacetic and maleic anhydride were inert toward CB at room temperature in chloroform; however, trifluoroacetic anhydride reacted slowly in refluxing $CHCl_3$.[17]



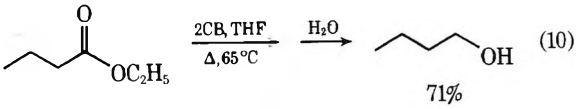
(8)

Acetyl chloride reacted very slowly with CB taking 2 equiv to produce the corresponding alcohol. Presumably, the reduction proceeds through initial reduction of the acid chloride to give the corresponding aldehyde which in turn produces the alcohol (eq 9). As would be expected, only a trace of aldehyde was detected in this reduction.



(9)

Ethyl butyrate did not react at room temperature in $CHCl_3$ but reacted slowly to produce the alcohol in good yields in refluxing THF or $CHCl_3$ (eq 10).

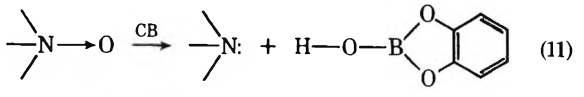


(10)

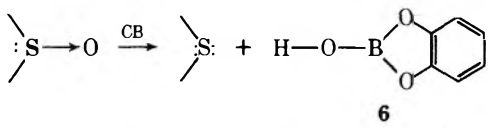
The lactone, coumarin, was also examined and was found to be inert toward CB at room temperature in $CHCl_3$.

Acetamide liberated less than 1 equiv (62%) of the theoretical amount of hydrogen for the two acidic hydrogens, and a mixture of products was produced. However, benzamide liberated 2 equiv of hydrogen but did not undergo further reaction. The tertiary amide *N,N*-dimethylacetamide underwent reduction at room temperature to give the corresponding amine in 40% yield. It should be noted that *N,N*-dimethylacetamide was cleanly reduced to dimethylethylamine by utilizing a 50% excess of CB and running the reaction in refluxing chloroform solution.

Amine Oxides and Sulfoxides. Both the amine oxide and sulfoxide functionalities are readily reduced by CB. Trimethylamine oxide and dimethyl sulfoxide react rapidly with 2 equiv of CB to liberate 1 equiv of hydrogen gas and to produce trimethylamine and dimethyl sulfide, respectively. By analogy with borane, and from spectral data, the following reactions appeared to occur (eq 11 and 12). The liberation of hydrogen



(11)

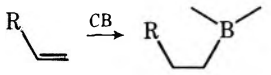


(12)

6

resulted from the reaction of CB with the acidic hydrogen of 6 produced as a common intermediate of the reductions.

Alkenes.[8] Terminal and interanal alkenes were examined. Surprisingly, CB reduces alkenes extremely slowly at room temperature with only 5% reduction of 1-octene over approximately a 2-day period. This should allow many selective reductions to be performed which are not possible with borane. Good yields of the corresponding 2-alkyl-1,3,2-benzodioxaborole 7 (eq 13) were obtained when the reactions were

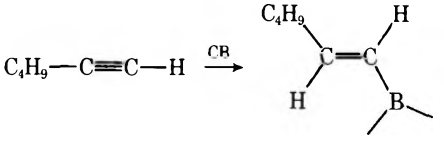


(13)

carried out at 60–70 °C. The rate of hydroboration of alkenes is dependent on the solvent to a certain extent (Table I). For example, 1-octene was hydroborated faster in refluxing THF than in refluxing $CHCl_3$. This might be attributed to two possible factors: (1) the catalytic action of ethers for the reduction of alkenes by boranes[11] and (2) the slightly higher reflux temperature of THF. At these concentrations, the hydroboration of 1-octene proceeded smoothly until it reached a maximum of approximately 81%; beyond this point, isomerization of the 1-octene occurred, producing increasing amounts of internal alkene (presumably via hydroboration–dehydroboration) with a concomitant decrease in yield of the alkylborane.

The secondary alkene, cyclohexene, did not undergo hydroboration at room temperature but slowly reacted in refluxing THF and $CHCl_3$ producing 2-cyclohexyl-1,3,2-benzodioxaboraole.

Alkynes.[8] Terminal alkynes were found to react much faster than alkenes. For example, hydroboration of 1-hexyne with CB was a fast reaction at room temperature producing the corresponding vinylborane in both THF and $CHCl_3$. 1-Hexyne reacted with CB to give cis addition[8] and formation of 2-alkenyl-1,3,2-benzodioxaborole (8, eq 14) which is a useful



(14)

8

synthetic intermediate. As a result of the increased reactivity of alkynes, they can be selectivel reduced in the presence of alkenes.

Other Functional Groups. Propylene oxide and styrene oxide reacted at a moderate rate with 1 equiv of CB to give a mixture of products. However, propylene oxide reacted rapidly and quantitatively with 2 equiv of CB to give the ring-opened alcohols, 2-propanol (79%) and 1-propanol (21%).

The aliphatic nitro group of nitromethane and the aromatic nitro group of *p*-nitrophenylacetic acid were inert to CB at room temperature.

As noted earlier, dimethyl sulfoxide reacted rapidly with CB. However, tetramethylenesulfone and dimethyl disulfide were found to be inert toward CB at room temperature. The disulfide group is also inert toward CB under refluxing conditions in THF.

Primary alkyl bromides and iodides are inert toward CB at room temperature, as determined using *n*-octyl bromide and *n*-pentyl iodide.

Selective Reductions. Systematic exploration of the reducing characteristics of CB has revealed a broad diversity of reactivity of CB toward various functional groups. This range of reactivity makes possible many selective reductions.

Table V. Selective Reduction of Heptanal in Presence of Various Substrates[a]

Substrate	% unreacted substrate[b]	% heptanol[b,c]
$C_6H_{13}COCH_3$	93	94
$C_8H_{17}CH{=}CH_2$[d]	97	99
Cyclohexene	100	100
$C_2H_5C{\equiv}N$	100	100
CH_3COCl	100	92
$C_3H_7CO_2C_2H_5$	100	100
n-$C_8H_{17}Br$	100	100

[a] Reductions were carried out using an initial substrate concentration of ≃0.5 M. CB was added dropwise to a −5 °C solution. The solution was allowed to sit for 0.5 h at −5 °C, warmed to 0 °C for 0.5 h, and allowed to sit for 6 h at room temperature and then analyzed. [b] Reactions analyzed by GLC. [c] Heptanol is produced by hydrolyzing the reaction product, 2-heptoxy-1,3,2-benzodioxaborole. [d] Registry no., 872-05-9.

Table VI. Selective Reduction of Cyclohexanone in the Presence of Various Substrates[a]

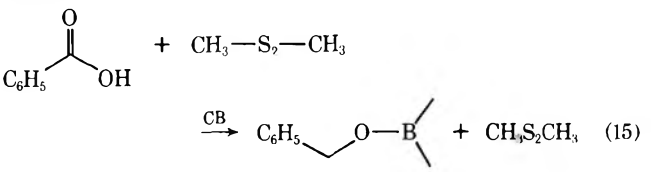
Substrate	Unreacted substrate, %[b]	Cyclohexanol, %[b,c]
$C_8H_{17}CH{=}CH_2$	100	98
Cyclohexene	100	98
$C_2H_5C{\equiv}N$	100	98
CH_3COCl	95	98
$C_3H_{17}CO_2C_2H_5$	100	98
n-C_4H_9Br[d]	100	98

[a] Reductions were carried out using an initial substrate concentration of ≃0.5 M. CB was added to a −5 °C solution. The solution was allowed to sit for 5 h at −5 °C, warmed to 0 °C for 15 h, and allowed to sit for 23 h at room temperature and then analyzed. [b] Reactions analyzed by GLC. [c] Cyclohexanol is produced by hydrolyzing the reaction product, 2-cyclohexoxy-1,3,2-benzodioxaborole. [d] Registry no., 109-65-9

In competitive experiments, various substrates, in equal molar quantities, were allowed to compete for a limited quantity of CB. A number of selective reductions were observed. Table V displays the selective reduction of an aldehyde in the presence of various functional groups. Table VI presents the selective reduction of a given ketone in the presence of various functional groups. These two tables are representative of the utility of CB as a selective reducing agent.

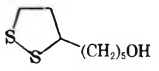
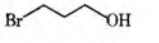
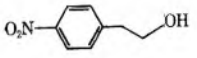
Examination of Tables V and VI reveals that CB will preferentially reduce an aldehyde in the presence of a ketone in quantitative yield (Table V); this reduction is not possible using borane. Also in contrast to borane, CB reacts with terminal alkynes to give the monohydroboration product. For example, CB will readily hydroborate 1-hexyne in the presence of cyclohexene.

CB does not cleave the disulfide linkage even at elevated temperatures; this is in contrast to sodium borohydride[18] and lithium aluminum hydride.[19] Thus, it should be possible to reduce a variety of functional groups in the presence of the disulfide linkage; indeed, two acids were reduced in the presence of the disulfide group in quantitative yields (eq 15 and 16).

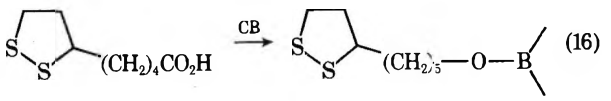


(15)

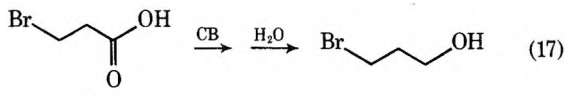
Table VII. Characterization of Products Obtained via Selective Reduction

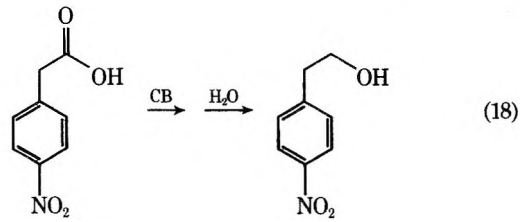
Compd	Registry no.	^{1}H NMR ($CDCl_3$), δ	Obsd bp, °C	Ref bp, °C
	539-55-9	1.5 (broad, 8 H, alkyl), 2.4 (quintet, 2 H, ring CH_2), 3.15 (t, 2 H, $-CH_2S-$), 3.6 (m, 3 H, −CHRS and $-CH_2O-$), 4.9 (s, 1 H, −OH)	*a*	*a*
	627-18-9	2.1 (quintet, 2 H, $-CH_2-$), 3.5 (t, 2 H, $-CH_2Br$), 3.9 (t, 2 H, $-CH_2O-$), 4.2 (s, 1 H, −OH)	75–77 (14 mm)	76 (14 mm)[25]
	100-27-6	3.0 (t, 2 H, $-CH_2Ar$), 3.9 (t, 2 H, $-CH_2O$), 5.2 (s, 1 H, −OH), 7.7 (A_2X_2, 4 H, ArH)	63.5–4.5	64[b,26]
	96-48-0	2.5 (complex m, 4 H, $-CH_2CH_2CO-$), 4.4 (t, 2 H, $-CH_2O-$)	250	206 (760 mm)[27]

[a] This alcohol is notoriously unstable and has not been characterized in its pure form. The spectral data and solution characteristics of the product obtained in the CB reduction are in complete agreement with data presented by earlier workers.[24] [b] Melting point.

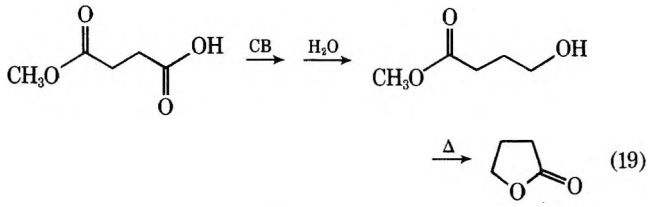

(16)

Unlike lithium aluminum hydride,[20] CB does not reduce alkyl halides or nitro compounds over long periods of time at room temperature; therefore, many functional groups can be reduced in the presence of halides (Tables V and VI) or nitro groups. For example, acids can be quantitatively reduced in the presence of a bromide or a nitro group (eq 17 and 18).

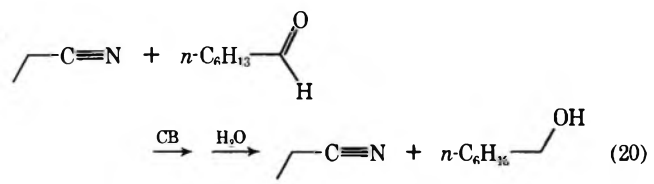

(17)


(18)

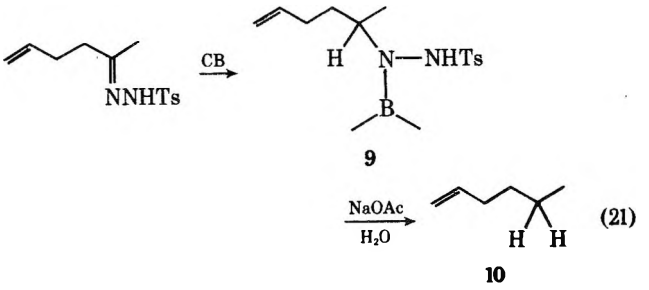
Esters are unreactive at room temperature. Thus, CB and borane will quantitatively reduce aldehydes (Table V), ketones (Table VI), or acids in the presence of an ester (eq 19).


(19)

Unlike borane, CB reduces nitriles extremely slowly and, thus, it is possible to reduce many of the functional groups present in Table II in the presence of nitriles (Tables V and VI) in quantitative yields (eq 20).


(20)

The quantitative reductions of an aldehyde and a ketone by CB in the presence of a terminal and secondary alkene were successfully performed (Tables V and VI). In a similar manner, an imine derivative was selectively reduced in the presence of a terminal alkene and a tosyl group to give the corresponding hydrazinoborane derivative **9** in quantitative yield (eq 21). This valuable synthetic intermediate may be converted to the deoxygenated compound, **10**.[21,22]


(21)

9

10

Summary. Catecholborane (1,3,2-benzodioxaborole) has been shown to be an important and versatile reducing agent for many selective reductions. It exhibits some reductive properties which are unique and complementary to other substituted boranes, such as thexylborane, disiamylborane, and 9-borabicyclononane.

Experimental Section

Analysis and Spectra. GLC analysis was carried out on a Varian Aerograph Model 1700 instrument using SE-30 (5% on 60–80 Chromosorb W, 0.25 in. × 6 ft column). The NMR spectra were recorded on a Varian T-60.

Materials. The substrates used for the reductions are all commercially available and were used without further purification. A standard solution of borane in THF was prepared according to published procedures.[23] Catechol (99+% purity) was dried at 25 °C over P_2O_5 under vacuum for 24 h.

Solvent Purification. Both $CHCl_3$ and THF were dried and stored under nitrogen. THF was dried over $LiAlH_4$ and distilled. $CHCl_3$ was washed several times with concentrated sulfuric acid followed by several water washes to remove the ethanol which is added as a stabilizer and then dried with $MgSO_4$. $CHCl_3$ was then distilled from fresh $MgSO_4$ under nitrogen and stored at 0 °C in the dark to prevent decomposition.

Preparation of Catecholborane (1,3,2-Benzodioxaborole). A 2.14 M solution of borane in THF (770 mmol, 396 ml) maintained under nitrogen was placed in a dry 1000-ml flask which was connected to a hood vent through a mercury bubbler. The reaction flask was immersed in an ice bath and catechol (770 mmol, 77 g) in THF (200 ml) was added over a 6-h period to the rapidly stirred borane solution. After addition of catechol, the solution was stirred overnight at room temperature to complete the reaction. Removal of THF and distillation under nitrogen afforded 39.5g (~50%) of catecholborane, bp 40 °C (26 mm).

Reduction Procedure. The substrate (2.5 mmol) was placed into a flame-dried 25-ml flask, fitted with a stirring bar and septum, and connected to a mercury bubbler to maintain a nitrogen atmosphere. $CHCl_3$ was added along with an appropriate internal standard for either GLC or NMR analysis. The flask was maintained at 25 °C via

a water bath. Catecholborane (2.6 mmol, a 5% excess) was added dropwise as a neat liquid to the stirred reaction mixture.

Aliquots were withdrawn at various time intervals, quenched with water, and analyzed by GLC or NMR.

Isolation. Reduction of aldehydes, ketones, acids, acid chlorides, anhydrides, and esters produces the corresponding alkoxy-1,3,2-benzodioxaboroles. The reduction of palmitic anhydride is representative of the general procedure utilized in this study. Palmitic anhydride (2.15 g, 4.32 mmol) was placed in a 25-ml flask which was assembled as described previously. Chloroform (70 ml) was then added and catecholborane (2.03 ml, 18.6 mmol) was added dropwise. The mixture was refluxed until the reduction was complete (3 days, monitored by NMR). The solution was extracted with one 25-ml portion of H_2O followed by six 25-ml extractions using a 1.0 N NaOH solution to remove catechol. The solution was then dried and separated using column chromatography; the column support was silica gel (Sargent-Welch, 60–200 mesch). The hexadecanol was eluted using a ligroin–ether mixture (98 and 2%, respectively). The first material eluted from the column was the hexadecanol (96% isolated, 2.02 g, 8.24 mmol).

Characterization of Products. The spectral data and physical constants of a number of products obtained via selective reduction with CB are summarized in Table VII.

Registry No.—Borane, 13283-31-3; catechol, 154-23-4; CB, 274-07-4.

References and Notes

(1) Presented in part at the 170th National Meeting of the American Chemical Society, Chicago, Ill. August 1975, Abstracts, No. ORGN-77.
(2) C. F. Lane, H. L. Myatt, J. Daniels, and H. B. Hopps, *J. Org. Chem.*, **39**, 3052 (1974).
(3) H. C. Brown, P. Heim, and N. M. Yoon, *J. Am. Chem. Soc.*, **92**, 1637 (1970).
(4) H. C. Brown, P. Heim, and N. M. Yoon, *J. Org. Chem.*, **37**, 2942 (1972).
(5) H. C. Brown, D. B. Bigley, S. K. Arora, and N. M. Yoon, *J. Am. Chem. Soc.*, **92**, 7161 (1970).
(6) S. Krishnamurthy, N. M. Yoon, and H. C. Brown, *J. Org. Chem.*, **41**, 1778 (1976).
(7) C. F. Lane and G. W. Kabalka, *Tetrahedron*, **32**, 981 (1976).
(8) H. C. Brown and S. K. Gupta, *J. Am. Chem. Soc.*, **97**, 5249 (1975).
(9) N. Ravindran, Ph.D. Thesis, Purdue University, 1972.
(10) H. C. Brown and A. W. Moerikofer, *J. Am. Chem. Soc.*, **84**, 1478 (1962).
(11) H. C. Brown and B. C. Subba Rao, *J. Org. Chem.*, **22**, 1136 (1957).
(12) The initial product was the 2-alkoxy-1,3,2-benzodioxaborole which was readily hydrolized to the corresponding alcohol. As an example, the initial product in the reduction of heptanal exhibits the following NMR ($CDCl_3$); δ 0.90 (m, 3 H, $-CH_3$), 1.33 (m, 10 H, alkyl), 4.13 (t, 2 H, $-OCH_2-$), 7.1 (s, 4 H, Ar). In general, the hydrogens of the $-CCH_2-$ moiety appear 0.5 δ to lower field in the borole derivatives than they do in the free alcohols.
(13) H. C. Brown, R. S. Fletcher, and R. B. Johannesen, *J. Am. Chem. Soc.*, **73**, 212 (1951).
(14) B. Fleming and H. I. Bolker, *Can. J. Chem.*, **52**, 388 (1974).
(15) H. C. Brown, S. Krishnamurthy, T. P. Stocky, N. M. Yoon, and C. S. Pak, *J. Org. Chem.*, **38**, 2786 (1973).
(16) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **82**, 681 (1960).
(17) After 95 h (refluxing $CHCl_3$), the yield of 2,2,2-trifluorethanol was 52% (NMR in $CDCl_3$ exhibits a quartet at δ 3.93).
(18) L. Field and P. M. Giles, Jr., *J. Org. Chem.*, **36**, 309 (1971).
(19) R. C. Arnold, A. P. Lien, and R. M. Alm, *J. Am. Chem. Soc.*, **72**, 731 (1950).
(20) H. C. Brown and S. Krishnamurthy, *J. Org. Chem.*, **34**, 3918 (1969).
(21) G. W. Kabalka and J. D. Baker, Jr., *J. Org. Chem.*, **40**, 1834 (1975).
(22) G. W. Kabalka, D. T. C. Yang, and J. D. Baker, Jr., *J. Org. Chem.*, **41**, 574 (1976).
(23) G. Zweifel and H. C. Brown, *Org. React.*, **13**, 1 (1963).
(24) A. F. Wagner, E. Walton, G. E. Boxer, M. P. Pruss, F. W. Holly, and K. Folkers, *J. Am. Chem. Soc.*, **78**, 5079 (1956).
(25) K. Kakemi, F. Kusada, and R. Morii, *J. Pharm. Soc. Jpn.*, **75**, 109–110 (1955).
(26) F. Ehrlich and P. Pistschimuka, *Ber.*, **45**, 2432 (1912).
(27) S. Sircar, *J. Chem. Soc.*, 898 (1928).

Simple Models of Nucleic Acid Interactions. 1. Base–Base Interactions in 1,2-Di(adenosin-N^6-yl)ethane and 1,4-Di(adenosin-N^6-yl)butane[1a,b]

Jiří Žemlička* and James Owens

Michigan Cancer Foundation and the Department of Oncology, Wayne State University School of Medicine, Detroit, Michigan 48201

Received June 11, 1976

Treatment of 6-chloro-9-β-D-ribofuranosylpurine (I) with 1,2-diaminoethane in dimethylformamide at room temperature in the presence of triethylamine gave 1,2-di(adenosin-N^6-yl)ethane (IIIb). Compound IIIb was also prepared by coupling of I with N^6-(2-aminoethyl)adenosine (IVa). Similarly, condensation of 6-chloro-9-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)purine (V) with IVa afforded 2′,3′-*O*-isopropylidene-1,2-di(adenosin-N^6-yl)ethane (VI), a derivative of IIIb with functionally differentiated ribose residues. Coupling of I with 1,4-diaminobutane gave 1,4-di(adenosin-N^6-yl)butane (IIIc) and N^6-(4-aminobutyl)adenosine (IVb). UV and CD spectra of IIIb and IIIc in water are consistent with an intramolecular base–base interaction (stacking). Thus, the hypochromism of IIIb is greater than that of IIIc. Both IIIb and IIIc exhibit an increased molecular ellipticity in CD spectra over the corresponding model compounds VIIa and VIIb. This increase is more pronounced in IIIc than IIIb. In 0.01 N HCl IIIb still exhibits a considerable hypochromism whereas that of IIIc virtually disappeared. By contrast, the CD spectra of IIIb and IIIc show a sharp drop in the molecular ellipticity which in both cases does not substantially differ from that in model compounds VIIa or VIIb. The effect of protonation on stacking, UV and CD spectra of IIIb and IIIc is discussed.

Interactions between the strands of nucleic acids are essential for the biological roles of both DNA and RNA in phenomena such as replication of DNA, transcription of genetic information from DNA to RNA, codon–anticodon interaction of mRNA with tRNA, etc., wherein two molecules (strands) approach one another closely enough to form a complex. The stability of these complexes derives mainly from the formation of specific hydrogen bonds between complementary bases (Watson–Crick or "wobble" pairing). In another type of interaction, the portions of nucleic acid molecules do not form hydrogen-bonded structures but, nevertheless, interact with each other through base stacking: the heterocyclic residues in the DNA or RNA are held in parallel planes in a sandwichlike arrangement. This base stacking is of importance for maintaining the proper secondary structure of DNA and RNA. It may also be of significance in some other cases where portions of DNA or RNA molecules are close enough but cannot form a hydrogen-bonded complex because of lack of the corresponding complementary bases. This situation may arise in the crucial step of protein synthesis where the pepti-

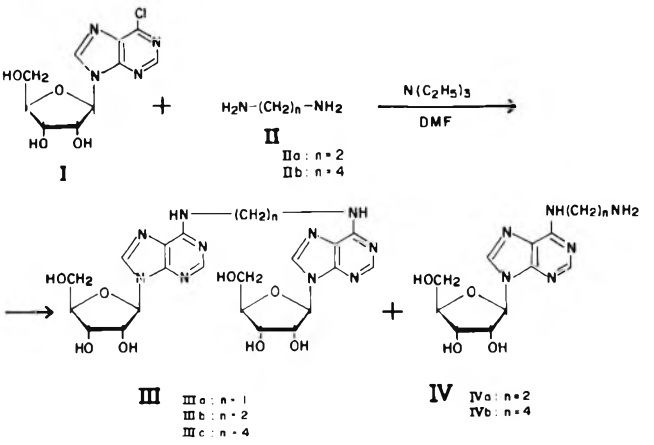
dyl- and aminoacyl-tRNA may interact during formation of the new peptide bond.[2] Because both molecules contain the identical 3′ terminal sequence (C-C-A), it would be difficult to envision a Watson–Crick type of interaction. However, as can be shown with Corey–Pauling–Koltun (CPK) space-filling models, base stacking of both C-C-A ends would be possible bringing together peptidyl and aminoacyl moieties in precise stereoelectronic fashion necessary for the synthesis of the peptide bond.[3] Further examination of CPK models has shown that more constrained model systems, such as 1,2-di(adenosin-N^6-yl)ethane (IIIb) and 1,4-di(adenosin-N^6-yl)butane (IIIc), would adequately approximate the situation. Thus, the terminal adenosine units of peptidyl- and aminoacyl-tRNA may be represented by one molecule containing peptidyl and aminoacyl moiety on the 3′ hydroxyl groups. More recently, two adenosine units have been covalently joined through their respective ribose moieties to form another type of a constrained model of a transition state of protein biosynthesis.[4] The model, as previously indicated, inhibited protein biosynthesis in a ribosomal system.[4] However, no data on possible stacking of adenine rings are available. In addition, it has been reported that the phosphate derivative of IIIa inhibits the mitotic activity of the cells and reproduction of certain viruses.[5] An interesting antitumor activity of 1,2-di(adenin-N^6-yl)ethane has also been briefly described.[6] More recently, similar derivatives (IIIa) have been considered as potentially valuable metabolites for use in cancer therapy.[7] All these considerations led us to the synthesis and spectroscopic investigation of compounds IIIb and IIIc.

The syntheses of 1,2-di(adenin-N^6-yl)ethane[6a,b,8] and 1,3-di(adenin-N^6-yl)propane,[9] as well as 1,1-di(adenosin-N^6-yl)methane (IIIa),[10] and compound IIIb[11] have been described. α,ω-Di(adeninyl)alkanes and some analogous compounds derived from other nucleic acid bases have been a subject of spectroscopic studies.[9,12] The former are regarded as good models of base–base interactions in nucleic acids because of absence of complicating factors (hydrogen bonding of ribose residues and electrostatic interactions of phosphodiester linkages). However, no data on a possible base–base interaction (stacking) in 1,1-di(adenosin-N^6-yl)methane (IIIa) and the corresponding homologues IIIb and IIIc are available to date. Compounds IIIb and IIIc are more complicated since both adenines carry a ribose residue, although the phosphodiester linkage is missing, and thus represent a link in stacking models between simple bases[9,12] and dinucleoside phosphates whose base–base interactions have been extensively studied.[13] The presence of the D-ribofuranose moiety makes study of IIIb and IIIc by a simple CD technique possible. The comparison of results obtained from UV and CD spectra is also of interest.

Results and Discussion

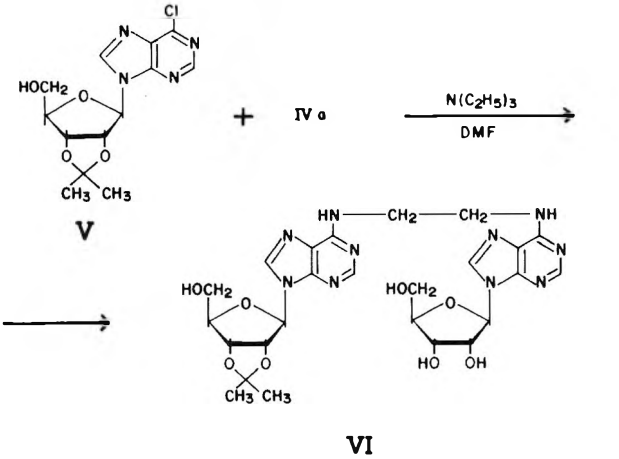
Synthesis. The preparation of the title compounds (IIIb and IIIc) followed a general route which was worked out some time ago[14] for the synthesis of various N^6-substituted adenosines from the 6-chloro-(9-β-D-ribofuranosyl)purine (I) and corresponding amine in the presence of triethylamine in dimethylformamide (DMF). The method has a distinct advantage of working at room temperature. Thus, the reaction of I with 1,2-diaminoethane (IIa) in stoichiometric amounts in the presence of triethylamine in DMF gave IIIb in 30% yield in addition to recovered starting material I (26%) along with N^6-(2-aminoethyl)adenosine (IVa, 21%, Scheme I). Compound IVa can also be employed as a convenient starting material for the preparation of IIIb. The synthesis of IIIb was described,[11] but the yield of the product was rather low (10%). Moreover, the intermediate IVa in the synthesis of IIIb could not be obtained in a crystalline form but as a syrup characterized only by acid hydrolysis to N^6-(2-aminoethyl)adenine.[11]

Scheme I



Our method, which employs a simple ion-exchange separation technique, makes possible the isolation of all reaction products and the preparation of IVa as a crystalline solid. The method of choice for the preparation of IIIb (40% yield) is the reaction of IVa with I (100% molar excess) in DMF using triethylamine as a coupling reagent. The latter procedure made possible the preparation of compound VI with functionally differentiated ribose moieties. Thus, the isopropylidene derivative V was coupled with IVa using triethylamine in DMF to give VI (60%, Scheme II). Product VI may be useful for the preparation of

Scheme II



compounds containing different substituents in the ribose portion. The reaction of I with 5 molar excess of IIb gave predominantly derivative IVb (78%) along with IIIc (21%). The condensation of I (ca. 2 molar excess) with IVb gave bridged nucleoside IIIc in 36% yield. A similar method, reaction of I with the appropriate amine in the presence of triethylamine at room temperature, was employed for the preparation of both spectroscopic models VIIa and VIIb.

NMR spectra of IIIb and IIIc, which supported the proposed structures, failed to reveal any information about base–base interactions as a probable consequence of a poor choice of both concentration (ca. 0.1 M) and solvent (CD_3SOCD_3). Thus, it is known that high concentration favors self-association and, moreover, CH_3SOCH_3 causes a considerable destacking of bases in dinucleoside phosphates.[15] It was not possible to measure NMR spectra in water because of a very limited solubility of IIIb and IIIc. The chemical shifts of H_8, H_2, $H_{1'}$, and the coupling constant $J_{1',2'}$ in IIIb and IIIc are virtually identical with those of the corresponding model compounds VIIa and VIIb, though both H_8 and H_2 in IIIb are slightly less shielded relative to VIIa.

UV and CD spectra. UV and CD studies have provided a considerable body of information about the interaction of both

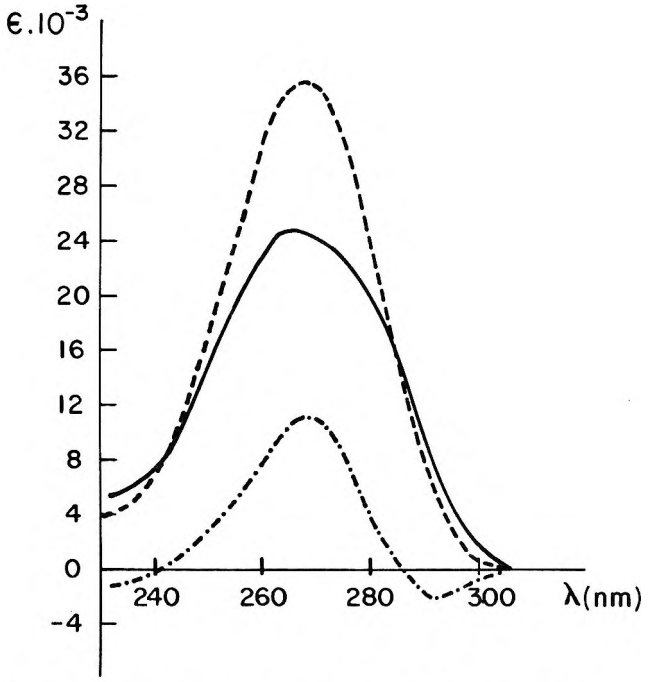


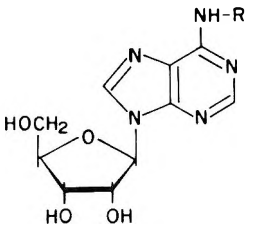
Figure 1. UV spectra of IIIb and VIIa in water (pH 7): —, IIIb: - - -, VIIa; – · – · –, difference spectrum.

Table I. Hypochromism (*H*) and Hypochromicity (*h*) of 1,2-Di(adenosin-N^6-yl)ethane (IIIb) and 1,4-Di(adenosin-N^6-yl)butane (IIIc)

Compd	H^a	h^a	H^b	h^b
IIIb	19.2[c]	30.6	14.8	29.3
IIIc	8.2[c]	12.3	None	None

[a] In percent, H_2O (pH 7). [b] In percent, 0.01 N HCl. [c] Values of 14.2 (IIIb) and 6.8 (IIIc) reported in our preliminary report[1b] refer to measurements in distilled water whose pH was not adjusted to 7.

adenine residues in IIIb and IIIc. The measurements were carried out at ca. 50–100 μM, which excluded concomitant intermolecular interactions (self-association) (cf. ref 9). As model compounds we used N^6-ethyladenosine (VIIa) for IIIb and N^6-butyladenosine (VIIb) for IIIc. Similar models (i.e., N^6-propyladenine) have been used in a spectroscopic study of base–base interactions in α,ω-(adeninyl)alkanes.[9,12] Both UV and CD spectra in water are indicative of interaction of adenine residues in IIIb and IIIc. Thus, a hypochromic effect is seen in the UV spectrum of IIIb (Figure 1, Table I) together with a hypsochromic shift of the absorption maximum relative to model compound VIIa and a shoulder at ca. 275 nm.[11] A CD spectrum of IIIb in water[16] exhibited a profound increase in



VII

VII a : R = C_2H_5

VII b : R = $CH_3(CH_2)_3$

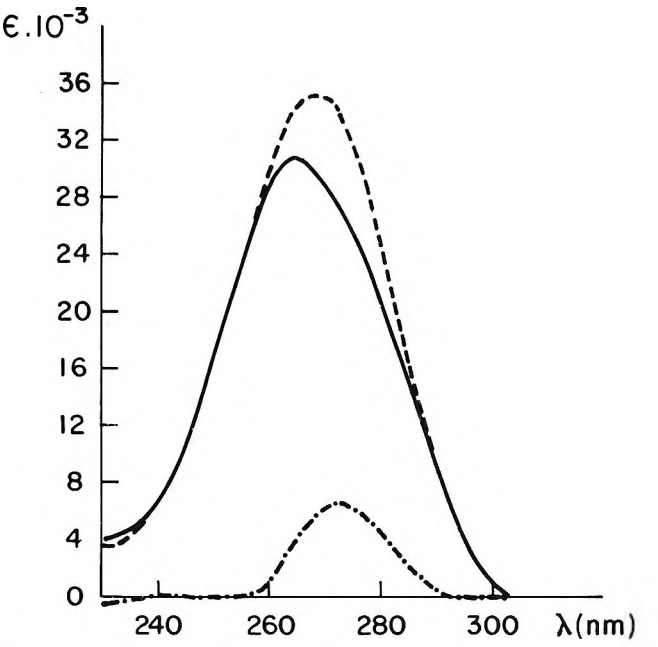


Figure 2. UV spectra of IIIc and VIIb in water (pH 7): —, IIIc; - - -, VIIb; – · – · –, difference spectrum.

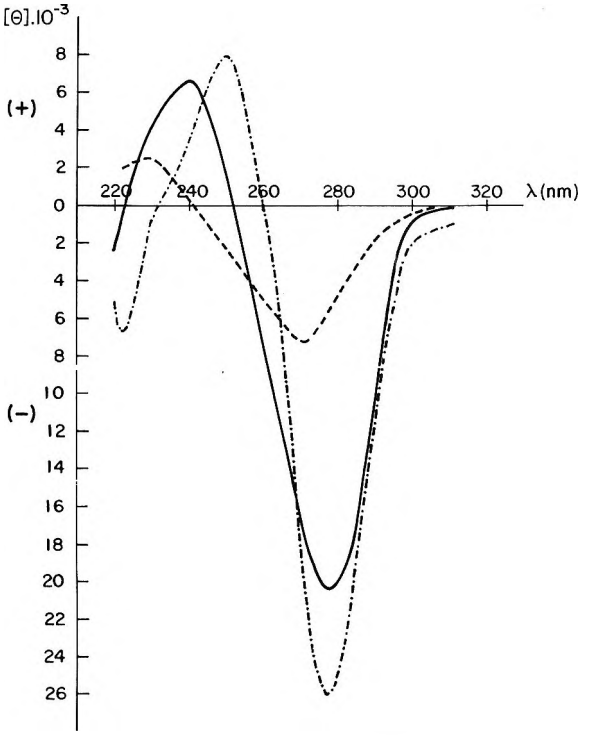


Figure 3. CD spectra of IIIb, IIIc, VIIa, and VIIb in water (pH 7): —, IIIb; – · – · –, IIIc; - - -, VIIa. (The curve of VIIb is almost superimposable on that of VIIa.)

the magnitude of the Cotton effect and a bathochromic shift of its maximum relative to the model VIIa (Figure 3). A similar increase in the intensity of the Cotton effect has been noted earlier for a series of dinucleoside phosphates and explained in terms of intramolecularly stacked structures.[13] Thus, it seems reasonable to assume an extensive base–base interaction in IIIb. The UV spectrum of IIIc in water also showed a hypochromic effect (Figure 2, Table I), although considerably smaller than in IIIb. The pronounced shoulder at ca. 275 nm apparent in IIIb is indistinct with IIIc. The magnitude of the Cotton effect in IIIc is greater than in IIIb but the whole band is narrower (Figure 3). This is surprising because the magni-

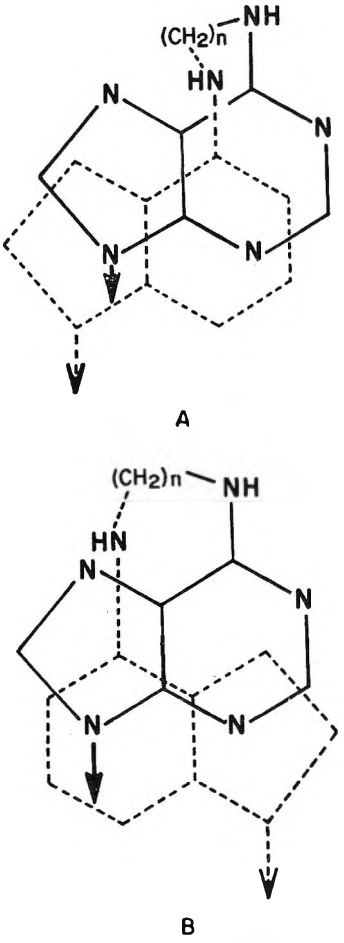


Figure 4. Two stacked conformers of bridged nucleosides IIIb and IIIc (n = 2 or 4). For the sake of simplicity endo nitrogen atoms are omitted from the second purine residues indicated by an interrupted line. Arrow indicates attachment of the ribofuranose. A, imidazole–imidazole and pyrimidine–pyrimidine overlap; B, pyrimidine–imidazole overlap.

tude of the Cotton effect in IIIb and IIIc does not correlate with a sharp drop in hypochromism observed in IIIc relative to IIIb (Table I). It is realized, however, that unlike the UV spectra, the CD can reflect effects other than a simple time-averaged separation of bases such as base orientation and/or conformation in the stack.[17] The latter influences may well be different in IIIb and IIIc. Once again, a bathochromic shift of the maximum of the CD curve is observed relative to VIIb. The differences in hypochromism between IIIb and IIIc undoubtedly reflect the influence of the lengthening of the aliphatic chain and, consequently, a greater time-averaged separation of residues in IIIc. Of interest is also the comparison of hypochromism (H) values of IIIb and IIIc with that of 1,3-di(adenin-N^6-yl)propane. As can be expected, the H value of the latter (15.5)[9] is lower than that of IIIb (19.2). The hypochromism (H) of IIIc (Table I) is very close to that of ApA (6.8)[19] and indeed, as can be seen from CPK models, the distance between stacked adenines in ApA corresponds more to that in IIIc than in IIIb. However, CD spectra clearly indicate important differences between the three diadenosine phosphates[20] and compounds IIIb and IIIc. Thus, CD curves of IIIb and IIIc are quite similar (apart from an increased ellipticity) to those of simple adenosine derivatives (negative Cotton effect), but the adenosine phosphodiesters exhibit one positive and one negative Cotton effect. This again stresses the importance of the phosphodiester group and handedness of its screw axis for CD properties of oligonucleotides.[20]

UV and CD spectra of IIIb and IIIc in acid are also of interest. The stacking of bases in dinucleoside phosphates (ApA) and thus the hypochromic effect is usually greatly reduced in acid because of unfavorable electrostatic effects associated with protonation of bases.[19] It is, therefore, of interest that IIIb shows a considerable hypochromism in 0.01 N HCl while that of IIIc virtually disappeared (Figure 5, Table I). The same trend was observed in CD spectra of IIIb and IIIc, respectively. In both cases, there is a profound decrease in the magnitude of the Cotton effect (ellipticity) in 0.01 N HCl (Figure 6). Once again, the sharp drop in the molar ellipticity does not correlate with a significant hypochromism of IIIb. It is also of interest to note that both IIIb and IIIc exhibit a hypsochromic shift of the UV absorption maximum and a bathochromic shift of the maximum of the Cotton effect relative to the corresponding model compounds VIIa and VIIb (Figures 5 and 6).

Scheme III is proffered in an attempt to rationalize the results. It is reasonable to assume that addition of one proton

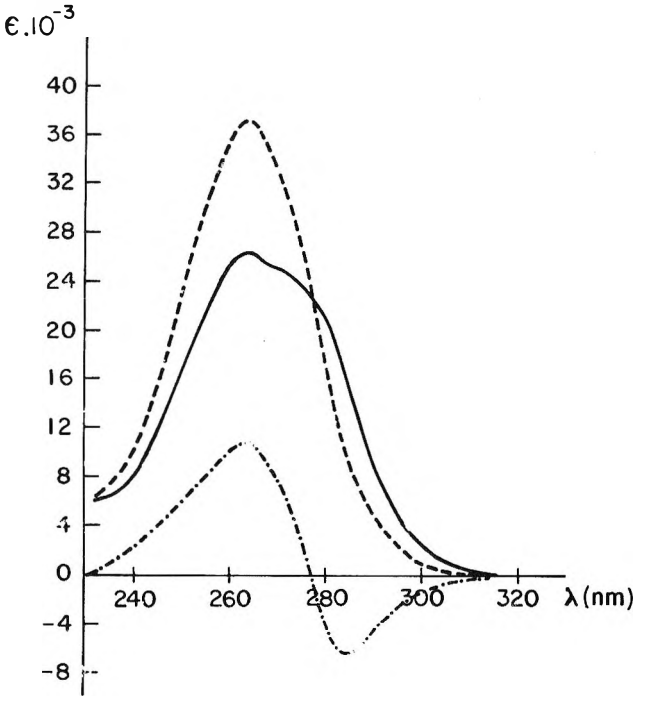


Figure 5. UV spectra of IIIb and VIIa in 0.01 N HCl: —, IIIb; - - -, VIIa; – · – · –, difference spectrum.

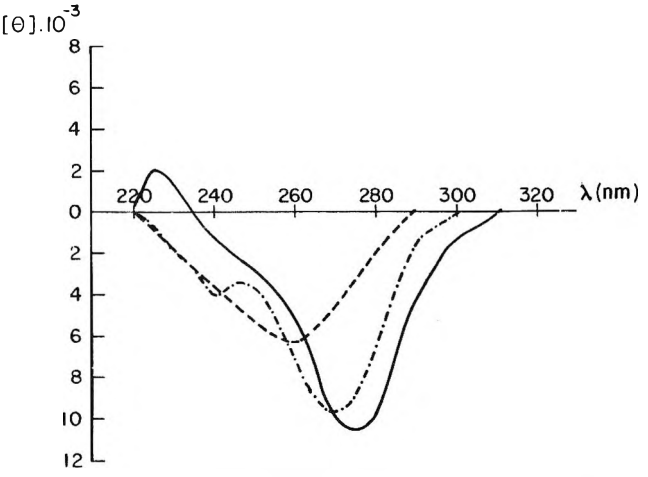
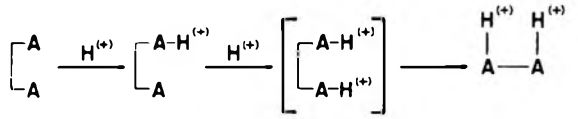


Figure 6. CD spectra of IIIb, IIIc, VIIa, and VIIb in 0.01 N HCl: —, IIIb; – · – · –, IIIc; - - -, VIIa. (The curve of VIIb is almost superimposable on that of VIIa.)

Scheme III



A = adenosin-N^6-yl, $\begin{bmatrix} A \\ A \end{bmatrix}$ designates a stacked species, A—A stands for an unstacked form

to either IIIb or IIIc need not necessarily lead to destacking of bases. However, the situation may change dramatically with the addition of a second proton because of electrostatic forces which will result in maximum separation of base residues. Therefore, there is little probability of base stacking in the case of a diprotonated species.[19] Furthermore, the degree of protonation may be influenced by the time-averaged separation of bases. Thus, while it is not necessary to expect a substantial difference in the ease of attachment of one proton in both IIIb and IIIc, it seems quite likely that the attachment of the second proton to IIIb (assuming a monoprotonated stacked structure, Scheme III) would be more difficult than to IIIc. In this respect, the situation is considerably different from that found in most dinucleoside phosphates in acid where a negatively charged phosphodiester grouping may compensate one positive charge and thus enable the addition of the second proton. Thus, the UV data may reflect a difference in the base stacking dependent on the extent of protonation of IIIb and IIIc. The UV spectrum of IIIb in 0.01 N HCl (Figure 5, Table I) suggests a considerable stacking due probably to the presence of a monoprotonated form. It is not surprising that differences in protonation may also influence the CD properties. On the other hand, the CD data may reflect, in addition to destacking, changes in orientation or conformation of the base in the protonated stack.

Compounds IIIb, IIIc, IVa, IVb, VIIa, and VIIb were tested in murine leukemia L1210 in vitro system. The first five derivatives did not inhibit DNA synthesis in this system at 0.5–1.0 mM whereas VIIb was inhibitory (ID_{50} 22 μM). It is of interest to note that the latter compound was also reported to inhibit the growth of sarcoma 180 cells, mouse mammary carcinoma TA-3 cells, and murine leukemia L1210 in vivo.[21] The results of the biological testing of the above compounds and some related derivatives in a human cell system will be reported elsewhere.[22]

Experimental Section

General Procedures. Evaporations were carried out with a Büchi rotary evaporator in vacuo at a bath temperature below 35 °C unless stated otherwise. Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. Samples for analysis were dried for 8 h at 10^{-3} mm over P_2O_5 at 100 °C unless stated otherwise. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill. Thin layer chromatography (TLC) was performed on 6 × 2 cm, precoated, silica gel F-254 aluminum foils (Merck, Darmstadt, Germany) in solvents S_1 (dichloromethane–methanol, 9:1) and S_2 (dichloromethane–methanol, 4:1). For preparative TLC 4 mm thick, 35 × 15 cm loose layers of silica gel (70–325 mesh ASTM, Merck, Darmstadt, Germany) containing 1% of fluorescent indicator (Luminous Pigment ZS Super No. 54030, Hoechst Corp., Somerville, N.J.) were used. TLC in solvent S_3 (2-propanol–concentrated ammonium hydroxide–water, 7:1:2) was performed on glass plates (6 × 2 cm) coated with microcrystalline cellulose (Avicel) and the above fluorescent indicator. For preparation of the plates see ref 23. For paper chromatography solvents S_3 and S_4 (1-butanol–acetic acid–water, 4:1:5) on Whatman No. 1 paper were used. Paper electrophoresis was conducted on an electrophoresis flat plate (Savant Instruments, Inc., Hicksville, N.Y.) using 0.05 M $Na_2B_4O_7$ (pH 9.0) and 0.05 M sodium citrate (pH 3.5) as buffers on Whatman No. 1 paper at 40 V/cm for 1 h. For R_f values and electrophoresis mobilities see Table II. UV-absorbing compounds were detected using a Mineralight lamp, ninhydrin-positive substances with 0.1% ninhydrin in ethanol. Optical rotations were determined with a Perkin-Elmer Model 141 polarimeter. Ion-exchange chromatography was performed with Dowex 50 WX 2, 200–400 mesh resin. NMR spectra were obtained using a Varian A-60A spectrometer; $(CH_3)_4Si$ was used as internal standard with CD_3COCD_3, DSS (sodium 2,2-dimethyl-2-silapentane-5-sulfonate) as external reference with CD_3SOCD_3. DMF was dried with Linde molecular sieves, 4A.

Table II. R_f Values and Electrophoretic Mobilities of Products[a]

Compd	R_f (S_3)	R_f (S_4)	Mobility in Borate[b]	Mobility in Citrate[b]
IIIb	0.49	0.40	1.25	0.44
IIIc	0.64	0.54	1.25	0.50
IVa	0.56	0.25	0	1.9
IVb	0.63	0.30	−0.27	2.0
VI	0.83		0.61	0.02
VIIa	0.87	0.75		
VIIb	0.93	0.88		

[a] For details see general procedures. [b] Relative to adenosine = 1.00.

Starting Materials. 6-Chloro-(9-β-D-ribofuranosyl)purine (I) was either a commercial product (Sigma Chemical Co., St. Louis, Mo.) or it was prepared according to the literature.[14] 1,2-Diaminoethane (IIa) and 1,4-diaminobutane (IIb) were products of Aldrich Chemical Co., Milwaukee, Wis.

Ultraviolet (UV) and Circular Dichroism (CD) Measurements. For measurements either analytical samples were used or compounds whose purity checked by NMR, nitrogen analysis, and paper electrophoresis corresponded to that of analytical samples. Samples for measurements accurately weighed (ca. 7 mg) on Cahn electrobalance RTL (Cahn Division, Ventron Instruments, Paramount, Calif.) were dissolved in water whose pH was adjusted to 7 with NaOH. The corresponding aliquots were diluted immediately before the measurement with water (pH 7) or HCl;[24] approximate final concentrations were 50–100 μM. UV spectra of the solutions were scanned at ambient temperature in a 1-cm cell between 200 and 400 nm using a Cary recording spectrophotometer, Model 11. The resultant curves were replotted as molar extinction coefficients ϵ or, in the case of model compounds VIIa and VIIb, 2ϵ against the wavelength. The difference UV spectra were obtained graphically (Figures 1, 2, and 5). A minimum of two sets of measurements was done in each case. To obtain hypochromism H, the recorded UV spectra were integrated[12] by a computer from the vicinity of the absorption minimum (ca. 230 nm) to the zero absorption at long wavelengths (ca. 310–320 nm) in 2-nm intervals. The values of H were then calculated from the corresponding oscillator strengths,[12] $f = 4.32 \times 10^{-9} \int \epsilon\lambda/\lambda^2 \, d\lambda$ and $H = (1 - f^A/2f^B) \times 100$, where f^A is the oscillator strength of IIIb or IIIc and f^B the oscillator strength of the model compound VIIa or VIIb. Hypochromicity values h were calculated from the expression $h = (1 - \epsilon^A{}_{max}/2\epsilon^B{}_{max}) \times 100$ where ϵ_{max} are the appropriate extinction coefficients at λ_{max}.

CD curves were obtained using the solution made for UV spectra on a JASCO optical rotatory dispersion recorder, Model ORD/UV-5, in a CD modification SS-10 (Sproul Scientific, Boulder Creek, Calif.) between 500 and 200 nm at ambient temperature in a 1-cm cell. The CD data were digitized by hand after a smooth curve had been drawn through the data. The results were plotted as molar ellipticities $[\theta]$ (in the case of VIIa and VIIb $2[\theta]$ against the wavelength, Figures 3 and 6).

6-Chloro-9-β-D-(2,3-*O*-isopropylidene)ribofuranosylpurine (V). This compound, which was described earlier,[25] was prepared by a modified[26] method. The mixture of nucleoside I (0.9 g, 3.14 mmol), acetone (0.45 ml, 4.5 mmol), ethyl orthoformate (1.2 ml, 8 mmol), 3.05 M HCl in DMF (1.44 ml, 4.95 mmol), and DMF (25 ml) was briefly shaken and the resultant clear solution was kept for 22 h at ambient temperature. Sodium bicarbonate (0.84 g, 10 mmol) was added followed by concentrated NH_4OH (0.5 ml), and the solids were filtered off and washed with DMF. The filtrate was evaporated at 0.1 mm and room temperature and the residue was partitioned between water (10 ml) and chloroform (2 × 25 ml). The dried ($MgSO_4$) chloroform extract was evaporated to a syrup. Coevaporation with ethanol afforded a white solid, 1.02 g (100%), which was crystallized from a minimum amount of ethanol to give 6.75 g (73%) of V, mp 154–157 °C (lit.[25]

158–159 °C), on TLC (S_1) homogeneous, UV max (95% ethanol) 264 nm (ϵ 9300), inflex ca. 250 (6400); NMR (CD_3COCD_3) δ 8.47 (s, 2, H_8 + H_2, resolved into two singlets after addition of D_2O), 6.21 (d, 1, $H_{1'}$, $J_{1',2'}$ = 3 Hz), 5.31 (q, 1, $H_{2'}$), 5.00 (q, 1, $H_{3'}$), 4.33 (m, 2, after addition of D_2O 1 proton, $H_{4'}$ + OH), 3.77 (broad t, sharp doublet after addition of D_2O, 2, $H_{5'}$), 1.55 and 1.33 (s, 6, CH_3 of isopropylidene).

1,2-Di(adenosin-N^6-yl)ethane(IIIb)andN^6-(2-Aminoethyl)-adenosine (IVa). A. From I and IIa. The solution of chloro nucleoside I (1 g, 3.48 mmol), 1,2-diaminoethane (IIa, 0.12 ml, 1.8 mmol), and triethylamine (0.61 ml, 4.38 mmol) in DMF (15 ml) was kept for 2 days at room temperature. Triethylamine hydrochloride was filtered off and the filtrate was evaporated at room temperature and 0.1 mm to afford a residue which was dissolved in water (25 ml) and applied to Dowex 50 column (60 ml, H^+ form). Elution with water (600 ml) and evaporation of the eluate yielded 0.26 g (26%) of the starting material I. Further elution with 5% pyridine (600 ml) afforded product IIIb (0.59 g, 30%) which according to electrophoresis (citrate), TLC (S_2), and $AgNO_3$ test contained a small amount of I. Repeated Dowex 50 (H^+) purification (as above) gave IIIb (0.51 g) still contaminated with I. Pure IIIb was obtained by crystallization of this material from 50% ethanol (150 ml): yield 0.2 g (10%); mp >250 °C dec [lit.[11] 251–252 °C (trihydrate)], uniform on paper chromatography (S_3) and electrophoresis ($Na_2B_4O_7$); $[\alpha]^{25}D$ −39° (*c* 0.5, CH_3SOCH_3); UV max (H_2O) 265 nm (ϵ 24 800), inflex ca. 278 (21 400); (0.01 N HCl) 263 nm (ϵ 26 300),[27] inflex ca. 278 (22 700); NMR (CD_3SOCD_3) δ 8.29 (s, 1, H_8), 8.16 (s, 1, H_2), 5.87 (d, 1, $H_{1'}$, $J_{1',2'}$ = 6 Hz), the rest of the ribose protons are overlapped with hydroxy and methylene groups in the region of δ 3.5–4.6. Anal. Calcd for $C_{22}H_{28}N_{10}O_8 \cdot 2H_2O$: C, 44.29; H, 5.41; N, 23.48. Found: C, 44.10; H, 5.26; N, 23.63. After drying at 100 °C immediately before the analysis the compound was analyzed for a monohydrate. Anal. Calcd: C, 45.67; H, 5.23; N, 24.21; H_2O, 3.11. Found: C, 45.66; H, 4.96; N, 24.28; H_2O, 3.40.

Elution of the column with 3% aqueous NH_3 (600 ml) afforded compound IVa (0.23 g, 21%): mp 202–204 °C, after recrystallization from water 203–205 °C; $[\alpha]^{22}D$ −69° (*c* 0.5, CH_3SOCH_3); UV max (95% ethanol) 267 nm (ϵ 17 800); (0.01 N HCl) 274 nm (ϵ 17 300); NMR (CD_3SOCD_3) δ 8.33 (s, 1, H_8), 8.18 (s, 1, H_2), 5.89 (d, 1, $H_{1'}$, $J_{1',2'}$ = 6 Hz). Compound IVa gives a positive ninhydrin reaction. Anal. Calcd for $C_{12}H_{18}N_6O_4$: C, 46.44; H, 5.85; N, 27.09. Found: C, 46.33; H, 5.81; N, 27.35.

B. From I and IVa. The solution of chloro nucleoside I (1 g, 3.48 mmol), aminoethyl derivative IVa (0.54 g, 1.74 mmol), and triethylamine (1.61 ml, 7.18 mmol) in DMF (20 ml) was kept for 5 days at room temperature. Evaporation at room temperature and 0.1 mm afforded a solid which was partly dissolved in 50% ethanol and stirred for ca. 30 min with Dowex 50 (H^+). The suspension was then applied to a Dowex 50 (H^+) column (total volume 60 ml) and the elution followed the procedure described in the preceding experiment (50% ethanol was used instead of water). Elution with 50% pyridine afforded product IIIb (0.39 g, 40%) identical (UV, NMR) with the sample described above.

2',3'-*O*-Isopropylidene-1,2-di(adenosin-N^6-yl)ethane (VI). The solution of isopropylidene derivative V (0.33 g, 1 mmol), aminoethyl nucleoside IVa (0.31 g, 1 mmol), and triethylamine (0.7 ml, 5 mmol) in DMF (5 ml) was kept for 4 days at room temperature. Crystalline triethylamine hydrochloride which separated was filtered off and washed with DMF (2 ml). The filtrate was evaporated at room temperature and 0.1 mm. The residue, after trituration with acetone (5 ml), afforded a white solid (465 mg) which was filtered off and washed with acetone (5 ml), containing according to TLC (S_2), product VI and some IVa (no isopropylidene derivative V was detected). This material was dissolved in 5% pyridine, applied to a column of Dowex 50 (25 ml, pyridinium form) and the column was eluted with the same solvent (250 ml). Evaporation of the eluate gave a glassy solid which was washed with acetone–ether to afford 0.4 g (62%) of VI contaminated, according to TLC (S_2), with a slower moving impurity. The above material was dissolved in methanol, and the solution was applied to a loose layer of silica gel and chromatographed in S_2. The main UV-absorbing band was eluted with dichloromethane–methanol (1:1) and the eluate was evaporated. The resultant amorphous solid was washed with acetone–ether to give 140 mg (22%) of VI, mp 154–155 °C (foaming), homogeneous on TLC (S_2) and electrophoresis ($Na_2B_4O_7$). UV (0.01 N HCl) was essentially identical with that of IIIb. NMR (CD_3SOCD_3 + D_2O) δ 8.40 (s, 2, H_8), 8.30 and 8.28 (2 partially overlapped singlets, H_2), 6.18 (d, 1, $H_{1'}$ of 2',3'-*O*-isopropylideneribofuranose, $J_{1',2'}$ = 3 Hz), 5.95 (d, 1, $H_{1'}$ of ribofuranose, $J_{1',2'}$ = 6 Hz), 5.40 (q, 1, $H_{2'}$ of 2',3'-*O*-isopropylideneribofuranose), 5.02 (q, 1, $H_{3'}$ of 2',3'-*O*-isopropylideneribofuranose), the rest of the ribose protons are at δ 4.67 (t, 1, not well resolved) and between δ 3.6 and 4.3, 1.62 and 1.40 (2 s, 6, CH_3). Anal. Calcd for $C_{25}H_{32}N_{10}O_8 \cdot 2.5H_2O$: C, 46.51; H, 5.78; N, 21.70. Found: C, 46.31; H, 5.37; N, 21.46. After drying at 100 °C immediately before the analysis the compound contained 1.5 mol of H_2O. Anal. Calcd: C, 47.84; H, 5.62; N, 22.32. Found: C, 47.58; H, 5.22; N, 22.31.

1,4-Di(adenosin-N^6-yl)butane (IIIc)' and N^6-(4-Aminobutyl)adenosine (IVb). A. From I and IIb. A solution of chloro nucleoside I (0.99 g, 3.45 mmol), 1,4-diaminobutane (IIb, 0.88 g, 10 mmol), and triethylamine (2.08 ml, 15 mmol) in DMF (5 ml) was kept at room temperature for 20 h. The mixture containing precipitated triethylamine hydrochloride was evaporated to dryness at room temperature and 0.1 mm. The solid residue was dissolved in 50% ethanol and the solution was applied to a Dowex 1 X 2, 200–400 mesh column (HCO_3^- form, 25 ml) which was eluted with 50% ethanol (500 ml).[28] This eluate was evaporated to a white solid which was dissolved in 50% ethanol (100 ml) and the solution was applied to a Dowex 50 column (H^+ form, 40 ml). The column was eluted with 50% ethanol (1 l.) and then with 5% pyridine (1 l.). The latter eluate afforded, after evaporation in vacuo, a solid which was filtered off after addition of acetone (10 ml), 0.21 g (21%) of IIIb, mp 202–204 °C dec, ninhydrin negative; TLC (S_3) showed the presence of a trace of faster moving impurity. This material (0.1 g) was crystallized from 50% ethanol to give 50 mg of IIIc: mp 228–232 °C dec; on TLC (S_3) homogeneous; $[\alpha]^{20}D$ −19.2° (c 0.5, CH_3SOCH_3); UV max (H_2O) 264 nm (ϵ 30 800); (0.01 N HCl) 264 nm (ϵ 38 100); NMR (CD_3SOCD_3) δ 8.27 (s, 2, H_8), 8.15 (s, 2, H_2), 5.87 (d, 2, $H_{1'}$, $J_{1',2'}$ = 6 Hz), 5.33 and 5.07 (poorly resolved m, disappeared on addition of D_2O, 6, OH), the rest of the ribose bands (including *N*-methylene groups) are not well resolved between 3.6–4.7, 1.67 (poorly resolved m, 4, CCH_2). Anal. Calcd for $C_{24}H_{32}N_{10}O_8 \cdot 2.5H_2O$: C, 45.49; H, 5.89; N, 22.11. Found: C, 45.55; H, 5.63; N, 22.27. After drying at 100 °C immediately before the analysis, the compound contained 1.25 mol of H_2O. Anal. Calcd: C, 47.17; H, 5.69; N, 22.92; H_2O, 3.55. Found: C, 47.13; H, 5.43; N, 23.01; H_2O, 3.82.

The Dowex 50 column was eluted further with 0.5 and 3% aqueous ammonia (1 l. each). Evaporation of the effluents gave only a very little of the UV-absorbing material; therefore the elution continued with 3% NH_3 in 50% ethanol (1 l.). After evaporation of the eluate, product IVb was obtained (0.91 g, 78%), mp 186 °C, ninhydrin positive and TLC (S_3) homogeneous. An analytical sample was crystallized from ethanol: mp 191–192 °C; $[\alpha]^{25}D$ −52.8° (*c* 0.5, CH_3SOCH_3); UV max (95% ethanol) 269 nm (ϵ 16 800); (0.01 N HCl) 264 nm (ϵ 19 300); NMR (CD_3SOCD_3) δ 8.23 (s, H_8, 1), 8.10 (s, 1, H_2) 5.84 (d, 1, $H_{1'}$, $J_{1',2'}$ = 6 Hz), 3.5–4.5, the rest of the ribose protons, OH's and NCH_2– are not well resolved, ca. 1.5 (poorly resolved m, 8, 2 protons disappeared on addition of D_2O, CCH_2 and NH_2). Anal. Calcd for $C_{14}H_{22}N_6O_4 \cdot H_2O$: C, 47.18; H, 6.79; N, 23.58. Found: C, 47.23; H, 6.62; N, 23.47. After drying at 100 °C immediately before the analysis the compound lost 1 mol of H_2O. Anal. Calcd: C, 49.69; H, 6.55; N, 24.84; H_2O, 5.06. Found: C, 49.47; H, 6.52; N, 24.62; H_2O, 4.53.

B. From I and IVb. A solution of chloro nucleoside I (1 g, 3.5 mmol), compound IVb (0.585 g, 1.64 mmol), and triethylamine (0.61 ml, 4.4 mmol) in DMF (20 ml) was stirred at room temperature for 4 days. After cooling (0 °C) the triethylamine hydrochloride was filtered off and the filtrate evaporated in vacuo. The residue was suspended in 50% ethanol, absorbed on Dowex 50 (H^+), and added to the column of the same resin (final column volume was 70 ml). The column was washed at 0 °C (cold room) with 50% ethanol (1 l.). Evaporation of the eluate recovered crude I (0.5 g, 50%). Elution with 5% pyridine in 50% ethanol (1 l.) gave after evaporation of the eluate bridged nucleoside IIIc (0.37 g, 36% yield). Finally, the column was washed with 3% NH_3 in 50% ethanol (1 l.) to recover IVb (0.12 g, 21%).

N^6-Ethyladenosine (VIIa). A solution of chloro nucleoside I (0.2 g, 0.70 mmol), ethylamine hydrochloride (0.114 g, 1.4 mmol), and triethylamine (0.49 ml, 3.5 mmol) in DMF (1.5 ml) was kept at room temperature for 2 days. The reaction mixture containing precipitated triethylamine hydrochloride was evaporated to dryness at room temperature and 0.1 mm. The residue was crystallized from methanol to give 150 mg (73%) of VIIa: mp 191–193 °C (lit.[21] 191–192 °C); $[\alpha]^{25}D$ −29.8° (c 0.5, CH_3SOCH_3); UV max (H_2O) 267 nm (ϵ 17 800); (0.01 N HCl) 263 nm (ϵ 18 600); NMR (CD_3SOCD_3) δ 8.23 (s, 1, H_8), 8.12 (s, 1, H_2), 7.65 (poorly resolved t, disappeared on addition of D_2O, 1, NH), 5.85 (d, 1, $H_{1'}$, $J_{1',2'}$ = 6 Hz), ca. 5.2 (m, 3, disappeared on addition of D_2O, OH), the rest of the ribose proton signals and NCH_2 at δ 3.4–4.6 are not well resolved, 1.18 (t, 3, CH_3). Anal. Calcd for $C_{12}H_{17}N_5O_4 \cdot H_2O$: C, 46.00; H, 6.11; N, 22.35. Found: C, 45.93; H, 6.07; N, 22.29. After drying at 150 °C in vacuo immediately before the analysis an anhydrous compound was obtained. Anal. Calcd: C, 48.80; H, 5.81; N, 23.72; H_2O, 5.75. Found: C, 48.66; H, 5.77; N, 23.57; H_2O, 5.91.

N^6-Butyladenosine (VIIb) was prepared in analogy to VIIa from chloro nucleoside I (0.2 g, 0.70 mmol), 1-aminobutane (0.14 ml, 1.4 mmol), and triethylamine (0.29 ml, 2.1 mmol) in DMF (1.5 ml). After evaporation, the residue was crystallized from methanol to give 0.16 g (71%) of VIIb: mp 171–173 °C (lit.[21] 176 °C); $[\alpha]^{25}D$ −36.4° (*c* 0.5, CH_3SOCH_3); UV max (H_2O) 268 nm (ε 17 600); (0.01 N HCl) 264 nm (ε 17 900); NMR (CD_3SOCD_3) δ 8.22 (s, 1, H_8), 8.10 (s, 1, H_2), 5.83 (d, 1, $H_{1'}$, $J_{1'2'}$ = 6 Hz), 7.63 (poorly resolved t, disappeared on addition of D_2O, NH), ca. 5.2 (poorly resolved m, disappeared on addition of D_2O, OH), the rest of the ribose proton signals and NCH_2 at δ 3.3–4.5 are not well resolved, ca. 1.47 and 0.88 (poorly resolved m, 7, CCH_2 and CH_3). Anal. Calcd for $C_{14}H_{21}N_5O_4$: C, 52.00; H, 6.56; N, 21.66. Found: C, 51.88; H, 6.60; N, 21.82.

Acknowledgments. The authors are indebted to Dr. P. A. Scherr for computer calculations and to Dr. E. B. Hills for measurement of the NMR spectra. Biological tests in murine leukemia L1210 in vitro system were performed by Dr. D. Kessel.

Registry No.—I, 23828-03-7; IIa, 107-15-3; IIb, 110-60-1; IIIb, 60687-64-1; IIIc, 60687-65-2; IVa, 35662-04-5; IVb, 60687-66-3; V, 39824-26-5; VI, 60687-67-4; VIIa, 14357-08-5; VIIb, 23096-10-8; ethylamine HCl, 557-66-4; butylamine, 109-73-9.

References and Notes

(1) (a) This investigation was supported in part by U.S. Public Health Service Research Grants GM-19108 and GM-21093 from the National Institute of General Medical Sciences and in part by an institutional grant to the Michigan Cancer Foundation from the United Foundation of Greater Detroit. (b) Presented in part at the 9th International Symposium on Chemistry of Natural Products, Ottawa, Canada, June 1974, Abstract, p 31B.
(2) For a review of protein biosynthesis, see P. Lengyel and D. Soll, *Bacteriol. Rev.*, **33**, 264 (1969).
(3) The possibility of stacking of both peptidyl and aminoacyl tRNA "donor–acceptor stacking" was recognized earlier: (a) I. D. Raacke, *Biochem. Biophys. Res. Commun.*, **43**, 168 (1971); (b) J. Zemlicka, S. Chládek, D. Ringer, and K. Quiggle, *Biochemistry*, **14**, 5239 (1975).
(4) (a) F. Seela and F. Cramer, *Chem. Ber.*, **108**, 1329 (1975); (b) F. Seela and V. A. Erdmann, *Biochim. Biophys. Acta*, **435**, 105 (1976).
(5) M. Ya. Feldman, E. S. Zalmanson, and L. N. Mikhailova, *Mol. Biol. (Moscow)*, **5**, 847 (1971).
(6) (a) H. Lettré and H. Ballweg, *Naturwissenschaften*, **45**, 364 (1958); (b) *Justus Liebigs Ann. Chem.*, **649**, 124 (1961).
(7) T. Alderson, *Nature (London) New Biol.*, **244**, 3 (1973).
(8) J. H. Lister, *J. Chem. Soc.*, 3394 (1960).
(9) N. J. Leonard and K. Ito, *J. Am. Chem. Soc.*, **95**, 4010 (1973).
(10) (a) M. Ya. Feldman, *Biokhimiya*, **27**, 378 (1962); (b) *Prog. Nucleic Acid Res. Mol. Biol.*, **13**, 11 (1973).
(11) H. Lettré and H. Ballweg, *Justus Liebigs Ann. Chem.*, **656**, 158 (1962).
(12) D. T. Browne, J. Eisinger, and N. J. Leonard, *J. Am. Chem. Soc.*, **90**, 7302 (1968).
(13) C. R. Cantor, M. M. Warshaw, and H. Shapiro, *Biopolymers*, **9**, 1059 (1970), and references cited therein.
(14) J. Zemlicka and F. Sorm, *Collect. Czech. Chem. Commun.*, **30**, 1880 (1965).
(15) P. S. Miller, K. N. Fang, N. S. Kondo, and P. O. P. Ts'o, *J. Am. Chem. Soc.*, **93**, 6657 (1971).
(16) CD measurements in 5×10^{-2} M Tris buffer (pH 7.4) gave essentially identical results with those in water (pH 7.0). No influence of 1×10^{-2} M $MgCl_2$ on the CD curve of IIIb and IIIc has been found in the above buffer.
(17) Two conformers of IIIb and IIIc with respect to the mutual orientation of bases in a stacked structure are possible[18] (Figure 4) if we neglect the differences in rotameric composition owing to the presence of an aliphatic chain, ribose residues (syn–anti conformers), and situations not involving a total overlap of bases.
(18) C. E. Bugg, U. T. Thewalt, and R. E. Marsh, *Biochem. Biophys. Res. Commun.*, **33**, 436 (1968), Figure 2.
(19) M. M. Warshaw and I. Tinoco, Jr., *J. Mol. Biol.*, **20**, 29 (1966).
(20) N. S. Kondo, H. M. Holmes, L. M. Stempel, and P. O. P. Ts'o, *Biochemistry*, **9**, 3479 (1970).
(21) M. H. Fleysher, *J. Med. Chem.*, **15**, 187 (1972).
(22) J. J. McCormick, V. M. Maher, and J. Zemlicka, *Biochem. Pharmacol.*, submitted.
(23) J. Zemlicka, R. Gasser, J. V. Freisler, and J. P. Horwitz, *J. Am. Chem. Soc.*, **94**, 3213 (1972).
(24) Compounds IIIb and IIIc are not well soluble in water or in 0.01 N HCl. Moreover, it has been found that IIIb is less stable toward acids (HCl) than ordinary purine ribonucleosides. It is, therefore, imperative not to prepare stock solutions of IIIb and IIIc in 0.01 N HCl.
(25) A. Hampton and M. H. Maguire, *J. Am. Chem. Soc.*, **83**, 150 (1961).
(26) S. Chládek and J. Smrt, *Collect. Czech. Chem. Commun.*, **28**, 1301 (1963).
(27) These values differ from those reported in the literature[11] (ϵ_{max} 28 300 and 28 800, respectively, for pH 7 and 1). The Beer's law was followed for both IIIb and IIIc at pH 7 within the absorbancy range 0.25–1.4.
(28) In one case where the triethylamine hydrochloride was not removed, the crude mixture was directly put on the Dowex 50 column, and the chromatography was run at room temperature, a partial cleavage of the nucleoside bond in IIIc was observed as detected by electrophoresis in borate buffer. This was apparently due to the presence of an excess HCl released from the triethylamine hydrochloride by the action of Dowex 50 (H^+ form).

Protection of Aspartic Acid, Serine, and Threonine in Solid-Phase Peptide Synthesis

Donald Yamashiro

Hormone Research Laboratory, University of California, San Francisco, California 94143

Received August 11, 1976

N-Boc-β-(4-bromobenzyl)aspartic acid, *N*-Boc-*O*-(4-bromobenzyl)serine, and *N*-Boc-*O*-(4-chlorobenzyl)threonine have been synthesized for use in solid-phase peptide synthesis. The side-chain protecting groups were five to seven times more stable than the parent benzyl protection in 50% trifluoroacetic acid in dichloromethane and were completely removed in liquid hydrogen fluoride at 0 °C in 10 min.

Included among recent improvements in solid-phase peptide synthesis[1] is the development of side-chain protecting groups based on quantitative measurements of their stabilities.[2,3] Since *N*-Boc protection[4,5] is commonly employed along with final deblocking in liquid hydrogen fluoride,[6] the ideal protecting group is completely stable during removal of the Boc group and completely removed in HF. We now report the synthesis and properties of three new derivatives directed toward this end.

The removal of the Boc group is effectively accomplished in 50% trifluoroacetic acid in dichloromethane.[7] Benzyl protection of the side chains of serine, threonine, and aspartic acid has been shown to be sufficiently stable in this reagent for synthesis of peptides of moderate size.[2,3] However, it would be desirable to have protecting groups for these amino acids of even greater stability. Therefore, *N*-Boc-β-(4-bromobenzyl)aspartic acid (I), *N*-Boc-*O*-(4-bromobenzyl)serine (II), and *N*-Boc-*O*-(4-chlorobenzyl)threonine (III) were synthesized with II and III isolated as dicyclohexylamine salts. All three compounds were prepared by procedures analogous to those developed for the corresponding benzyl derivatives. The steric purity of the new derivatives was assessed by two criteria.

For testing the behavior of the new protecting groups, compounds I, II, and III were converted to *N*-acetylamide derivatives (Ia, IIa, and IIIa in Table I), where any influence

Table I. Stabilities of Side-Chain Protecting Groups in Trifluoroacetic Acid

Compd tested[a]	Time of treatment, h[f]	Loss of protection, %
Benzyl N^{α}-acetylisoasparaginate (benzyl 3-acetaminosuccinamate)[b]	23	4
4-Bromobenzyl N^{α}-acetylisoasparaginate (4-bromobenzyl 3-acetaminosuccinamate, Ia)[c]	71	2.5
N^{α}-Acetyl-*O*-benzylserineamide[b]	23	3
N^{α}-Acetyl-*O*-(4-bromobenzyl)serineamide[d] (IIa)	71	1.3
N^{α}-Acetyl-*O*-benzylthreonineamide[b]	23	5
N^{α}-Acetyl-*O*-(4-chlorobenzyl)-threonineamide[e] (IIIa)	71	2.5

[a] Prepared by conversion of the Boc-amino acid to the amide by the mixed anhydride method followed by treatment with TFA and acetylation with acetic anhydride in pyridine. [b] Data from ref 2. [c] Mp 145–146.5 °C. Anal. Calcd for $C_{13}H_{15}BrN_2O_4$ (343.18): C, 45.50; H, 4.41; N, 8.16. Found: C, 45.57; H, 4.43; N, 8.13. [d] Mp 151–152 °C. Anal. Calcd for $C_{12}H_{15}BrN_2O_3$ (315.17): C, 45.73; H, 4.80; N, 8.89. Found: C, 45.86; H, 4.82; N, 8.89. [e] Mp 187.5–190 °C. Anal. Calcd for $C_{13}H_{17}ClN_2O_3$ (284.74); C, 54.8≤; H, 6.02; N, 9.84. Found: C, 54.92; H, 6.01; N, 9.99. [f] In 50% TFA in CH_2Cl_2 at 24 °C.

of the amino and α-carboxyl groups is removed. Each was treated with 50% trifluoroacetic acid in dichloromethane and the loss of side-chain protection estimated by thin layer chromatography as shown in Table I. All three protecting groups were about five to seven times more stable than the corresponding benzyl protection. Even more stable protecting groups are possible but the use of these must be weighed against ease of removal in HF since excessive exposure to this reagent is not recommended.[8] All three protecting groups were removed completely (>99%) by treatment with HF for 10 min at 0 °C.

Experimental Section

Melting points were determined on a Fisher-Johns block and are uncorrected. Microanalyses were performed by the Microanalytical Laboratory, Department of Chemistry, University of California, Berkeley. Thin layer chromatography (TLC) was run on silica gel in the following solvents: chloroform–acetic acid, 15:1 (CA); 1-butanol–acetic acid–water, 4:1:1 (BAW).

β-4-Bromobenzyl Aspartate. This compound was prepared by the general method of Ledger and Stewart[9] with the exception that the volume of water used in preparing lithium copper(II) aspartate was reduced fourfold to eliminate a time-consuming evaporation step: overall yield 26%; mp 220–223 °C; TLC (BAW) R_f 0.55; $[\alpha]^{24}D$ +14.1° (c 2, 80% acetic acid).

Anal. Calcd for $C_{11}H_{12}BrNO_4$ (302.13): C, 43.73; H, 4.00; N, 4.64. Found: C, 43.82; H, 3.89; N, 4.57.

***N*-Boc-β-(4-Bromobenzyl)aspartic Acid (I).** This compound was prepared from β-(4-bromobenzyl)aspartate (20 g) by the Me_2SO method[10] and crystallized from ether–petroleum ether: yield 20.4 g (77%); mp 128.5–130 °C; TLC (CA) R_f 0.43; $[\alpha]^{24}D$ −15.5° (c 2.08, DMF).

Anal. Calcd for $C_{16}H_{20}BrNO_6$ (402.25): C, 47.77; H, 5.01; N, 3.48. Found: C, 47.85; H, 4.88; N, 3.74.

***N*-Boc-*O*-(4-Bromobenzyl)serine Dicyclohexylamine Salt (II).** The alkylation of *N*-Boc-serine hydrate (4.0 g, 18 mmol) with 4-bromobenzyl bromide was carried out as described by Hruby and Ehler.[11] After removal of the liquid ammonia the residue was shaken in a mixture of 100 ml of saturated aqueous NaCl, 10 ml of water, and 100 ml of ethyl acetate. The aqueous layer was discarded. To the ethyl acetate layer was added water (50 ml) and, while cooling and stirring, 3 N HCl was added to pH ca. 2. The ethyl acetate layer was washed with two 100-ml portions of water and dried over anhydrous $MgSO_4$. Removal of drying agent and solvent gave an oil (4.3 g) which was dissolved in ether (20 ml) and mixed with dicyclohexylamine (2.5 ml, 12.8 mmol). Removal of the ether gave a solid which was collected with use of petroleum ether: 5.3 g. This was dissolved in $CHCl_3$ (20 ml), evaporated in vacuo to an oil, and crystallized from ether–petroleum ether: 4.3 g (43%); mp 147–149 °C; $[\alpha]^{24}D$ +23° (c 2.2, $CHCl_3$).

Anal. Calcd for $C_{27}H_{43}BrN_2O_5$ (555.57): C, 58.37; H, 7.80; N, 5.04. Found: C, 58.83; H, 8.15; N, 5.32.

***O*-(4-Chlorobenzyl)threonine 4-Chlorobenzyl Ester Hydrogen Oxalate.** This compound was prepared as with the corresponding benzyl derivative[12] except that 4-chlorobenzyl alcohol (from reduction of 4-chlorobenzaldehyde with $NaBH_4$) was used. The crude product from 21.3 g (179 mmol) of threonine was crystallized from 8 l. of absolute ethanol: 20.5 g (25% yield); mp 192–193.5 °C; $[\alpha]^{24}D$ −67° (c 1.18, 80% acetic acid).

Anal. Calcd for $C_{20}H_{21}Cl_2NO_7$ (458.29): C, 52.42; H, 4.62; N, 3.06. Found: C, 52.17; H, 4.67; N, 3.23.

***N*-Boc-*O*-(4-Chlorobenzyl)threonine Dicyclohexylamine Salt (III).** The hydrogen oxalate salt just described (25.5 g, 55.6 mmol) was carried through the same procedure for the benzyl derivative. The resulting crude oil (20 g) was dissolved in ether (200 ml), mixed with dicyclohexylamine (12 ml), and allowed to crystallize at room temperature: 22 g. A portion (15.6 g) was dissolved in $CHCl_3$ (50 ml), evaporated in vacuo to an oil which was quickly dissolved in ether (200 ml), and allowed to crystallize: 15.0 g. The process was repeated with 400 ml of ether to give 14.0 g (68% yield): mp 150–153 °C; $[\alpha]^{24}D$ +26.5° (c 2, $CHCl_3$).

Anal. Calcd for $C_{28}H_{45}ClN_2O_5$ (525.03): C, 64.05; H, 8.63; N, 5.33; Cl, 6.75. Found: C, 63.84; H, 8.47; N, 5.18; Cl, 6.82.

Optical Purity of Derivatives. Samples of I, II, and III (1.0 mmol of each) were each treated in HF (20 ml) for 30 min at 0 °C in the presence of anisole (1.5 ml). After removal of HF, the residue was dissolved in 1 N HCl (20 ml), washed with two 20-ml portions of ether, and evaporated in vacuo to dryness. Quantitative amino acid analyses[13] gave yields of 100, 102, and 97% for aspartic acid, serine, and threonine, respectively. Optical rotation in 5 N HCl at 24 °C gave +24 (c 2.6), +14 (c 2), and −14° (c 2.4), respectively [lit.[14] $[\alpha]^{25}D$ (c 2, 5 NHCl) +25.4, +15.1, and −15°, respectively].

N-Boc-β-(4-BrBzl)Asp-OH, *N*-Boc-*O*-(4-BrBzl)Ser-OH, and *N*-Boc-*O*-(4-ClBzl)Thr-OH were coupled to H_2N-Phe-resin by in situ anhydride coupling[15] with 4 equiv of Boc-amino acid and 2.5 equiv of DCC in CH_2Cl_2 for 2.5 h at 24 °C. The corresponding dipeptides were obtained by treatment with HF (30–45 min at 0 °C) in the presence of anisole. Each dipeptide (2 μmol) was treated in 0.25 ml of 0.05 M Tris buffer of pH 8 (0.01 M Mg^{2+}) with 12 μg of leucineaminopeptidase (Worthington) for 24 h at 37 °. Quantitative amino acid analyses of the digests gave for H-Asp-Phe-OH, $Asp_{1.00}Phe_{0.95}$; for H-Ser-Phe-OH, $Ser_{0.95}Phe_{1.00}$; for H-Thr-Phe-OH, $Thr_{1.00}Phe_{0.97}$. The dipeptides H-Asp-Phe-OH and H-Ser-Phe-OH were separable from their constituent amino acids by TLC (BAW). The dipeptide H-Thr-Phe-OH was separable from its constituent amino acids by paper electrophoresis at pH 3.7 (pyridine acetate buffer). Each digest showed less than 1% of unhydrolyzed dipeptide by these criteria.

Stabilities of Protecting Groups in TFA and HF. The following reference derivatives were prepared by treatment of Ia, IIa, and IIIa in liquid HF for 15 min at 0 °C.

N-Acetylisoasparagine (3-acetaminosuccinamic acid, Ib), mp 165–167 °C. Anal. Calcd for $C_6H_{10}N_2O_4$ (174.16): C, 41.38; H, 5.79; N, 16.09. Found: C, 41.44; H, 5.75; N, 15.96.

N-Acetylserineamide (IIb), mp 141–143 °C. Anal. Calcd for $C_5H_{10}N_2O_3$ (146.15): C, 41.09; H, 6.90; N, 19.17. Found: C, 41.18; H, 6.85; N, 19.11.

N-Acetylthreonineamide (IIIb), mp 123–125 °C. Anal. Calcd for $C_6H_{12}N_2O_3$ (160.17): C, 44.99; H, 7.55; N, 17.49. Found: C, 45.03; H, 7.48; N, 17.49.

Samples (10 mg) of Ia, IIa, and IIIa were treated in 50% TFA in CH_2Cl_2 (10 ml, 24 °C, 71 h) and in liquid HF (5 ml containing 0.1 ml of anisole, 0 °C, 10 min). After removal of solvents by evaporation below reaction temperatures, the resulting products were dissolved in glacial acetic acid and run on TLC (BAW). The derivatives Ia, IIa, and IIIa all traveled with R_f's close to 0.70. The derivatives Ib, IIb, and IIIb gave R_f's of 0.29, 0.36, and 0.45, respectively. Estimates of side-chain removal in TFA or HF were made on TLC by running the treated derivatives along with serial aliquots of appropriate untreated derivatives and comparing color intensities revealed by chlorine–tolidine reagent.

Acknowledgment. The author wishes to thank Professor C. H. Li for his interest and encouragement and K. Hoey and

W. F. Hain for skilled technical assistance. This work was supported in part by U.S. Public Health Service Grant GM-2907.

Registry No.—I, 60803-65-8; Ia, 60803-66-9; Ib, 60803-67-0; II, 60803-69-2; IIa, 60803-70-5; IIb, 23361-38-8; III, 60803-72-7; IIIa, 60803-73-8; IIIb, 60828-33-3; β-(4-bromobenzyl) aspartate, 60828-77-5; *N*-Boc-serine, 3262-72-4; 4-bromobenzyl bromide, 589-15-1; dicydohexylamine, 101-83-7; *O*-(4-chlorobenzyl)threonine 4-chlorobenzyl ester hydrogen oxalate, 60803-75-0; chlorobenzyl alcohol, 873-76-7; H_2N-Phe, 63-91-2; H-Asp-Phe-OH, 13433-09-5; H-Ser-Phe-OH, 16875-28-8; H-Thr-Phe-OH, 16875-27-7.

References and Notes

(1) R. B. Merrifield, *J. Am. Chem. Soc.*, **85**, 2149 (1963).
(2) D. Yamashiro, R. L. Noble, and C. H. Li in "Chemistry and Biology of Peptides, Proceedings of the Third American Peptide Symposium", J. Meienhofer, Ed., Ann Arbor Science Publishers, Ann Arbor, Mich., 1972, p 197.
(3) B. W. Erickson and R. B. Merrifield in ref 2, p 191.
(4) L. A. Carpino, *J. Am. Chem. Soc.*, **79**, 98 (1957).
(5) Symbols and abbreviations are in accordance with the recommendations of the IUPAC-IUB Commission on Biochemical Nomenclature, *Biochemistry*, **11**, 1726 (1972). Other abbreviations used follow: DCC, *N,N*^{1}-dicyclohexylcarbodiimide; Me_2SO, dimethyl sulfoxide; TFA, trifluoroacetic acid.
(6) S. Sakakibara, Y. Shimonishi, Y. Kishida, M. Okada, and H. Sugihara, *Bull. Chem. Soc. Jpn.*, **40**, 2164 (1967); J. Lenard and A. B. Robinson, *J. Am. Chem. Soc.*, **89**, 181 (1967).
(7) B. Gutte and R. B. Merrifield, *J. Am. Chem. Soc.*, **91**, 501 (1969).
(8) R. S. Feinberg and R. B. Merrifield, *J. Am. Chem. Soc.*, **97**, 3485 (1975).
(9) R. Ledger and F. H. C. Stewart, *Aust. J. Chem.*, **18**, 1477 (1965).
(10) J. M. Stewart and J. D. Young, "Solid Phase Peptide Synthesis", W. H. Freeman, San Francisco, Calif., 1969, p 29.
(11) V. J. Hruby and K. W. Ehler, *J. Org. Chem.*, **35**, 1690 (1970).
(12) T. Mizoguchi, G. Levin, D. W. Woolley, and J. M. Stewart, *J. Org. Chem.*, **33**, 903 (1968).
(13) D. H. Spackman, W. H. Stein, and S. Moore, *Anal. Chem.*, **30**, 1190 (1958).
(14) J. P. Greenstein, *Adv. Protein Chem.*, **9**, 121 (1954).
(15) J. Rebek and D. Feitler, *J. Am. Chem. Soc.*, **96**, 1606 (1974).

A Convenient Total Synthesis of (±)-(7*E*,9*E*)-Trisporic Acid B Methyl Ester

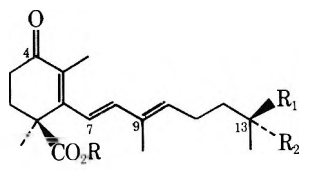
John A. Secrist III,* Charles J. Hickey,[1] and Robert E. Norris[1]

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

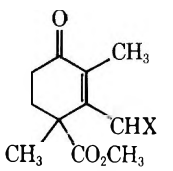
Received July 7, 1976

A brief converging total synthesis of the title compound is reported, utilizing as the key step a Michael-aldol sequence on the β-keto ester **4b** to form the highly functionalized cyclohexenone **2b.**

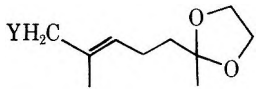
The sexual cycle of the fungi *Blakeslea trispora* and *Mucor mucedo* is mediated by a series of hormones, the trisporic acids (**1a–c,** R = H).[2] These hormones are derived biosynthetically from β-carotene,[3] and recently several prohormones have been isolated with lower oxidation levels at C-4 and the carboxylic acid carbon,[4] indicating that these are the sites of last modification in the biosynthesis. Synthetic efforts have thus far resulted in two syntheses of methyl trisporate B (**1b,** R = CH_3) and/or C (**1c,** R = CH_3),[5,6] and some work has recently been carried out on the utilization of Hagemann's ester for the formation of a potential intermediate in trisporic acid synthesis.[7] We wish to describe a convenient converging synthesis of the methyl ester of (±)-(7*E*,9*E*)-trisporic acid B (**1b,** R = CH_3), which is also a fully active compound.[4]



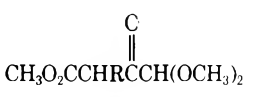
1a, $R_1 = R_2 = H$
b, $R_1 = R_2 = O$ (and 9-cis)
c, $R_1 = H$; $R_2 = OH$ (and 9-cis)



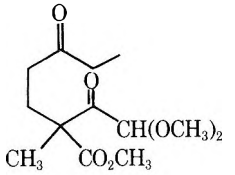
2a, X = O
b, X = $(OCH_3)_2$



3a, Y = OH
b, Y = Br
c, Y = $^+PPh_3^-$



4a, R = H
b, R = CH_3



5

The striking feature of this molecule is certainly the cyclohexenone moiety, suggesting a Michael-aldol sequence for its formation. We felt that the potential power of this sequence dictated its use, but contrary to previous work,[5,6] we wished to carry out the formation of the ring as quickly as possible, before the appendage at C-6 was attached. With this in mind we chose as our target molecules the aldehyde **2a** and the phosphonium salt **3c,** which we planned to join via a Wittig reaction. The choice of **2a** and **3c** provides us with two molecules each of which should be available in a few steps, thus portending a very direct overall route.

Analysis of the aldehyde **2a** indicates that the most effective means of applying the Michael-aldol sequence is to form the six-membered ring by joining a four-carbon unit to a two-carbon unit. Treatment of pyruvaldehyde dimethyl acetal with sodium hydride and dimethyl carbonate afforded the β-keto ester **4a,**[8] which was methylated with sodium hydride and methyl iodide to provide **4b.**[8] At this point there were several options available to us for the conversion to **2b.** In principle the Michael adduct might be first isolated, and then cyclized to **2b** under mild conditions, or the entire Michael-aldol sequence might be carried out at one time with a somewhat stronger base. The highly functionalized nature of **4b** suggested the former approach as the more promising one. Treatment of a solution of **4b** in methanol containing a catalytic amount of sodium methoxide with ethyl vinyl ketone did indeed afford **5,** which could be cyclized under various conditions to **2b.** More conveniently, however, the best procedure turned out to involve treatment of a solution of **4b** in methanol containing 1 equiv of sodium methoxide at room temperature with ethyl vinyl ketone over 3 h. This method provided **2b** directly in 45–50% yield, with no contamination by **5.** In this procedure methyl vinyl ketone also worked well as the Michael

acceptor. Unmasking of the aldehyde **2a** was accomplished by mild acidic hydrolysis of **2b.**

Synthesis of the phosphonium salt **3c** was accomplished starting with the alcohol **3a,** available conveniently in three steps from 6-methyl-5-hepten-2-one.[9,10] Addition of PBr_3 to a solution of **3a** and 2,4,6-collidine gave the unstable allylic bromide **3b,** which was immediately dissolved in ether and heated at reflux with triphenylphosphine overnight to afford the colorless salt **3c.**

On the basis of precedent in the vitamin A literature,[11] which indicates that in areas of extended conjugation the Wittig reaction will introduce a trans double bond exclusively, it was expected that the reaction of **2a** and the ylide of **3c** would provide only the 7*E* isomer. In addition, molecular models indicated that the 7*Z* isomer would have increased steric constraints owing to the methyl at C-5 and the quaternary carbon at C-1. Thus, the ylide generated from **3c** was condensed with aldehyde **2a** and the ketal functionality removed in situ by the addition of 5% HCl. Isolation by preparative TLC gave the pure methyl ester of (±)-(7*E*,9*E*)-trisporic acid B, in 28% yield for the two steps. Examination of a wide variety of conditions provided no improvement in the yield for these steps, though individually both half molecules gave excellent yields in other Wittig reactions. The synthetic material gave a correct exact mass and showed identical spectral properties with the natural product.[5,6] The facile conversion of methyl trisporate B to C has been reported.[6]

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus, and are corrected. Boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 467 grating infrared spectrophotometer. Nuclear magnetic resonance spectra were measured with a Varian A-60A spectrometer; chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. Mass spectra were recorded with an AEI-MS9 spectrometer at 70 eV.

Toluene was dried by distillation from CaH_2; tetrahydrofuran and diethyl ether were dried by distillation from sodium and benzophenone; methanol was dried by distillation from magnesium methoxide; hexane was distilled and stored over molecular sieves. Sodium hydride was weighed directly into the reaction vessels as a 50% dispersion in mineral oil, and then washed four times with toluene to remove the oil.

Methyl 4,4-Dimethoxy-3-oxobutyrate (4a). To a suspension of 15.6 g (0.65 mol) of NaH in 150 ml of toluene was added 58.5 g (0.65 mol) of dimethyl carbonate, and the mixture heated to reflux with mechanical stirring. A solution of 38.5 g (0.326 mol) of pyruvaldehyde dimethyl acetal in 40 ml of toluene was added over 1 h, and the mixture heated at reflux for a total of 6 h. The solution was cooled to ambient temperature and 75 ml of acetic acid added slowly, followed by 200 ml of water. The organic layer was separated, and the aqueous layer washed with benzene. The combined organic layer was washed with water, dried, and evaporated in vacuo. The residue was vacuum distilled to afford 39.2 g (68%) of the β-keto ester: bp 66–67 °C (0.75 mm) [lit.[8] bp 76 °C (5 mm)]; IR (neat) 1752, 1729 cm^{-1}; NMR ($CDCl_3$) δ 3.40 [s, 6, $(OCH_3)_2$], 3.56 (s, 2, $-CH_2-$), 3.71 (s, 3, CO_2CH_3), 4.55 [s, 1, $CH(OCH_3)_2$].

Methyl 4,4-Dimethoxy-2-methyl-3-oxobutyrate (4b). To a suspension of 4.34 g (0.181 mol) of NaH in 150 ml of toluene was added 31.9 g (0.181 mol) of ester **4a** in 30 ml of toluene dropwise, with mechanical stirring. After addition was complete the mixture was brought to reflux for 0.5 h and cooled to ambient temperature. To the salt was added 51 g (0.36 mol) of CH_3I dropwise, and the mixture heated at 90 °C for 3 h. After cooling the NaI was filtered off and washed with toluene, and the filtrate washed with water, dried, and evaporated in vacuo. Distillation of the residue afforded 29.56 g (86%) of the colorless monomethylated product: bp 77–78 °C (1.5 mm) [lit.[8] bp 88 °C (5 mm)]; IR (neat) 1751, 1727 cm^{-1}; NMR ($CDCl_3$) δ 1.31 (d, 3, *J* = 7 Hz, CH_3CH), 3.38 [s, 6, $CH(OCH_3)_2$], 3.69 (s, 3, CO_2CH_3), 3.83 (q, 1, *J* = 1 Hz, $CHCH_3$), 4.65 [s, 1, $CH(OCH_3)_2$].

Methyl 2-Dimethoxymethyl-1,3-dimethyl-4-oxocyclohex-2-enyl-1-carboxylate (2b). To a stirred solution of 31 g (0.163 mol) of ester **4b** in 150 ml of methanol containing 0.18 mol of sodium methoxide was added 18 g (0.214 mol) of ethyl vinyl ketone dropwise over a period of several hours, and the solution stirred at ambient temperature overnight. Addition of 150 ml of water was followed by evaporation of the methanol and extraction several times with CH_2Cl_2. The organic extracts were dried, the solvent removed in vacuo, and the residue briefly vacuum distilled to remove nonvolatile and colored materials. Direct crystallization utilizing ether–petroleum ether afforded 10.9 g (26%) of colorless crystals, mp 59–60 °C. Chromatography of the mother liquors on silica gel eluting with 1:1 ether–petroleum ether, allows the isolation of additional pure material, the total yield generally being in the neighborhood of 45–50%: IR (KBr) 1733, 1675, 1615 cm^{-1}; NMR ($CDCl_3$) δ 1.50 (s, 3, $CH_3CCO_2CH_3$), 1.83 (s, 3, $CH_3C{=}C$), 1.75–2.63 (m, 4, $-CH_2CH_2-$), 3.31 and 3.38 [2 s, 6, $(OCH_3)_2$], 3.68 (s, 3, CO_2CH_3), 5.03 [s, 1, $CH(OCH_3)_2$].

Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.94; H, 7.81. Found: C, 61.16; H, 7.96.

Methyl 1,3-Dimethyl-2-formyl-4-oxocyclohex-2-enyl-1-carboxylate (2a). A solution of the acetal **2b** (1.105 g, 4.32 mmol) in 15 ml of 1:1:1 water–methanol–acetic acid was allowed to stand at ambient temperature for 12 h. After evaporation of the methanol in vacuo the solution was poured slowly into an excess of 5% aqueous sodium bicarbonate and extracted several times with ether. The ether extracts were dried and evaporated to give a quantitative yield of the aldehyde as a pale yellow syrup. Crystallization from ether–petroleum ether afforded 0.78 g (86%) of pure aldehyde as pale yellow crystals: mp 80–81 °C; IR (KBr) 1732, 1677 cm^{-1} (br); NMR ($CDCl_3$) δ 1.49 (s, 3, $CH_3CCO_2CH_3$), 2.21 (s, 3, $CH_3C{=}C$), 1.76–2.79 (m, 4, $-CH_2CH_2-$), 3.68 (s, 3, CO_2CH_3), 10.29 (s, 1, CHO).

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.86; H, 6.67. Found: C, 62.58; H. 6.74.

(*E*)-6,6-Ethylenedioxy-2-methyl-2-heptenyltriphenylphosphonium Bromide (3c). To a stirred solution of 558 mg (3.0 mmol) of alcohol **3a**[10] and 726 mg (6.0 mmol) of 2,4,6-collidine in 5 ml of 1:1 ether–hexane at 0 °C protected from moisture was added 543 mg (2.0 mmol) of PBr_3 in 1 ml of hexane dropwise over 0.5 h. Stirring was continued for an additional 1 h, and the reaction mixture worked up by the addition of water and extraction several times with ether. The ether extracts were dried, solvent was removed in vacuo, and the crude allylic bromide **3b** and 600 mg (2.3 mmol) of triphenylphosphine were immediately dissolved in 5 ml of ether and heated at reflux for 16 h. Filtration and washing with ether yielded 551 mg (36% overall) of phosphonium salt **3c**: mp 166–172 °C; IR (KBr) 3045, 2785, 1614 cm^{-1}; NMR ($CDCl_3$) δ 1.23 [s, 3, $CH_3C(-O-)O-$], 1.50 (br d, 3, $CH_3C{=}C$), 1.4–2.4 (m, 4, CCH_2CH_2C), 3.87 (s, 4, $-OCH_2CH_2O-$), 4.57 (d, 2, *J* = 14.5 Hz, $CH_2P^+Ph_3$), 5.42 (br t, 1, C=CH), 7.73 (m, 15, Ph_3). This compound proved difficult both to purify and analyze, and would not give a molecular ion in the mass spectrum. Since it was obtained in reasonable purity after filtration, the salt was dried and used directly.

(±)-Methyl (7*E*,9*E*)-Trisporate B. To a stirred suspension of powdered phosphonium salt **3c** (364 mg, 0.712 mmol) in 5 ml of THF under N_2 at ambient temperature was added *n*-BuLi (0.57 ml of a 2.15 M solution) dropwise, the salt gradually dissolving to yield a deep red solution of the ylide. After 0.25 h the ylide was cooled to −50 °C and a solution of aldehyde **2a** (149.5 mg, 0.712 mmol) in 1.5 ml of THF added dropwise via syringe. Stirring was continued for 1 h at −50 °C, when TLC analysis (1:1 ether–petroleum ether) showed no aldehyde present, and then 5 ml of 5% HCl was added, and the solution stirred at 0 °C for 1 h. Addition of 5 ml of water was followed by evaporation of the THF in vacuo and extraction several times with ether. The ether extracts were dried, solvent removed in vacuo, and the residue immediately subjected to preparative thin layer chromatography under N_2 in the dark (elution with 3:2 ether–petroleum ether). Isolation of the appropriate band gave 63 mg (28%) of (±)-trisporic acid B methyl ester, spectrally identical with the natural material (IR, UV, NMR); mass spectrum calcd *m/e* 318.1831, obsd *m/e* 318.1836.

Acknowledgment. We wish to thank S. Scott Stewart for carrying out certain experiments bearing on this work, Dr. P. L. Fuchs of Purdue University for helpful discussions, and the Ohio State University Department of Chemistry for its generous support.

Registry No.—**1b,** 60760-98-7; **2a,** 60705-21-7; **2b,** 60705-22-8; **3a,** 21488-96-0; **3b,** 60705-23-9; **3c,** 60705-24-0; **4a,** 60705-25-1; **4b,** 60705-26-2; dimethyl carbonate, 616-38-6; pyruvaldehyde dimethyl acetal, 6342-56-9; CH_3I, 74-88-4; ethyl vinyl ketone, 1629-58-9; PBr_3, 7789-60-8; triphenylphosphine, 603-35-0.

References and Notes

(1) Undergraduate Research Participants, 1974–1975.
(2) H. Van Den Ende and D. Stegwee, *Bot. Rev.*, **37**, 22 (1971); J. D. Bu'Lock, D. Drake, and D. J. Winstanley, *Phytochemistry*, **11**, 2011 (1972); J. D. Bu'Lock, D. J. Austin, G. Snatzke, and L. Hruban, *Chem. Commun.*, 255 (1970); A. W. Barksdale, *Science*, **166**, 831 (1969); T. Reschke, *Tetrahedron Lett.*, 3435 (1969).
(3) D. J. Austin, J. D. Bu'Lock, and G. W. Gooday, *Nature (London)*, **223**, 1178 (1969).
(4) J. D. Bu'Lock, B. E. Jones, and N. Winskill, *J. Chem. Soc., Chem. Commun.*, 708 (1974).
(5) J. A. Edwards, V. Schwarz, J. Fajkos, M. L. Maddox, and J. H. Fried, *Chem. Commun.*, 292 (1971).
(6) S. Isoe, Y. Hayase, and T. Sakan, *Tetrahedron Lett.*, 3691 (1971).
(7) J. D. White and W. L. Sung, *J. Org. Chem.*, **39**, 2323 (1974).
(8) E. E. Royals and A. G. Robinson, III, *J. Am. Chem. Soc.*, **78**, 4161 (1956). This reference synthesizes both **4a** and **4b** by "mixed ester condensation". We prefer the carbomethoxylation–methylation sequence as a straightforward, high-yield alternative readily adaptable to large-scale runs.
(9) M. Mousseron-Canet, M. Mousseron, P. Legendre, and J. Wylde, *Bull. Soc. Chim. Fr.*, 376 (1963).
(10) O. P. Vig, B. S. Balgir, and K. L. Matta, *Indian J. Chem.*, **6**, 564 (1968). The sequence utilized by these researchers involved SeO_2 oxidation of the ethylene ketal of 6-methyl-5-hepten-2-one[9] to the aldehyde followed by reduction with $NaBH_4$ to the allylic alcohol. In our hands we found it necessary to modify the procedure of this last step. We dissolved the aldehyde in 2-propanol, cooled to −50 °C, added the $NaBH_4$, then allowed the solution to warm slowly to room temperature, and followed with the normal workup and isolation of the alcohol. These workers also incorrectly draw the cis stereochemistry for the aldehyde and alcohol.
(11) H. Pommer, *Angew. Chem.*, **72**, 811 (1969); A. Maercker, *Org. React.*, **14**, 270 (1965).

Rearrangement of α-Bromocamphoric Anhydride. 2. Competitive Mechanisms in the Formation of Laurolenic Acid[1,2a–c]

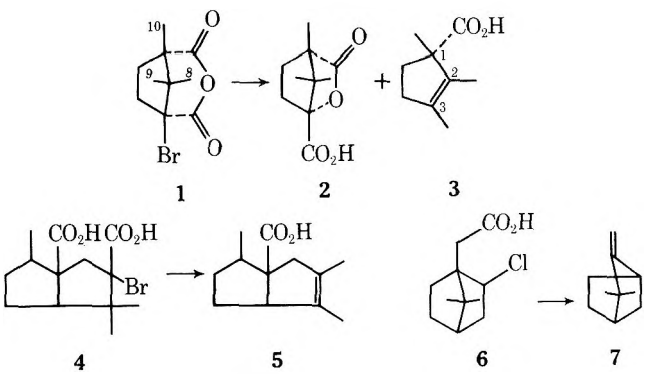
Walter L. Meyer,* Charles E. Capshew,[2d] John H. Johnson,[2e] Alan R. Klusener,[2d] Angelo P. Lobo, and Richard N. McCarty

Department of Chemistry, University of Arkansas, Fayetteville, Arkansas 72701

Received April 21, 1976

α-Bromocamphoric anhydride (**1**) is converted by aqueous sodium carbonate into camphanic acid (**2**) and the rearranged product laurolenic acid (**3**). L(+)-α-Bromocamphoric anhydride-*8,8,8-d*$_3$ was prepared from L(−)-camphor-*8,8,8-d*$_3$ by oxidation with selenium dioxide and then hydrogen peroxide, followed by bromination. Rearrangement of this labeled anhydride produces L(−)-laurolenic acid in which 71% of the CD_3 group is located at the 1 position and 29% is at the 3 position. In conjunction with earlier work, these results indicate that the rearrangement is not unimechanistic, but follows at least two competitive pathways. One of these involves loss of the carboxyl γ to the bromine by a path which is concerted with migration of the 8-methyl to the initially brominated carbon. Another process involves loss of the α-carboxyl, but the present results do not determine whether or not this is also concerted with the stereoselective 8-methyl migration. Even if it is, concerted γ-decarboxylation predominates over concerted α-decarboxylation. Optically and isotopically pure L(−)-camphor-*8,8,8-d*$_3$ was prepared in 41% overall yield from L(−)-8-apoisoborneol-7-carboxylic acid lactone by lithium aluminum deuteride reduction to L(+)-8-hydroxyisoborneol-*8,8-d*$_2$ (**17**-*d*$_2$), selective preparation of the 8-benzoate, Jones oxidation and saponification to afford L(−)-8-hydroxycamphor-*8,8-d*$_2$ (**25**-*d*$_2$), treatment with phosphorus tribromide to produce the 8-bromo ketone, and tri-*n*-butyltin deuteride reduction. Small amounts of the 2,8-dibenzoate **20** and the 2-monobenzoate **21** are by-products of the benzoylation, the latter being converted to carboxy ester **29** in the oxidation step. Conversion of the undeuterated diol **17** to ketol **25** by selective 8-tritylation, Sarett oxidation, and hydrolysis of keto trityl ether **23** is also described. 2-Hydroxy- and 2-keto-8-*p*-toluenesulfonates **22** and **26** are both converted by lithium aluminum hydride into cyclic ether **30**, which is also produced by attempted tosylation of **17** at room temperature.

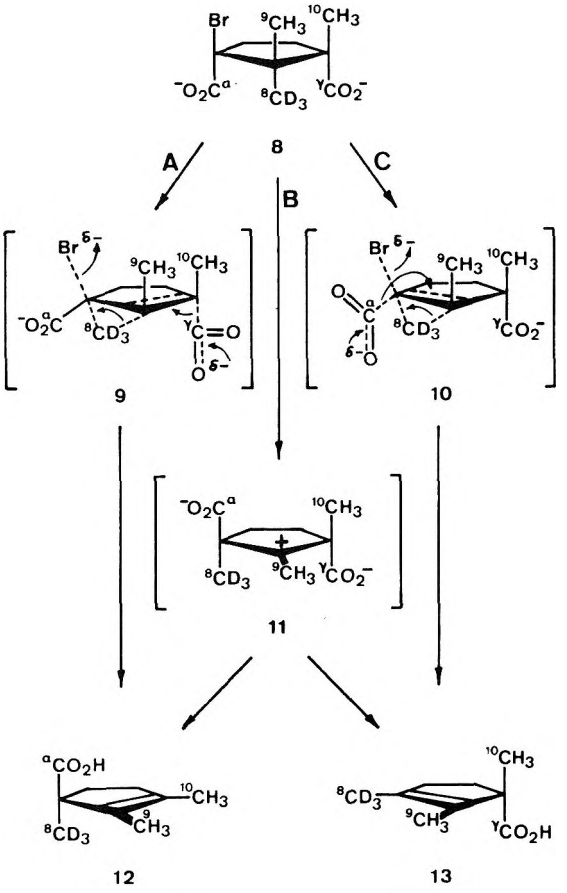
One of the most striking molecular rearrangements of organic chemistry is the solvolytic conversion of α-bromocamphoric anhydride (**1**) to laurolenic acid (**3**), first reported by Fittig and Woringer in 1885.[3] This unsaturated acid accompanies the major unrearranged product, camphanic acid (**2**),



in about 15% yield when the solvolysis is conducted at pH 11,[4] and its formation involves the unusual combination of bromide loss, 1,2-methyl migration, and decarboxylation of an α- or γ-bromo acid. Other examples of potentially analogous reactions are extremely rare, but include the rearrangement of bromonorcedrenedicarboxylic acid (an α-bromo acid, **4** → **5**)[5] and of 2-chloro-1-apocamphaneacetic acid (a γ-bromo acid, **6** → **7**).[6] A few related base-catalyzed rearrangements of α-bromo acids not accompanied by decarboxylation are also known.[7]

Some time ago we became interested in the mechanism of this peculiar reaction, particularly in the stereoselectivity of methyl migration and in the regioselectivity of decarboxylation. Owing to the particular juxtaposition of functional groups in the camphoric acid system, the latter is not intuitively obvious as it is in the cases of **4** and **6**. In an earlier paper we reported the results of research showing that the methyl migration which occurs during formation of laurolenic acid is completely stereoselective and therefore concerted with bromide loss, and that neither an α-lactone (or its mechanistic equivalent), a carbene, nor camphanic acid is involved in the rearrangement.[1] It is also known that the rearrangement product is at least 96% optically pure[8] and has the same configuration at C-1 as does the bromo anhydride from which it is derived.[1,8–10] These results limit the mechanistic possibil-

Scheme I



ities to pathways such as those depicted in Scheme I or related processes,[1] but shed no light on the decarboxylation stages of the reaction. They leave unanswered questions as to whether carboxyl loss is specific or statistical, whether carboxyl loss is also concerted with methyl rearrangement, which carboxyl is lost, and whether an intermediate such as the protio analogue of carbonium ion **11**, with equivalent carboxylates or carboxyls, can be involved. We have now completed a further examination of this reaction, and herein report results which show that carboxyl loss is *neither* specific *nor* statistical, so that at least two pathways are followed during decarboxylation and at least one of them involves a concerted loss of carbon dioxide.

These aspects of the rearrangement have been studied by labeling the 8-methyl of bromocamphoric anhydride[11] with deuterium and determining the location of the deuteriomethyl group in the resulting laurolenic acid. This labeled methyl is the group which migrates in the reaction,[1] so its ultimate location serves to mark the carbon which initially held the bromine. The direct question then, of course, is simply whether that carbon has retained or lost its carboxyl.

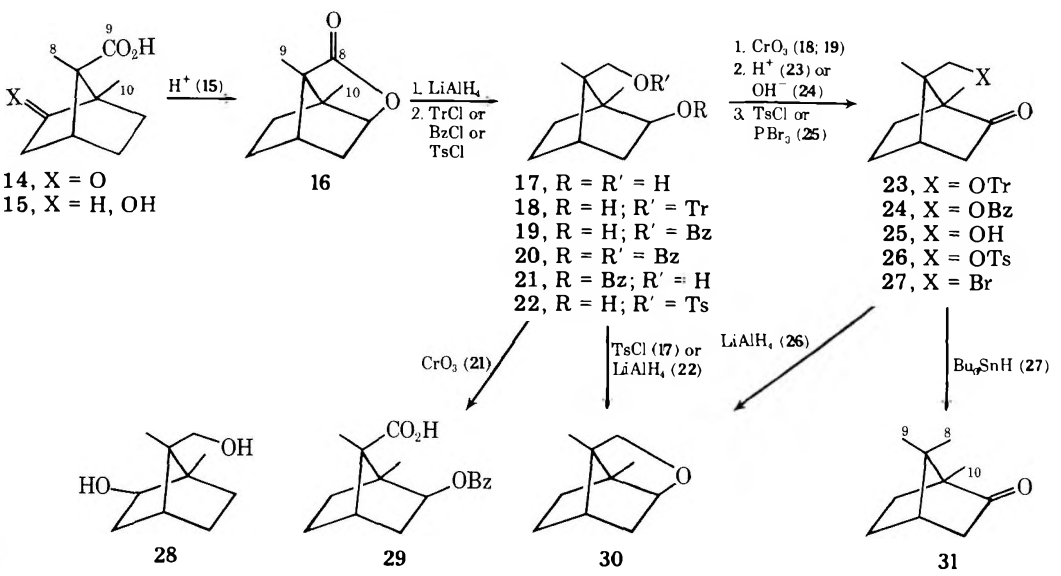
Synthesis of L(−)-Camphor-*8,8,8-d*$_3$ and L(+)-α-Bromocamphoric Anhydride-*8,8,8-d*$_3$. Preparation of the necessary labeled bromo anhydride required availability of the correspondingly labeled camphor. Although for this study the optical purity of the anhydride was not important, in connection with other research we needed a series of 8-deuterated camphor derivatives which were high in optical purity as well as containing complete and specific deuterium substitution for one, two, or all three of the 8-hydrogen atoms, respectively. Therefore a synthesis which could satisfy all of these requirements was developed (Scheme II).

The sequence is initiated with conversion of D(+)-camphor into D(+)-isoketopinic acid (**14**) as described earlier,[1,12-14] a transformation which is known to proceed with complete retention of configuration.[1,15] In order to transmogrify this keto acid into a substance with a reducible function in the 8 rather than the 9 position, advantage was taken of the known rearrangement of the corresponding hydroxy acid **15** to lactone **16**.[14] This process, which occurs by way of a 2,6-hydride shift,[14] actually brings about the necessary interchange of carbons 8 and 9 by converting the ring system functionality from the D to the L enantiomeric series.[16] Although the point had apparently not been previously substantiated, it is clear from the present work that subtle rearrangements which induce partial racemization do not intervene during lactone formation, for the L-camphor ultimately derived from this lactone proves to be optically pure.[17]

Conversion of the racemate of lactone **16** into camphor has been described by Finch and Vaughan[18] and by Rodig and Sysko,[19] and our sequence for conducting this transformation starts in a similar manner with lithium aluminum hydride reduction to form the 2,8-diol **17**. However, for a variety of reasons including not only a desire for high yields, but also for ease of manipulation of intermediates and purification of products and particularly for specificity and efficiency in the incorporation of deuterium as well as protium into the products, many of the subsequent stages in our synthesis differ from those reported earlier.[18,19]

The potentially direct route for removing the primary hydroxyl of diol **17** by means of the selective changes OH → OTs

Scheme II



→ H, in analogy with the procedure used with the isomeric anti diol **28**,[1] was discarded when we, too, found that cyclic ether **30** is difficult to reproducibly avoid as a by-product of the monotosylation,[18,19] and that in any event it is the main product from lithium aluminum hydride reduction of not only hydroxy tosylate **22**[18,19] but also keto tosylate **26**. Attempted reductive cleavage of this ether to isoborneol using lithium aluminum hydride–aluminum chloride[20] was unsuccessful, so the facile formation of ether **30** could not be turned to advantage.

The foregoing results augured ill for sequences utilizing lithium aluminum deuteride as the source of the final deuterium on C-8 without elaborate protection of the 2-oxygen function, and we preferred not to chance the possibility of hydrogen–deuterium exchange at various points in the molecule which might threaten to accompany catalytic replacement of an 8 substituent by molecular deuterium. Accordingly attention was turned to preparation of ketol **25** and examination of the sequence OH → Br → H, where a trialkyltin hydride or deuteride could be used for the last reductive step in the presence of a 2-keto group.[21] Selective Jones oxidation of diol **17** to ketol **25** was not explored in view of the reported poor yield,[18] and exposure to *N*-bromoacetamide produced lactone **16** rather than bringing about the normal preferential oxidation of the secondary alcohol.[22] However, diol **17** is selectively protected at the primary hydroxyl by either tritylation or benzoylation, and oxidation of either derivative followed by deprotection readily produces ketol **25**. We preferred the route through benzoyl derivatives, since it sometimes proved difficult to purify the hydroxy trityl ether **18**. Although benzoylation of the diol affords small amounts of diester **20** and the isomeric hydroxy ester **21** in addition to the required hydroxy ester **19**, these by-products are not troublesome. The diester is easily separated from the 11:1 mixture of hydroxy esters by chromatography, and in the oxidation step residual hydroxy ester **21** is converted to the acid **29** which can be removed by extraction. These techniques afford ketol **25** in 68% yield from diol **17**. Use of mesitoyl chloride rather than benzoyl chloride in an effort to improve the selectivity in monoacylation of **17** showed no advantage to lie with the more hindered acylating agent.

Ketol **25** is converted to bromo ketone **27**[23] by phosphorus tribromide,[18] and reduction by tri-*n*-butyltin hydride affords L(−)-camphor (**31**).[26] This product is optically pure (±4%, the uncertainty in our rotation measurements), as thus must be all of its predecessors.[17] The overall yield from lactone **16**, the crucial steps for deuterium introduction, is 41%, which compares favorably with the 16[18] and 43%[19] reported for other sequences, and with the 45% for conversion of methyl D-isoketopinate to optically pure D-camphor-*9,9,9-d*$_3$.[1]

Repetition of the sequence **16** → **17** → **19** → **24** → **25** → **27** → **31** with use of lithium aluminum deuteride and tri-*n*-butyltin deuteride in the appropriate reduction steps affords optically pure L-camphor-*8,8,8-d*$_3$ containing at least 97.5% of the d_3 species according to mass spectrometric analysis. ^{1}H NMR spectra of this product and all of its deuterated predecessors and progeny contain appropriate features[1] for location of all deuterium atoms specifically on the 8 carbon. These spectra, together with those obtained earlier from 9-deuterio derivatives,[1] have allowed unequivocal assignments of the methyl resonances in these compounds; assignments are listed in the Experimental Section and confirm earlier proposals concerning camphor and camphorquinone.[27]

It may be noted that by use of the isotopic reagent in one or the other but not both of the reduction steps the d_1 and d_2 derivatives will be available in equivalent optical and isotopic purity. Thus this sequence and that described earlier[1] make accessible optically pure camphor derivatives with mono-, di-, or trideuteration of either methyl-8 or methyl-9.[28] Undoubtedly one or the other sequence could also be adapted for deuteration of methyl-10 if the need should arise for samples with greater or more specific deuterium incorporation at that site than can be obtained by way of the 10-chloro sulfoxide.[24]

8-Labeled bromo anhydride for the rearrangement experiment was prepared by sequential oxidations of L(−)-camphor-*8,8,8-d*$_3$ with selenium dioxide and alkaline hydrogen peroxide, followed by bromination, as described earlier for the unlabeled and 9-labeled analogues.[1] Phosphorus tribromide–bromine has proven preferable to phosphorus pentachloride–bromine[1] for the bromination step, because on some occasions the latter reagent leads to significant amounts of unbrominated camphoric anhydride as a by-product.

Rearrangement of the 8-Labeled Bromo Anhydride. Rearrangement of the labeled bromo anhydride under conditions identical with those used in the previous study[1] affords labeled laurolenic acid (**3**-d_3) and labeled camphanic acid (**2**-d_3). The latter is devoid of τ 8.98 methyl resonance but has equal 3-proton intensity methyl resonances at τ 8.86 and 8.90, just as that from base treatment of the *9,9,9-d*$_3$ anhydride has 3-proton methyl resonances at τ 8.86 and 8.98 but none at 8.90.[1] These observations are all in accord with a mechanism for formation of the lactonic acid **2** which involves simple intramolecular displacement of bromide by the carboxylate which is γ to it, the τ 8.86, 8.90, and 8.98 resonances of camphanic acid being respectively those of the former 10-methyl, 9-methyl, and 8-methyl of the bromo anhydride.

The ^{1}H NMR spectrum of the labeled laurolenic acid contains the allylic methyl multiplet (ca. τ 8.41, 2-methyl plus 3-methyl)[1] and the quaternary 1-methyl singlet (τ 8.77)[1] in the intensity ratio of 86:14. Inasmuch as our earlier work has shown that 100% of the 9-methyl remains at C-2 (allylic) in laurolenic acid, this ^{1}H NMR result indicates that the ratio of *protonic* 3-methyl to *protonic* 1-methyl in the laurolenic acid derived from 8-labeled anhydride is 72:28. In view of the breadth and overlap of the C-2 and C-3 methyl resonances, and the possibility that they might overlap slightly with ring proton resonances in the spectrum of the unsaturated acid itself, this quantitative result was checked by conversion of the acid to its bromo lactone.[1,29] Integration of the three sharp methyl singlets in the spectrum of this derivative[1] showed their relative intensities to be 99 (τ 8.38, 2-CH_3):71 (τ 8.50, 3-CH_3):30 (τ 8.75, 1-CH_3). The excellent agreement of the 3-methyl:1-methyl resonance intensity ratio between this bromo lactone and the labeled acid from which it was derived requires that the τ 8.50 and 8.75 resonances of bromo lactone correspond to the τ 8.41 and 8.77 resonances of the unsaturated acid, respectively. This information confirms our earlier assignment of chemical shifts to the bromo lactone,[1] because both the chemical shift of the τ 8.41 resonance of the acid and its breadth due to homoallylic spin coupling demonstrate its allylic nature, which requires its assignment to the 2- and 3-methyls.

Comparison of the *m/e* 125 and 128 ions in mass spectra of the unlabeled and labeled bromo lactones ($C_7H_9O_2$ or $C_8H_{13}O$; no significant molecular ion appears in the spectrum) shows the latter to indeed contain at least 96% of the d_3 species.

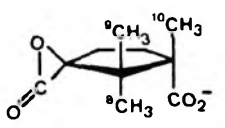
Discussion

This result and the earlier one show that while 100% of methyl 9 from the anhydride becomes the 2-methyl of laurolenic acid, 71% of methyl 8 becomes the 1-methyl and 29% becomes the 3-methyl. Thus under these reaction conditions the rearrangement products are the isotopic isomers **12** and **13** (Scheme I) in a 71:29 ratio, and loss of the carboxyl which was originally γ to the bromine predominates over loss of the α-carboxyl.

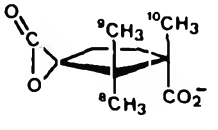
One immediate conclusion which follows is that rear-

rangement of the intermediate dianion 8[1] does *not* proceed exclusively through a species with equivalent carboxyls such as carbonium ion **11** (path B of Scheme I), which would require distribution of the labeled methyl to be 50:50 modified only slightly by any secondary deuterium isotope effects.[30] Likewise, the rearrangement does not proceed by a single concerted path, such as path A or path C, which would require exclusive loss of a particular carboxyl. More than one sequence is involved. It is possible that as much as 58% of the product is formed through a symmetric species (**11**, etc.), accounting for all of the 3-CD_3 acid **13** and a corresponding amount of the 1-CD_3 substance **12**, but even if this is the case there is an additional 42% of the product formed by specific loss of the γ-carboxyl. On the other hand, the result is equally consistent with a situation in which no laurolenic acid is produced through a system with equivalent carboxyls like **11**, but in which there are two (or more) competitive concerted pathways, the predominant one (71%) involving γ-carboxyl loss and a *minor one* (29%) involving specific α-carboxyl loss. Or, of course, all three processes could be operating to appropriate intermediate extents. In any event, this reaction is not completely analogous to either the bromonorcedrenedicarboxylic acid case (**4**, α-decarboxylation) nor the chlorocamphaneacetic acid case (**6**, γ-decarboxylation), but shows characteristics of both.

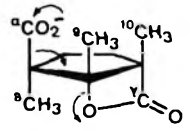
Thus far we have considered the decarboxylation only in terms of intermediates with two free carboxylate groups (Scheme I), but the possible intervention of lactonic species must also be examined. Of course the γ-lactone camphanic acid (**2**) was excluded earlier by the observation that it is not converted to laurolenic acid under these conditions.[1] α-Lactones **32** and **33** can be discarded on mechanistic grounds, the



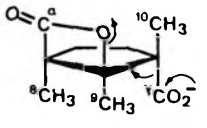
32



33



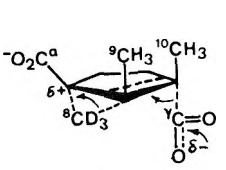
34



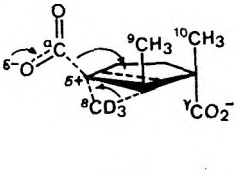
35

former because its formation would involve displacement of bromide with retention of configuration and the latter because its rearrangement would require methyl migration with retention of configuration at the migration terminus.[1] However, β-lactones **34** and **35** are not so readily dismissed.[31] In principle either could be individually produced by attack of the appropriate carboxylate on the cationic center which is developing at C-2 as the methyl group migrates, and the two of them could be generated in equal amounts[30] from cation **11**. Subsequent decarboxylative anti elimination as indicated would lead to laurolenic acid (**13** and **12**, respectively).[32] Actual intermediacy of these two lactones in any fraction of decarboxylation which occurs by way of cation **11** remains an open question, for their transient presence as equimolecular progeny of the latter is allowed but not required by the available data. On the other hand, independent genesis of lactone **35** seems quite improbable. Before the α-carboxylate oxygen can approach C-2 closely enough to start formation of the C-2–O bond of this β-lactone, methyl migration and inversion of configuration at the migration terminus must be nearly complete. If there were a need for the C-2 center to undergo nucleophilic collapse with a carboxylate oxygen before it reaches the fully charged state of **11**, it should be able to do so at a much earlier point in the reaction by bonding to the geometrically available γ-carboxylate, thereby affording **34** rather than **35**. We therefore feel that sequences for specific γ-decarboxylation through lactone **35** are not worthy of further consideration. Even though such purely geometric constraints do not similarly militate against preferential formation of lactone **34**, that process is also less than completely satisfying as a probable participant in the reactions under discussion. It requires that the γ-carboxylate attack the face of C-2 from which the migrating methyl is departing, and analogous β-lactonizations with retention of configuration do not occur in related reactions such as the solvolysis of *cis*-2-bromocyclopentanecarboxylic acid.[33] Nonetheless, we do not feel that this is a sufficiently strong argument to entirely exclude the possibility of selective α-decarboxylation by a route through lactone **34**.

Among the points which are more or less clear[30] regarding the decarboxylation mechanisms is that there is a process for specific γ-carboxyl loss. Of the possibilities we have considered, the most probable is direct decarboxylation concerted with methyl migration, by a route which resembles path A of Scheme I. The present data do not indicate whether this decarboxylation is also concerted with bromide loss, involving a transition state like **9** as is shown in Scheme I, or whether it only begins after completion of that bond rupture (e.g., through an alternative transition state such as **36**). They



36



37

simply show that loss of this carboxylate begins before methyl migration is completed with formation of a symmetric ion **11**. The other processes which could hypothetically lead to specific γ-decarboxylation are cycloreversion of lactone **34**, which should not occur under these conditions,[32-34] and β-decarboxylative elimination of lactone **35**, which should not be selectively generated in this system (see above).

The mechanism 8 → (**9** or **36**) → **12** corresponds to a syn 1,2 elimination with the migrating methyl as the leaving nucleophile. Such a stereochemical result is by no means uncommon for concerted eliminations from cyclopentane systems, with CO_2 as the departing electrophile[33] as well as with proton.[35] One should not, however, extrapolate the propensity of bromocamphorate to undergo syn γ-decarboxylation in preference to α-decarboxylation to the general case. Just as concerted 1,2-elimination reactions show a favored conformational relationship between the leaving groups (near coplanarity, either anti or syn), these decarboxylative rearrangements may well have a preferred geometry between the γ-carboxyl and the migrating alkyl group which is satisfied in the five-membered ring but would not be met in certain other structures. Even in the present instance the energy difference between transition states for γ-decarboxylation and α-decarboxylation is only about 0.6 kcal/mol (less if the latter proceeds through **11**). Thus if in a different system such conformational or other structural factors inhibited or precluded γ-decarboxylation, α-decarboxylation could easily become the predominant or sole process. This is, of course, vividly demonstrated in the cedrene series (**4** → **5**), where γ-decarboxylation is impossible. Finally it should be noted that the present example gives no information about the reactivity of a γ-carboxyl which is oriented trans to the migrating alkyl group. One would suspect that if such a carboxyl

could attain an approximately anti-coplanar conformation with respect to the migrating group, it would also be readily lost.

Little can be concluded about the process which is involved in α-decarboxylation, other than that it exists and energetically is not greatly inferior to the γ-decarboxylation route. It may proceed through the 2 cation **11**, accompanied by an equivalent amount of γ-decarboxylation (either with or without prior β-lactonization to **34** and **35**). It may proceed by a concerted path in which the γ-carboxyl is not at all involved, such as path C of Scheme I or its counterpart in which bromide departure precedes the onset of decarboxylation (cf. **37**). Or it may proceed through selective formation and decomposition of lactone **34** as discussed above. Analogous paths are also open to the cedrene analogue.

Experimental Section

All reactions were conducted in a N_2 atmosphere. Melting points, corrected for stem exposure, were determined in sealed evacuated capillaries unless marked (o) to indicate open capillaries. Spectra were obtained using Perkin-Elmer Model 337 (IR) and Varian A-60 or Bruker HFX-90 (90 MHz) (^{1}H NMR) spectrometers. The ^{1}H NMR solvent was $CDCl_3$ unless otherwise stated, with Me_4Si as internal standard. Chemical shifts (τ), multiplicities (s, d, t for singlet, doublet, triplet; m for unanalyzed multiplet), coupling constants (J, in hertz), and the number of protons are listed for prominent resonances. Methyl resonance assignments, where indicated, are based on peak absences from spectra of the 8-d_3 and 9-d_3[1] analogues. Mass spectra were obtained on a Hitachi RMU-6E double focusing spectrometer at an ionization potential of 80 eV, with direct solid introduction unless marked (v) to indicate vaporization of a volatile solid into the liquid introduction system; data are in the form *m/e* (% base peak intensity). Column chromatographic separations employed a 30–50:1 w/w ratio of absorbent to substrate, and eluent fractions of approximately half the column volume or less. Microanalyses were by Alfred Bernhardt, Mulheim, Germany (indicated B), or Spang Laboratory, Ann Arbor, Mich. (S). Optical rotations were observed in 95% EtOH unless indicated otherwise, on a Rudolph Model 80 polarimeter with a 2-dm tube, and are considered accurate to $[\alpha]$ ±1.5°. When no temperature is specified, operations were conducted at room temperature, ca. 23 °C. Unless otherwise specified, HCl, NaOH, KOH, $NaHCO_3$, K_2CO_3, and Na_2CO_3 solutions were aqueous; brine refers to saturated aqueous NaCl. General procedures for isolation of reaction products are abbreviated as follows: (A) the indicated mixture was thoroughly extracted with the specified organic solvent, which was washed with the indicated sequence of aqueous solutions followed by water or brine, dried ($MgSO_4$ or Na_2SO_4), and removed in vacuo; (B) the mixture was added to water followed by the steps in procedure A.

L(−)-8-Apoisoborneol-7-carboxylic Acid Lactone (16). Optically pure **14**, mp 251.8–252.3 °C, $[\alpha]^{25}$D +6.0° (*c* 0.99) [lit. mp 257–258,[1] 249–250 °C;[36] $[\alpha]^{23}$D +5.9° (*c* 0.90),[1] $[\alpha]^{27}$D +3.2° (*c* 5.0, absolute EtOH)[36]], obtained from D(+)-camphor (Eastman white label), mp 177–178 °C, $[\alpha]^{28}$D +40.3° (c 1.02) [lit. mp 178–179 °C;[1] $[\alpha]^{20}$D + 40.2° (*c* 1.0),[37] $[\alpha]^{20}$D + 47.3° (c 50),[37] $[\alpha]^{23}$D +49.5° (*c* 1.2)[1]], as described earlier,[1] was reduced by $NaBH_4$ and crude **15** was treated with F_3CCO_2H according to the procedures of Corey et al.[14] Lactone **16** was obtained as colorless prisms in 75–80% yield after sublimation at 90–100 °C (10 mm) without prior recrystallization. Resublimed **16** has mp 195–196 °C (lit. 190–196 °C,[14] D isomer 190–191 °C,[38] racemate 192–194 °C[18,19]); $[\alpha]^{25}$D −111.8° (*c* 0.99) [lit.[16a] D isomer $[\alpha]^{19}$D + 116.8° (c 2.1, absolute EtOH)]; IR ($CHCl_3$) 1765 cm^{-1}; ^{1}H NMR τ 5.83 (d, J = 3 Hz, 1 H), 8.92 (s, 3 H), 8.95 (s, 3 H); mass spectrum *m/e* 166 (4), 138 (36), 95 (64), 94 (100).

L(+)-8-Hydroxyisoborneol (17). The procedure was adapted from that of Finch and Vaughan.[18] A solution of 4.99 g (0.0301 mol) of **16**, mp 195–196 °C, in 30 ml of tetrahydrofuran (THF; freshly distilled from $LiAlH_4$) was added dropwise to a stirred slurry of 4.30 g (0.113 mol) of $LiAlH_4$ in 80 ml of dry THF, stirred at reflux for 24 h, and cooled. Excess hydride was destroyed by sequential addition of 4.3 ml of water, 4.3 ml of 15% NaOH, and 12 ml of water. Filtration and isolation B (ether) provided 5.05 g (99%) of crude **17**. Sublimation afforded 4.87 g (96%) of **17** as white rosettes: mp 259.5–260.5 °C (lit.[18,19] racemate 273–276 °C); $[\alpha]^{29}$D +38.4° (*c* 1.08); IR ($CHCl_3$) 3620, 3400 cm^{-1} (broad); ^{1}H NMR τ 6.20 and 6.48 (AB, J = 11 Hz, 2 H), 6.43 (m, 1 H), 6.98 (s, 2 H, exchanges with D_2O), 9.07 (s, 3 H), 9.12 (s, 3 H); mass spectrum *m/e* 152 (6), 109 (16), 108 (100), 95 (67), 94 (33), 93 (30), 67 (19), 55 (22).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.58; H, 10.59. Found (B): C, 70.32; H, 10.51.

L(+)-8-Hydroxyisoborneol-8,8-d_2 (17-d_2) was prepared in an identical manner by using $LiAlD_4$ (Metal Hydrides, Inc.) as the reductant. Diol **17**-d_2 has mp 250.0–250.3 °C; IR ($CHCl_3$) 3620, 3400 (broad), 2190, 2095 cm^{-1}; ^{1}H NMR like that of **17** without the τ 6.20 and 6.48 AB quartet; mass spectrum *m/e* 154 (5), 153 (5), 110 (30), 109 (93), 108 (22), 95 (100), 94 (58), 93 (19), 69 (21), 67 (15), 55 (22).

L(−)-2,8-Epoxybornane (30). A. From Diol 17. A solution of 80 mg (0.46 mmol) of **17**, mp 259.5–260.5 °C, and 154 mg (0.807 mmol) of TsCl, mp 71–72 °C, in 5 ml of dry pyridine was stirred for 25 h and diluted with 150 ml of 0.5 N HCl and 50 ml of pentane. Isolation A (pentane) left 60 mg (86%) of **30** as an oil. Fractional sublimation afforded 50 mg (72%) of pure **30** as white rosettes: mp 135–136 °C (lit. racemate 164–167,[18] 172–174 °C[19]); $[\alpha]^{23}$D −22.0° (*c* 1.10); IR (CCl_4) 1045, 1005 cm^{-1}; ^{1}H NMR (CCl_4) τ 6.28 and 6.52 (AB, J = 8 Hz, 2 H), 6.32 (d, J = 3 Hz, 1 H), 9.03 (s, 3 H), 9.13 (s, 3 H).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found (B): C, 79.00; H, 10.54.

B. From Keto Tosylate 26. A solution of 114 mg (0.370 mmol) of **26**, mp 109–110 °C (see below), in 25 ml of THF was treated with 14.2 mg (3.80 mmol) of $LiAlH_4$ and refluxed for 12 h. Excess hydride was destroyed by dropwise addition of water followed by 5 ml of concentrated NaOH, and isolation A (ether) followed by fractional sublimation afforded 47 mg (82%) of **30**, mp 135–136 °C, identical with the sample described above.

L(−)-8-Hydroxycamphor *p*-Toluenesulfonate (26). A cold (0 °C) solution of 63 mg (0.38 mmol) of **25**, mp 230–233 °C (preparation described below), in 1 ml of dry pyridine was treated with 76 mg (0.39 mmol) of TsCl and stirred at 0 °C for 2 h and at ca. 23 °C for 0.5 h. Isolation B (ether; 5% $NaHCO_3$ and 1% HCl washing) afforded 117 mg (97%) of **26** as a yellow oil. Recrystallization from ether–hexane yielded 96 mg (80%) of pure **26** as colorless needles: mp 109–110 °C (lit.[19] racemate 73–74 °C); $[\alpha]^{23}$D −69.7° (*c* 0.68); IR ($CHCl_3$) 1733 cm^{-1}; ^{1}H NMR τ 2.27 and 2.68 (A_2B_2, J_{AB} = 8 Hz, 4 H), 6.30 (s, 2 H), 7.57 (s, 3 H), 8.97 (s, 3 H), 9.13 (s, 3 H).

Anal. Calcd for $C_{17}H_{22}O_4S$: C, 63.32; H, 6.87; S, 9.94. Found (B): C, 63.51; H, 6.64; S, 9.86.

L(+)-8-Hydroxyisoborneol 8-Benzoate (19). A solution of 4.34 g (0.0310 mol) of BzCl (Eastman white label) in 15 ml of PhH (distilled from P_2O_5) was added dropwise to a stirred solution of 4.80 g (0.0282 mol) of **17**, mp 259.5–260.5 °C, in 2.68 g (0.0338 mol) of pyridine (distilled from BaO) and 250 ml of PhH. The stirred solution was heated under reflux for 47 h (pyridine hydrochloride precipitated), cooled, and washed sequentially with brine, 10% $NaHCO_3$, and brine. Each aqueous wash was extracted with ether, and the combined organic phases were dried (Na_2SO_4) and evaporated in vacuo to afford 8.37 g of an oily mixture of esters which was chromatographed on Baker silica gel (60–200 mesh) using cyclohexane–ether mixtures.

The 13:1 cyclohexane–ether fractions afforded 1.68 g (16%) of **20** as a semisolid, the ^{1}H NMR spectrum of which was identical with that of a purified sample. A portion was recrystallized from pentane to afford pure **dibenzoate 20** as colorless prisms: mp 71.5–72.0 °C; $[\alpha]^{24}$D +28.5° (c 1.10); IR ($CHCl_3$) 1715 cm^{-1} (broad); ^{1}H NMR τ 1.95–2.23 and 2.58–2.97 (m, 10 H), 5.07 (t, J = 5 Hz, 1 H), 5.26 and 5.65 (AB, J = 11.5 Hz, 2 H), 8.88 (s, 3 H), 8.91 (s, 3 H); mass spectrum *m/e* 136 (9), 109 (23), 105 (100), 77 (67).

Anal. Calcd for $C_{24}H_{26}O_4$: C, 76.17; H, 6.92. Found (S): C, 76.31; H, 6.84.

The 5:1 and 4:1 cyclohexane–ether fractions afforded 6.61 g (85%) of a mixture of **19** and **21**, mp 90–94 °C, the former preponderant [ca. 11:1 estimated from the result of the oxidation described below or from integration of the 2-H resonances at τ 5.20 (**21**) and 6.37 (**19**) in the spectrum of the corresponding d_2 sample]. Recrystallization of an early fraction from ether–pentane afforded an analytical sample of **19** as white rosettes: mp 100.2–100.8 °C; $[\alpha]^{27}$D +16.8° (*c* 1.00); IR ($CHCl_3$) 3610, 3500 (broad), 1715 cm^{-1}; ^{1}H NMR τ 2.03–2.20 and 2.57–2.88 (m, 5 H), 5.28 and 5.78 (AB, J = 11.5 Hz, 2 H), 6.37 (m, 1 H), 8.98 (s, 3 H), 8.98 (s, 3 H); mass spectrum *m/e* 152 (35), 109 (24), 108 (100), 105 (73), 95 (28), 93 (27), 77 (32).

Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found (B): C, 74.24; H, 8.14.

Reaction of 5.16 g (0.0307 mol) of diol **17** in PhH with 5.76 g (0.0313 mol) of mesitoyl chloride,[39] bp 65–67 °C (1.5 mm), and 3.20 ml (0.0412 mol) of pyridine by the same procedure at ca. 23 °C produced a mixture of the corresponding mesitoyl esters, chromatography of which afforded 1.57 g (11%) of the **2,8-dimesitoate** as an oil, 1.41 g (15%) of a nearly 50:50 mixture of the 2- and 8-monomesitoates, and 4.46 g

(48%) of the **8-monomesitoate.** Recrystallization of the latter from ether–pentane afforded colorless needles: mp 103–105 °C; $[\alpha]^{28}D$ +11.5° (c 1.00); IR ($CHCl_3$) 3630, 3500 (broad), 1720 cm^{-1}; ^1H NMR τ 3.18 (s, 2 H), 5.13 and 5.82 (AB, J = 11.5 Hz, 2 H), 6.35 (m, 1 H), 7.72 (s, 9 H), 9.03 (s, 6 H); mass spectrum *m/e* 147 (79), 119 (32), 108 (50), 95 (23), 93 (36), 91 (49), 84 (49), 54 (45), 41 (100).

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.90; H, 8.93. Found (B): C, 75.88; H, 8.58.

L(+)-8-Hydroxyisoborneol 8-Benzoate-*8,8-d*$_2$ (19-*d*$_2$) was prepared in an identical manner from **17**-d_2, and has mp 100.0–100.8 °C; IR ($CHCl_3$) 3610, 3500 (broad), 2150, 2050, 1715 cm^{-1}; ^1H NMR like that of **19** without the τ 5.28 and 5.78 AB quartet; mass spectrum *m/e* 154 (50), 110 (45), 109 (100), 105 (78), 95 (46), 77 (51).

L(−)-8-Benzoyloxycamphor (24). A cold (4 °C) solution of 6.44 g (0.0234 mol) of mixed hydroxy esters **19** and **21** (chromatographed) in 500 ml of Me_2CO (distilled from $KMnO_4$) was treated with 11.7 ml (0.0466 molar equiv of Cr^{VI}) of Jones reagent[40] (a solution of 2.68 g of CrO_3 in 2.30 ml of concentrated H_2SO_4 diluted to 10 ml with water) in one portion with vigorous stirring. The mixture was brought to ca. 23 °C over 3 h, neutralized with 1% NaOH, concentrated to 150 ml, and diluted with 1.6 l. of brine. Isolation A (ether; 1% NaOH washing) afforded 5.78 g (91%) of **24.** Recrystallization from ether–pentane produced pure **24** as white rosettes: mp 102.8–103.5 °C; $[\alpha]^{26}D$ −21.3° (*c* 0.94); IR ($CHCl_3$) 1740, 1720 cm^{-1}; ^1H NMR τ 2.07–2.23 and 2.53–2.87 (m, 5 H), 5.97 (s, 2 H, broad), 8.87 (s, 3 H), 8.98 (s, 3 H); mass spectrum *m/e* 272 (5), 167 (9), 122 (6), 107 (8), 105 (100), 77 (15).

Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.98; H, 7.39. Found (B): C, 75.18; H, 7.38.

The basic extract was acidified to pH 1 with concentrated HCl. Isolation A (ether) afforded 0.513 g (8%) of **8-apoisoborneol-7-carboxylic acid benzoate (29),** mp 98–99 °C. Recrystallization from pentane produced pure **29** as white plates: mp 197.5–198.0 °C; $[\alpha]^{28}D$ +41.7° (*c* 0.96); IR ($CHCl_3$) 3500, 3100 (broad), 1760, 1680 cm^{-1}; ^1H NMR τ −0.67 (broad s, 1 H), 2.17–2.37 and 2.65–3.00 (m, 5 H), 5.21 (m, 1 H), 8.77 (s, 3 H), 8.80 (s, 3 H); mass spectrum *m/e* 122 (100), 105 (100), 77 (76), 51 (38).

Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found (S): C, 71.19; H, 6.81.

Similar oxidation of a mixture of the corresponding monomesitoic esters afforded 91% of **L-8-mesitoyloxycamphor** as an oil, evaporative distillation of which (bath temperature 150 °C, 0.05 mm) produced the analytical sample as a clear oil: IR ($CHCl_3$) 1745, 1725 cm^{-1}; ^1H NMR τ 3.25 (s, 2 H), 5.98 (s, 2 H), 7.75 (s, 9 H), 8.92 (s, 3 H), 9.05 (s, 3 H); mass spectrum *m/e* 147 (100), 119 (41), 91 (62), 55 (52), 41 (51).

Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.33. Found (B): C, 76.33; H, 8.34.

The basic extract from this oxidation afforded 9% of **L-8-apoisoborneol-7-carboxylic acid mesitoate,** recrystallization of which from pentane produced colorless plates of the pure acid: mp 175.5–176.0 °C; IR ($CHCl_3$) 3520, 3200 (broad), 1715 cm^{-1} (broad); ^1H NMR τ 0.23 (broad s, 1 H), 3.39 (s, 2 H), 5.21 (m, 1 H), 7.83 (s, 9 H), 8.88 (s, 3 H), 9.00 (s, 3 H); mass spectrum *m/e* 95 (22), 94 (35), 55 (22), 43 (100).

Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found (S): C, 72.59; H, 7.90.

L(−)-8-Benzoyloxycamphor-*8,8-d*$_2$ (24-*d*$_2$) was prepared identically from **19**-d_2, and has mp 234.0–235.0 °C; IR ($CHCl_3$) 2200, 1740, 1720 cm^{-1}; ^1H NMR like that of **24** without the τ 5.97 singlet; mass spectrum *m/e* 274 (11), 169 (23), 124 (17), 109 (26), 105 (100), 77 (38).

L(+)-8-Hydroxyisoborneol 8-Triphenylmethyl Ether (18). A solution of 226 mg (1.33 mmol) of **17,** mp 261–262 °C, and 395 mg (1.43 mmol) of Ph_3CCl, mp 113–115 °C, in 2 ml of dry pyridine was warmed on a steam bath for 0.5 h and held at ca. 23 °C for 12 h. Isolation B (ether) afforded 498 mg (91%) of crude **18** as a yellow gum. Recrystallization from ether–hexane produced 469 mg (85%) of pure **18** as colorless crystals: mp 154–155 °C; $[\alpha]^{23}D$ +36.8° (*c* 1.12); IR ($CHCl_3$) 3665, 3500 cm^{-1}; ^1H NMR τ 2.40–2.95 (m, 15 H), 6.52 and 6.98 (AB, J = 10 Hz, 2 H), 6.62 (m, 1 H), 8.93 (s, 3 H), 9.18 (s, 3 H).

Anal. Calcd for $C_{29}H_{32}O_2$: C, 84.42; H, 7.81. Found (B): C, 84.41; H, 7.89.

L(−)-8-Hydroxycamphor Triphenylmethyl Ether (23). A cold (0 °C) solution of 175 mg (0.425 mmol) of **18,** mp 154–155 °C, in 10 ml of dry pyridine was added to a cold (0 °C) solution of 500 mg of CrO_3 in 5 ml of pyridine.[41] After 9 h at ca. 23 °C, isolation B (ether) afforded 158 mg (78%) of a yellow gum. Recrystallization from ether–hexane produced 136 mg (67%) of **23** as colorless crystals: mp 124–125 °C; $[\alpha]^{23}D$ −21.3° (c 0.84); IR ($CHCl_3$) 1730 cm^{-1}; ^1H NMR τ 2.50–2.90 (m, 15 H), 7.12 and 7.32 (AB, J = 10 Hz, 2 H), 8.87 (s, 3 H), 9.25 (s, 3 H).

Anal. Calcd for $C_{29}H_{30}O_2$: C, 84.81; H, 7.36. Found (B): C, 84.56; H, 7.39.

L(−)-8-Hydroxycamphor (25). A. From Benzoate 24. A solution of 5.77 g (0.0209 mol) of **24,** mp 102.8–103.5 °C, in 250 ml of 10% methanolic KOH was heated at reflux for 30 h, cooled, concentrated to 150 ml, and diluted with brine. Isolation A (ether) left 3.40 g (97%) of **25** as a white solid. Recrystallization from cyclohexane–ether produced 3.08 g (88%) of **25** as white needles: mp 233–234 °C (lit. D isomer 233–234 °C,[38b] racemate 232–234 °C[18]); $[\alpha]^{28}D$ −24.9° (*c* 1.07), $[\alpha]^{26}D$ −32.6° (c 3.00, absolute EtOH) [lit.[38b] D isomer $[\alpha]^{15}D$ +40.7° (c 3.07, absolute EtOH)]; IR ($CHCl_3$) 3620, 3450, 1750 cm^{-1}; ^1H NMR τ 6.67 (broad s, 2 H), 7.70 (s, 1 H, exchanges with D_2O), 8.95 (s, 3 H), 9.11 (s, 3 H); mass spectrum *m/e* 168 (2), 108 (100), 95 (34), 93 (63), 67 (41), 55 (42).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found (S): C, 71.13; H, 9.83.

B. From Trityl Ether 23. A solution of 105 mg (0.612 mmol) of **23,** mp 124–125 °C, in 25 ml of saturated methanolic HCl was stirred for 6 h. Isolation B (ether; 5% $NaHCO_3$ washing) afforded 38 mg of crude **25,** mp 184–193 °C. Recrystallization from hexane produced 31 mg (93%) of **25** as colorless crystals, mp 230–233 °C, identical (IR, ^1H NMR) with the product from procedure A.

L(−)-8-Hydroxycamphor-*8,8-d*$_2$ (25-*d*$_2$) was prepared in an identical manner from **24**-d_2. Ketol **25**-d_2 has mp 233.0–234.0 °C; IR ($CHCl_3$) 3620, 3450, 2170, 2070, 1750 cm^{-1}; ^1H NMR like that of **25** without the τ 6.67 singlet; mass spectrum *m/e* 170 (5), 109 (100), 95 (60), 94 (47), 69 (22), 67 (23), 55 (20).

L(−)-8-Bromocamphor (27). The procedure is modified from that of Finch and Vaughan.[18] To an ice-cold stirred solution of 2.21 g (0.0135 mol) of **25,** mp 233–234 °C, in 10 ml of PhBr was added 2.0 ml (0.0169 mol) of quinoline (distilled from Zn dust) followed by 1.00 ml (0.0150 mol) of PBr_3 (Eastman White Label). After 30 min the ice bath was removed and the yellowish mixture was heated at 130–140 °C for 24 h, cooled, diluted with 25 ml of ether followed by 20 ml of 5% HCl, stirred for 30 min, and diluted with ether. Isolation A (ether) left a residual PhBr solution which was chromatographed through a 2.2 × 65 cm column of Baker silica gel (60–200 mesh) with cyclohexane–ether mixtures to afford 2.20 g (73%) of **27,** mp 80–81 °C. Recrystallization from pentane produced pure **27** as colorless needles: mp 84.5–85.0 °C (lit. 121.5–122.5 °C,[14] racemate 120–122 °C,[18] D isomer 83–85 °C[25]);[23] $[\alpha]^{26}D$ −72.5° (c 0.81) [lit. $[\alpha]^{26}D$ −95° (solvent and concentration not reported),[14] D isomer $[\alpha]D$ +76.7° (c 4.08)[25]];[23] IR ($CHCl_3$) 1745 cm^{-1}; ^1H NMR τ 6.90 (broad s, 2 H), 8.87 (s, 3 H), 9.08 (s, 3 H); mass spectrum *m/e* 151 (2), 109 (19), 108 (28), 107 (23), 95 (11), 93 (17), 91 (12), 81 (31), 67 (42), 41 (100).

Anal. Calcd for $C_{10}H_{15}BrO$: C, 51.96; H, 6.54. Found (S): C, 51.98; H, 6.56.

L(−)-8-Bromocamphor-*8,8-d*$_2$ (27-*d*$_2$) was prepared in an identical manner from **25**-d_2, and has mp 83.8–84.3 °C; IR ($CHCl_3$) 1745 cm^{-1}; ^1H NMR like that of **27** without the τ 6.90 singlet; mass spectrum *m/e* 153 (2), 109 (32), 108 (10), 95 (15), 93 (9), 81 (24), 69 (35), 41 (100).

L(−)-Camphor (31). The procedure was adapted from an analogous one of Kuivila et al.[21] To 800 mg (19.0 mmol) of $LiAlH_4$ in 50 ml of peroxide-free ether was added in one portion 15.0 g (46.2 mmol) of $(n\text{-}Bu)_3SnCl$ (Aldrich), and the mixture was stirred at reflux for 4 h, diluted with ether and 100 ml of cold saturated potassium sodium tartrate, and extracted with ether which was washed with brine, dried ($MgSO_4$), and removed in vacuo. The residual liquid was distilled at 76–78 °C (0.5 mm) [lit.[21a] 81 °C (0.9 mm)] to afford 8.12 g (60%) of $(n\text{-}Bu)_3SnH$. A solution of 4.50 g (0.0154 mol) of this hydride in 2 ml of ether was added with stirring to an ether solution of 2.84 g (0.0124 mol) of **27,** mp 84.5–85.0 °C, and the solution was stirred in the dark at ca. 23 °C for 24 h, diluted with pentane, washed with brine, dried ($MgSO_4$), and evaporated. Sublimation at 100 °C (752 mm) afforded 2.00 g (106%) of crude camphor, mp 167–172 °C, which was filtered through a 1.4 × 53 cm column of Woelm grade I Al_2O_3 with pentane to yield 1.66 g (87%) of L-camphor, mp 174–176 °C. A small portion was resublimed to afford a sample with mp 176.9–177.5 °C; $[\alpha]^{28}D$ −41.1° (c 1.04) [lit. mp 177–178 °C;[42] $[\alpha]^{25}D$ −42.0° (c 0.12, absolute EtOH);[42] $[\alpha]^{32}D$ −44.8° (c 1.82[17]]; IR ($CHCl_3$) 1740 cm^{-1}; ^1H NMR τ 9.04 (s, CH_3-9), 9.09 (s, CH_3-10), 9.17 (s, CH_3-8);[24,27] mass spectrum (v) *m/e* 152 (27), 137 (4), 109 (31), 108 (50), 95 (100), 81 (26), 69 (41), 55 (30), 41 (51).

L(−)-Camphor-*8,8,8-d*$_3$ (31-*d*$_3$) was prepared from **27**-d_2 in an identical manner by using $LiAlD_4$ for reduction of $(n\text{-}Bu)_3SnCl$. The camphor-d_3 has mp 176.5–177.0 °C; IR ($CHCl_3$) 1740 cm^{-1}; ^1H NMR τ 9.04 (s, 3 H), 9.09 (s, 3 H); mass spectrum (v) *m/e* 155 (50), 140 (4),

137 (2), 112 (37), 111 (83), 98 (100), 95 (37), 81 (41), 69 (69), 58 (18), 55 (19), 44 (17), 41 (70).

Comparison of the mass spectrum of L-camphor-*8,8,8-d*$_3$ with that of D-camphor in the *m/e* 151–158 region indicated that the former contained 97.5% of the d_3 species, 2.5% of the d_2 species, and negligible amounts of d_1 and d_0 species, ±0.5% (average of 17 scans of each spectrum).[43]

Reduction of D-9-bromocamphor by tri-*n*-butyltin hydride[26] was carried out by the same procedure using 285 mg (1.23 mmol) of 9-bromocamphor, mp 93–95 °C,[1] and 657 mg (2.26 mmol) of the distilled hydride to afford 131 mg (70%) of crude (once sublimed) D-camphor, mp 161–167 °C.

L(+)-Camphorquinone-*8,8,8-d*$_3$. The procedure was identical with that described for preparation of the D(−)-protio analogue.[1] The diketone-d_3 has mp 198–199 °C (o); IR ($CHCl_3$) 1770, 1760 cm^{-1}; ^{1}H NMR τ 7.38 (d, J = 4.5 Hz, 1 H), 8.90 (s, CH_3-10), 8.93 (s, CH_3-9), no resonance at 9.07[1] (CH_3-8);[27] mass spectrum *m/e* 169 (6), 141 (13), 126 (7), 113 (9), 98 (98), 86 (88), 69 (100).

L(−)-Camphoric Acid-*8,8,8-d*$_3$. The procedure was identical with that described for preparation of the D-(+)-protio analogue.[1] The deuterated acid has mp 187–188 °C (o); IR (KBr) 2900 (broad), 1695 cm^{-1} (broad); ^{1}H NMR (CD_3COCD_3) τ 8.71 (s, CH_3-9), 8.75 (s, CH_3-10), no resonance at 9.12[1] (CH_3-8); mass spectrum *m/e* 157 (30), 139 (40), 112 (40), 111 (44), 71 (86), 70 (66), 69 (62), 41 (100).

D(−)-α-Bromocamphoric Anhydride (1). The procedure is modified from that of Meyer, Lobo, and McCarty.[1] A solution of 0.109 g (6.87 mmol) of Br_2 in 2.0 ml of CCl_4 was treated with 1.85 g (6.87 mmol) of PBr_3 (Eastman Yellow Label, freshly distilled, bp 167–168 °C) in one portion. After 10 min, 651 mg (3.26 mol) of camphoric acid [Eastman White Label, mp 186–187 °C (o)] was added and the mixture was heated at 70–75 °C for 4.5 h to afford a clear solution which was cooled to 60 °C, treated with 0.610 g (3.81 mmol) of Br_2 in one portion, and reheated at 70–75 °C for 7.5 h. The dark red solution was added to 25 g of ice, and the resulting suspension was stirred for 30 min. Isolation B (ether) afforded 773 mg (90%) of an 8.5:1 mixture of the bromo anhydride and camphoric anhydride (determined by integration of the τ 8.60–9.00 region of the ^{1}H NMR spectrum). Recrystallization from $CHCl_3$–ether afforded 537 mg (67%) of 1 as colorless, rhombic crystals: mp 216–217 °C (o) (lit.[1,4] 216 °C); IR ($CHCl_3$) 1820, 1775 cm^{-1}; ^{1}H NMR τ 8.62 (s, CH_3-10), 8.85 (s, CH_3-9), 8.93 (s, CH_3-8); mass spectrum *m/e* 175 (18), 173 (18), 137 (100), 109 (5), 94 (17), 93 (10), 69 (64).

This procedure also converted a 2:2:1 mixture of bromo anhydride, camphoric anhydride, and camphoric acid almost completely to the bromo anhydride.

L(+)-α-Bromocamphoric Anhydride-*8,8,8-d*$_3$ (1-d_3) was prepared from the deuterated camphoric acid in an identical manner, and has mp 216–217 °C (o); IR ($CHCl_3$) 1815, 1770 cm^{-1}; ^{1}H NMR τ 8.62 (s, 3 H), 8.85 (s, 3 H); mass spectrum *m/e* 178 (13), 176 (14), 175 (4), 173 (3), 140 (100), 112 (5), 97 (9), 96 (6), 94 (6), 93 (4), 69 (70).

Rearrangement of L(+)-α-Bromocamphoric Anhydride-*8,8,8-d*$_3$. A 0.525-g (1.97 mmol) sample of anhydride 1-d_3, mp 216–217 °C, was treated with 100 ml of 15% Na_2CO_3 in the manner described by Meyer, Lobo, and McCarty for the D-protio analogue.[1] This afforded 0.069 g (21%) of labeled laurolenic acid: IR ($CHCl_3$) 3300 (broad), 2200, 1700 cm^{-1}; ^{1}H NMR τ 8.41 (broad, 2-CH_3 and 3-CH_3), 8.77 (s, 1-CH_3). Repeated integration (32 scans) of the τ 8.41 and 8.77 resonances showed their relative intensities to be 85.8:14.2 ± 0.5, respectively.

The **L(−) bromo lactone** of this labeled laurolenic acid was prepared as described[29] for the (+)-protio bromo lactone. It has mp 194.0–194.5 °C, identical with that of the corresponding D(+) lactone,[1,29] and shows IR ($CHCl_3$) 2350, 2215, 1790 cm^{-1}; ^{1}H NMR τ 8.38 (s, 2-CH_3), 8.50 (s, 3-CH_3), 8.75 (s, 1-CH_3); mass spectrum (v) *m/e* 128 (62), 112 (100), 96 (4), 94 (3), 93 (4), 91 (2). Repeated integration (64 scans) of the τ 8.38, 8.50, and 8.75 methyl resonances showed their intensity ratio to be 98.9 ± 1.7:71.2 ± 1.7:29.9 ± 1.0.

Comparison of the mass spectrum of the bromo lactone of this deuterated laurolenic acid with that of the bromo lactone of D(+)-laurolenic acid in the *m/e* region 124–130 showed the former to consist of 96.3% of the d_3 species, 2.6% of the d_2 species, 0.8% of the d_1 species, and 0.4% of the d_0 species, ±0.7% (average of 11 scans of each spectrum).[43]

In addition 0.197 g (49%) of **L(+)-camphanic acid-*d*$_3$** was obtained from the rearrangement. This was recrystallized from water to afford colorless needles: mp 200.0–200.3 °C; IR ($CHCl_3$) 3300 (broad), 2210, 1790, 1735 cm^{-1}; ^{1}H NMR τ 7.95 (m), 8.86 (s, CH_3-10), 8.90 (s, CH_3-9), no resonance at 8.98[1] (CH_3-8); mass spectrum *m/e* 173 (20), 155 (16), 141 (40), 112 (74), 86 (100), 43 (74), 41 (80).

Registry No.—**1**, 10333-96-7; **1**-d_3, 60966-74-7; **2**-d_3, 60966-75-8; **3**, 10333-98-9; **12**, 60934-69-2; **13**, 60934-70-5; **14**, 10334-07-3; **15**, 40724-61-6; **16**, 60966-76-9; **17**, 60966-77-0; **17**-d_2, 60934-71-6; **17** 2-monomesitoate, 60934-72-7; **17** 8-monomesitoate, 60934-73-8; **18**, 60966-78-1; **19**, 60934-74-9; **19**-d_2, 60949-92-0; **20**, 60934-75-0; **21**, 60934-76-1; **23**, 60966-79-2; **24**, 60934-77-2; **24**-d_2, 60934-78-3; **25**, 60966-80-5; **25**-d_2, 60966-81-6; **26**, 60966-82-7; **27**, 60966-83-8; **27**-d_2, 61008-83-1; **29**, 60934-79-4; **30**, 60966-84-9; **31**, 464-48-2; **31**-d_3, 60966-85-0; F_3CCO_2H, 76-05-1; $LiAlH_4$, 16853-85-3; $LiAlD_4$, 14128-54-2; L-8-mesitoyloxycamphor, 60934-80-7; L-8-apoisoborneol-7-carboxylic acid mesitoate, 60934-81-8; Ph_3CCl, 76-83-5; D-9-bromocamphor, 10293-09-1; tri-*n*-butyltin hydride, 688-73-3; D-camphor, 464-49-3; L(+)-camphorquinone-*8,8,8-d*$_3$, 61008-84-2; L(−)-camphoric acid-*8,8,8-d*$_3$, 60966-86-1; L(−)-laurolenic acid-d_3 bromo lactone, 10353-25-0.

References and Notes

(1) Part 1: W. L. Meyer, A. P. Lobo, and R. N. McCarty, *J. Org. Chem.*, **32**, 1754 (1967).

(2) (a) Abstracted in part from Ph.D. Dissertations of R.N.M., Indiana University, 1972, and J.H.J., University of Arkansas, 1974; (b) supported in part by National Science Foundation Research Grant GB-1606 and Undergraduate Research Participation Grants GY-53 and GY-4614, and by the University of Arkansas Research Reserve Fund; (c) the mass spectrometer and 90-MHz NMR spectrometer used in this research were obtained with the partial support of National Science Foundation Grants GP-6978 and GP-18291, respectively; (d) NSF Undergraduate Research Participants, 1966 (C.E.C.) and 1968 (A.R.K.); (e) Continental Oil Co. Fellow, 1971–1972.

(3) R. Fittig and L. Woringer, *Justus Liebigs Ann. Chem.*, **227**, 1 (1885).

(4) O. Aschan, *Ber.*, **27**, 2112, 3504 (1894); *Justus Liebigs Ann. Chem.*, **290**, 185 (1896).

(5) G. Stork and R. Breslow, *J. Am. Chem. Soc.*, **75**, 3292 (1953), and references cited therein.

(6) J. P. Bain, A. H. Best, B. L. Hampton, G. A. Hawkins, and L. J. Kitchen, *J. Am. Chem. Soc.*, **72**, 3124 (1950).

(7) Cf. W. R. Vaughan and A. C. Schoenthaler, *J. Am. Chem. Soc.*, **80**, 1956 (1958), and W. R. Vaughan, R. Caple, J. Csapilla, and P. Scheiner, *ibid.*, **87**, 2204 (1965), and references cited therein. It may be noted that decarboxylative elimination in these systems would have required formation of olefins which violated the Bredt rule.

(8) E. Baggiolini, H. P. Hamlow, and K. Schaffner, *J. Am. Chem. Soc.*, **92**, 4906 (1970).

(9) G. Snatzke and K. Schaffner, *Helv. Chim. Acta*, **51**, 987 (1968).

(10) R. B. Woodward, *Pure Appl. Chem.*, **17**, 519 (1968).

(11) The camphor numbering system is retained for the methyl groups of camphoric acid and its anhydride, i.e., C-8 is the methyl which is cis to the carboxyls; cf. structure **1**.

(12) E. J. Corey, S. W. Chow, and R. A. Scherrer, *J. Am. Chem. Soc.*, **79**, 5773 (1957).

(13) P. C. Guha and S. C. Bhattacharyya, *J. Indian Chem. Soc.*, **21**, 271 (1944).

(14) E. J. Corey, M. Ohno, S. W. Chow, and R. A. Scherrer, *J. Am. Chem. Soc.*, **81**, 6305 (1959).

(15) W. L. Meyer and A. P. Lobo, *J. Am. Chem. Soc.*, **88**, 3181 (1966).

(16) Cf. (a) Y. Asahina and M. Ishidate, *Ber.*, **68**, 555 (1935), and (b) Y. Asahina, M. Ishidate, and T. Sano, *ibid.*, **69**, 343 (1936), for results which confirm the structure and configuration of the enantiomeric D-(+)-lactone. That the rearrangement product is indeed the (−) form is shown by the present work.[17]

(17) Subsequent to the completion of our work G. L. Hodgson, D. F. MacSweeney, R. W. Mills, and T. Money, *J. Chem. Soc., Chem. Commun.*, 235 (1973), reported conversion of this optically active lactone to optically pure L-camphor by the sequence of Rodig and Sysko,[19] and their result also leads to this conclusion.

(18) A. M. T. Finch, Jr., and W. R. Vaughan, *J. Am. Chem. Soc.*, **91**, 1416 (1969).

(19) O. R. Rodig and R. J. Sysko, *J. Org. Chem.*, **36**, 2324 (1971).

(20) R. A. Lewis, O. Korpium, and K. Mislow, *J. Am. Chem. Soc.*, **90**, 4847 (1968).

(21) (a) H. G. Kuivila, *J. Appl. Chem.*, **7**, 366 (1957); (b) H. G. Kuivila and O. F. Beumel, *J. Am. Chem. Soc.*, **80**, 3798 (1958); (c) H. G. Kuivila, L. Menapace, and C. R. Warner, *ibid.*, **84**, 3584 (1962).

(22) W. Herz, C. Melchior, R. N. Mirrington, and P. J. S. Pauwels, *J. Org. Chem.*, **30**, 1873 (1965).

(23) The melting point of our L(−)-8-bromocamphor is 85 °C, whereas Corey et al.[14] report mp 122 °C for this substance. There is also a discrepancy between [α] of our sample and that reported earlier,[14] although the solvent and concentration for the previous measurement were not specified. Despite repeated attempts we have been unable to convert our sample to a higher melting crystalline form. From its spectroscopic properties as well as its method of synthesis and subsequent conversion to optically pure L-camphor and an *8,8,8-d*$_3$ analogue which differs from the known *9,9,9-d*$_3$[1] and *10,1C,10-d*$_3$[24] compounds, there can be no doubt about the structure of our substance. Furthermore, it is enantiomeric with the sample of mp 85 °C prepared by Eck, Mills, and Money,[25] the structure of which was confirmed by x-ray crystallography of the related 8-iodo compound (we are grateful to Professor Money for this information and for comparison of spectral and physical properties of the two samples prior to his publication). Perhaps ref 14 inadvertently noted the melting point of a racemic sample, for which the reported melting point is 122 °C.[18]

(24) G. C. Joshi and E. W. Warnhoff, *J. Org. Chem.*, **37**, 2383 (1972).

(25) C. R. Eck, R. W. Mills, and T. Money, *J. Chem. Soc., Chem. Commun.*, 911

(1973).
(26) Analogous reduction of 9-bromocamphor also proceeds well (the 70% yield reported in the Experimental Section resulted with no effort to optimize conditions), and thus reduction by tri-*n*-butyltin deuteride should be preferable to zinc–acetic acid-*d* for preparation of camphor-9-d_1; cf. K. M. Baker and B. R. Davis, *Tetrahedron*, **24**, 1655 (1968); D. R. Dimmel and W. Y. Fu, *J. Org. Chem.*, **38**, 3782 (1973).
(27) J. D. Connolly and R. McCrindle, *Chem. Ind. (London)*, 379 (1965).
(28) A shorter sequence to 8-perdeuterated derivatives may now be derivable through D(+)-8-bromocamphor, inasmuch as the latter has recently become readily available as a result of the work of Money et al.[25]
(29) W. L. Meyer, A. P. Lobo, and E. T. Marquis, *J. Org. Chem.*, **30**, 181 (1965).
(30) This argument applies, of course, only to a symmetric ion **11**. The observed isotopic distribution *could* result from a mechanism in which C-2–methyl bond breaking and C-3–methyl bond formation are both complete prior to the start of decarboxylation or lactonization (see below), i.e., through an ion formally similar to **11**, provided that the two carboxylates are differently solvated, as could occur if some or all of the decarboxylation begins before solvent reorganization around **11** is complete. There is no evidence to exclude this as a viable alternative to the sequences proposed in the main discussion. Unequal isotope distribution could also result from an ion **11** in which there is preferential intramolecular "solvation" of the cationic C-2 by one of the carboxylates, as could occur if some or all of the decarboxylation begins before reorientation of the two carboxylates of **11** is complete. None of our evidence would distinguish this situation from the β-lactonizations which are discussed, so it is not considered separately here. Finally, unequal isotope distribution could also arise from an ion which in other respects is similar to **11**, but which is specifically monoprotonated at either the α- or γ-carboxylate, but this seems unlikely at pH 11 inasmuch as the second dissociation of the bromo diacid probably has a pK_a of about 6; cf. footnote 39 of ref 1.
(31) The three other stereoisomers of **34/35**, each of which must be examined as a pair of isotopic isomers differing in the location of methyls 8 and 10, are not considered because there is no apparent reasonable mechanism for their formation under these reaction conditions.
(32) Another hypothetical mode of decomposition of lactones **34** and **35** to laurolenic acid would be by [2 + 2] cycloreversion of the β-lactone system, but this is considered improbable because under comparable conditions simple β-lactones hydrolyze rather than expel CO_2 in such a manner. For example, at 100 °C in water *cis*-2-hydroxycyclopentanecarboxylic acid lactone affords no cyclopentene but only hydroxy acids.[33] Thermal cycloreversion of analogous β-lactones is normally observed only at higher temperatures and in the absence of a nucleophilic solvent; cf. ref 34.
(33) W. R. Vaughan, W. F. Cartwright, and B. Henzi, *J. Am. Chem. Soc.*, **94**, 4978 (1972).
(34) T. Rull and G. Ourisson, *Bull. Soc. Chim. Fr.*, 1581 (1958); G. A. Boswell, W. G. Dauben, G. Ourisson, and T. Rull, *ibid.*, 1598 (1958); H. E. Zaugg, "Organic Reactions", Vol. VIII, R. Adams, Ed., Wiley, New York, N.Y., 1954, Chapter 7.
(35) Cf. C. H. DePuy, G. F. Morris, J. S. Smith, and R. J. Smat, *J. Am. Chem. Soc.*, **87**, 2421 (1965).
(36) Y. Asahina and M. Ishidate, *Ber.*, **66**, 1673 (1933); **68**, 947 (1935).
(37) C. F. Poe and E. M. Plein, *J. Phys. Chem.*, **38**, 883 (1934).
(38) (a) T. J. Hasselstrom, *J. Am. Chem. Soc.*, **53**, 1097 (1931); (b) Y. Asahina and M. Ishidate, *Ber.*, **67**, 71 (1934); (c) S. Beckman and H. Geiger, *Chem. Ber.*, **92**, 2411 (1959).
(39) D. M. Bowen, "Organic Syntheses", Collect. Vol. III, E. C. Horning, Ed., Wiley, New York, N.Y., 1967, pp 555–557.
(40) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).
(41) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).
(42) R. B. Woodward, T. P. Kohman, and G. C. Harris, *J. Am. Chem. Soc.*, **63**, 120 (1941).
(43) Cf. K. Biemann, "Mass Spectrometry, Organic Chemical Applications", McGraw-Hill, New York, N.Y., 1962, Chapter 5, for method and assumptions.

A Vanished Substituent Effect Predicted by the Kirkwood–Westheimer Electrostatic Field Model

Charles T. Wang and Edward J. Grubbs*

Department of Chemistry, San Diego State University, San Diego, California 92182

Received June 28, 1976

syn- (**2b**) and *anti-* (**3b**) *cis*-11,12,dichloro-9,10-dihydro-9,10-ethanoanthracene-1-carboxylic acids have been synthesized. Geometric assignments were made on the basis of their ^{13}C chemical shifts along with those of model compounds. The apparent pK_a's of **2b** and 9,10-dihydro-9,10-ethanoanthracene-1-carboxylic acid (**9b**) (previously reported by Stock) in aqueous ethanol are identical within experimental error. This result is predicted by the Kirkwood–Westheimer equation and is a consequence of the angular orientation of the dipole with respect to the site of ionization. The apparent pK_a of **3b** is approximately 0.47 units smaller than that of **9b**. These results are briefly discussed in terms of the Kirkwood–Westheimer electrostatic field model.

The Kirkwood–Westheimer expression[1] for calculating electrostatic effects of dipolar substituents upon acidities of carboxylic acids includes the angular orientation of the dipole with respect to the site of ionization (eq 1).

$$\log \frac{K}{K_0} = \frac{eu \cos \theta}{2.30\, kTR^2 D_E} \qquad (1)$$

That both the sign and magnitude of dipolar substituent effects can be dependent upon the angular disposition of the dipole relative to the carboxylate group has been experimentally verified.[2]

An interesting consequence of this electrostatic model is the prediction that for a dipole oriented perpendicular to a line joining its midpoint to the ionizing proton, the substituent effect should vanish. That is, for $\theta = 90°$, $K = K_0$. We report here a case where the resultant dipole of a vicinal dichloride possesses this geometric characteristic.

Results

Methyl *syn-cis*-11,12-dichloro-9,10-dihydro-9,10-ethano-1-anthroate (**2a**) and the corresponding anti-cis dichloro isomer **3a** were prepared by the cycloaddition of *cis*-1,2-dichloroethene and 1-methyl anthroate (**1**). The isomers were separated by a combination of chromatography and crystallization. Progress in effecting the separation was followed by NMR monitoring of the relative intensities of the C_9 proton signals (peri to CO_2Me), the singlets for which lie downfield (δ 6.12 for **2a** and 5.73 for **3a**) from the remaining nonaromatic protons. The geometric assignments for **2a** and **3a** were made

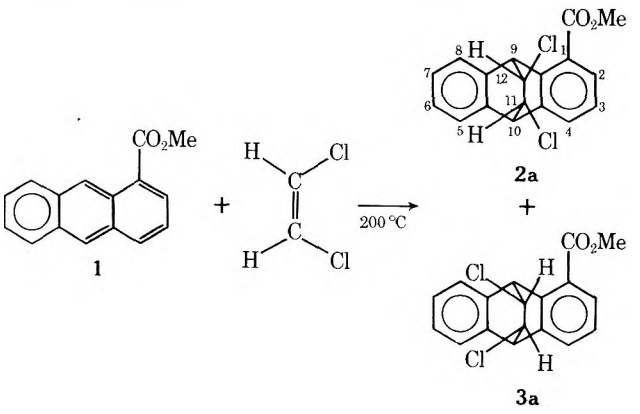


Table I. Apparent pK_a's[5] of Several Bridged Anthracene-1-carboxylic Acids in 50% Aqueous Ethanol at 25 °C

Acid	pK_a
2b	5.94, 5.94
3b	5.48, 5.50
9b[a]	5.96 ± 0.01

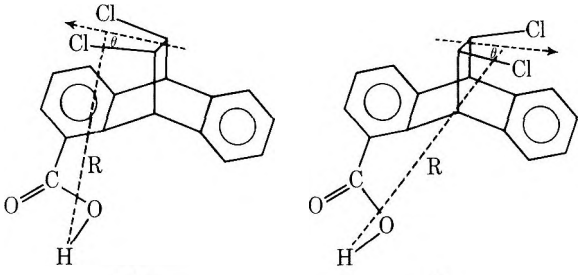
[a] Average of five runs determined potentiometrically in 50% by weight aqueous ethanol.

on the basis of the patterns of ^{13}C chemical shifts observed for the ring carbons.[3] They are consistent with the pK_a's determined for the corresponding acids **2b** and **3b** obtained by hydrolysis of the esters.

The apparent pK_a's for **2b** and **3b** were determined by potentiometric titration in 50% by volume aqueous ethanol at 25 °C. The results are summarized in Table I. Included for comparison is the apparent pK_a for 9,10-ethano-9,10-dihydro-1-anthroic acid (**9b**) reported by Stock.[4]

Discussion

An inspection of the data in Table I reveals the expected increase in acidity for the anti dichloro acid **3b** compared with the unsubstituted acid **9b.** The magnitude of this difference is comparable to the ΔpK_a (0.57) observed for the analogues bearing the carboxylate group at the 2 position.[2a] In the present case the shorter distance separating the site of ionization and the resultant dipole is compensated by a larger acute angle, θ, found in the K–W expression and perhaps by a larger effective dielectric constant. By contrast, the apparent pK_a of the syn-dichloro acid **2b** is, within experimental error, the same as that for the unsubstituted acid **9b.** This vanished substituent effect is predicted by the K–W equation. The results are not accommodated by the classical inductive model. The pertinent structural features of **2b** and **3b** are illustrated. The distances R and the angles θ were calculated assuming the geometry of ethanoanthracene adopted by Arbusov and Vereshchagen.[6,7] The distances and angles are with reference to a resultant dipole which bisects the C_{11}–C_{12} bond and lies in the plane containing the two chlorines.[8] For purposes of K–W calculations, the magnitude of the resultant dipole was estimated. Since two carbon–chlorine dipoles in close proximity are not electrically independent of one another, a vector summation of two single C–Cl bond moments cannot provide a reliable resultant.[9] Consequently the resultant dipole formed from the two C–Cl bonds in **2b** and **3b** was calculated from dipole moments experimentally determined[2a] for 9,10-dihydro-9,10-ethanoanthracene (**8**) and *cis*-11,12-dichloro-9,10-dihydro-9,10-ethanoanthracene (**6**). The dipole moment found for **8** is 0.92 D; that for **6** is 2.92 D. The measured dipole moment of **6** can be attributed to two contributing dipoles. The two carbon–chlorine dipoles (forming the "resultant" dipole whose value is sought) are assumed to lie in a plane 60° off the axis which bisects the C_{11}–C_{12} bond and bisects a line joining C_9 and C_{10}. The dipole moment of **8** is collinear with this same axis with the negative end in the direction of the region flanked by the aromatic rings. Using these vector quantities, the "resultant" moment formed by the two C–Cl bonds is calculated to be 3.27 D. Table II lists the calculated values for R's and θ's, as well as for D_E[10] and log K/K_0. The Tanford modification[11] was adopted with respect to placement of charges and dipoles relative to the cavity surface. The dielectric constant of the solvent (50% by weight aqueous ethanol) is 49.[12]



2b **3b**

Thus the K–W expression predicts a vanished substituent effect for **2b.**[13] This is the direct result of the value of θ, which is approximately 90° within the limits of uncertainty of the structural parameters used in its estimation.[13] The calculated ΔpK_a for the anti acid **3b** is, at best, in fair agreement with the experimental value when the Tanford ellipse cavity is employed. The Tanford spherical model leads to a major underestimation of D_E.

Experimental Section[14]

Anthraquinone-1-carboxylic Acid. Using the procedure developed by Coulson,[15] freshly recrystallized benzanthrone (20.0 g, 0.087 mol) was oxidized with 82 g of chromium trioxide. The product was obtained in 69% yield as a beige-colored solid, mp 298–300.5 °C (lit.[4] mp 292–293 °C).

1-Anthroic acid was prepared by the zinc reduction of anthraquinone-1-carboxylic acid as described by Stock.[4] Best results were obtained when the zinc was activated with 6 N HCl immediately prior to use. The product was obtained in 73% yield, mp 248–250 °C (lit.[4] mp 249 °C).

1-Methyl anthroate (1) was prepared in 93% yield by esterification with ethereal diazomethane. The ester was obtained as yellow plates, mp 100.5–103.5 °C (lit.[16] mp 104 °C), and was used without further purification in the reactions with *cis*-dichloroethylene.

Methyl *syn*- and *anti*-*cis*-11,12-Dichloro-9,10-dihydro-9,10-ethano-1-anthroates (2a and 3a). A sample of 5.0 g (0.021 mol) of 1-methyl anthroate, 0.1 g of 2,6-di-*tert*-butylphenol, 6.8 ml of freshly distilled *cis*-1,2-dichloroethylene, and 20 ml of toluene were combined in a heavy-walled, 25 × 200 mm tube. The mixture was degassed and the tube sealed. The tube was heated in a steel bomb at 194–203 °C for 72 h. The tube was opened and the mixture examined by NMR. The spectrum showed that over 90% of the methyl anthroate had reacted. Separation of the products and starting ester was performed by liquid chromatography in a 25 × 300 mm column packed with 100–200 mesh Florisil in hexane. The esters were eluted in the following order with partial resolution: methyl anthroate (~4/1 hexane–benzene), syn ester **2a** (~1/1 hexane–benzene), and anti ester **3a** (~pure benzene). Recrystallizations of appropriate fractions from CCl_4 afforded **2a** as a white solid, mp 156–158 °C, and **3a** as a white solid, mp 178–179 °C. Yields from several cycloadditions averaged in the range of 15–20% for each pure isomer.

The mass spectra of both isomers show a parent peak at *m/e* 332 and an intense peak at *m/e* 301 ($M^+ - OCH_3$). The infrared spectra (KBr disks) are very similar. They show the expected carbonyl stretch at approximately 1715 cm^{-1}. Small differences are observable in the 600–800-cm^{-1} region. A distinct difference in NMR spectra (taken in CCl_4) is observed. The C-9 proton of the syn (**2a**) ester appears at 6.12 ppm. The C-9 proton of the anti (**3a**) ester appears at 5.73 ppm. A similar deshielding of C-9 protons in a number of 1-substituted anthracenes has been described.[17]

Table II. Parameters and Calculated Values of Log K/K_H for *syn*- (2b) and *anti*- (3b) *cis*-11,12-dichloro-9,10-dihydro-9,10-ethano-1-carboxylic Acids

	Parameters			Tanford sphere		Tanford ellipse		Measured
	R, Å	μ, D	θ	D_E	Log K/K_H	D_E	Log K/K_H	Log K_X/K_H
2b	5.44	3.27	89	4.24	0.01	7.33	0.01	0.02 ± 0.02
3b	6.01	3.27	46.4	4.50	0.70	8.64	0.36	0.47 ± 0.02

Anal. Calcd for $C_{18}H_{14}Cl_2O_2$: C, 64.88; H, 4.20; Cl, 21.30. Found for **2a**: C, 64.95; H, 4.25; Cl, 21.18. For **3a**: C, 64.86; H, 4.28; Cl, 21.56.

***syn-cis*-11,12-Dichloro-9,10-dihydro-9,10-ethano-1-anthroic Acid (2b).** A 1.30-g (3.91 mmol) sample of **2a** was combined with 50 ml of methanolic NaOH (0.55 g NaOH in 50 ml of methanol) and boiled under reflux for 1 h. The mixtue was cooled, diluted to 200 ml with water, and filtered. The filtrate was acidified with 6 N HCl. The white solid was collected, repeatedly washed with water, and dried. The acid was thus obtained in 96.4% yield, mp 266–269 °C. Recrystallization from benzene raised the melting point to 267–270 °C.

The mass spectrum shows the parent ion at *m/e* 318. The infrared spectrum (KBr disk) shows a broad carboxylic acid O–H band centered at 3040 cm^{-1} and a carbonyl at 1680 cm^{-1}. The NMR spectrum (Me_2SO-d_6) shows (in addition to the aromatic protons) two apparent singlets at 4.78 and 6.05 ppm. The former is assigned to the protons at C-10, C-11, and C-12, and the latter to the proton at C-9.

Anal. Calcd for $C_{17}H_{12}Cl_2O_2$: C, 63.95; H, 3.76; Cl, 22.2. Found: C, 64.15; H, 3.88; Cl, 22.0.

***anti-cis*-11,12-Dichloro-9,10-dihydro-9,10-ethano-1-anthroic Acid (3b).** This acid was prepared by hydrolysis of **3a** as described for the syn isomer. The acid was initially obtained in 96% yield as white crystals, mp 251–254.5 °C. Recrystallization from chloroform yielded the pure acid, mp 258–259.5 °C.

The mass spectrum shows the parent ion at *m/e* 318. The infrared spectrum is similar to that of its isomer **2b** with slight differences observable in the fingerprint region. The NMR spectrum of **3b** (Me_2SO-d_6) shows, in addition to the aromatic proton signals, the C-9 proton as a singlet at 5.85 ppm. The peaks for the C-10, C-11, and C-12 protons coincide to give an apparent singlet at 4.73 ppm.

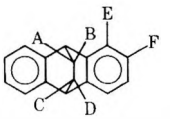
Anal. Calcd for $C_{17}H_{12}Cl_2O_2$: C, 63.95; H, 3.76; Cl, 22.2. Found: C, 63.81; H, 4.00; Cl, 22.3.

Acknowledgments. We wish to express our appreciation to Professor G. E. Maciel and Dr. D. Miiller for their invaluable help in confirming our geometric assignments in the course of their study of the ^{13}C NMR properties of a number of these bridged anthracene derivatives.

Registry No.—**1**, 25308-58-1; **2a**, 60573-54-8; **2b**, 60573-55-9; **3a**, 60618-77-1; **3b**, 60618-78-2; *cis*-1,2-dichloroethylene, 156-59-2.

References and Notes

(1) J. G. Kirkwood and F. H. Westheimer, *J. Chem. Phys.*, **6**, 506 (1938).
(2) See (a) E. J. Grubbs, R. Fitzgerald, R. E. Phillips, and R. Petty, *Tetrahedron*, 935 (1971); (b) C. L. Liotta, W. F. Fisher, E. L. Slighton, and C. L. Harris, *J. Am. Chem. Soc.*, **94**, 2129 (1972); (c) L. M. Stock, *J. Chem. Educ.*, **49**, 400 (1972); (d) A. B. Thigpen, Jr., and R. Fuchs, *J. Org. Chem.*, **34**, 505 (1969); (e) K. Bowden, *Can. J. Chem.*, **41**, 2781 (1963); and references cited therein.
(3) The ^{13}C study was conducted by Professor G. E. Maciel and Dr. D. Miiller at Colorado State University. The chemical shift assignments of **2a**, **3a**, **4**, and **5** were made largely on the basis of derived patterns of additivity relationships among the shifts of compounds **2a–10**, methyl benzoate (**11**), methyl *m*-toluate (**12**), and methyl 3,4-dimethylbenzoate (**13**). A set of shifts for all the above compounds **2a–10** was derived which was entirely self-consistent within an assumed framework of additivity of ^{13}C shifts of the ring carbons. ^{13}C–^1H splitting patterns and selective ^1H decouplings were also employed in making these assignments. The sources for several of these model compounds and a complete discussion of this investigation will be published elsewhere.
(4) R. Golden and L. M. Stock, *J. Am. Chem. Soc.*, **94**, 3080 (1972).
(5) Since Stock's value for the unsubstituted compound **9b** was reported in 50% by weight aqueous ethanol and ours were determined in 50% by volume aqueous ethanol, we repeated the titration of **2b** in 50% by weight aqueous ethanol. The value thus obtained, 5.93, is within the experimental error of that obtained in the 50% by volume aqueous ethanol shown in Table I.
(6) B. A. Arbusov and A. N. Vereshchagin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **No. 6**, 1004 (1964).
(7) The chlorines on carbons 11 and 12 were assumed to form tetrahedral angles with the C_{11}–C_{12} bond and to lie in a plane which forms a 120° angle with the plane of carbons 9, 10, 11, and 12. The bond lengths were taken to be C–Cl (1.77 Å), C_{sp^3}–C_{sp^3} (1.54 Å), C_{sp^3}–C_{sp^2} (1.50 Å), aromatic C–C (1.39 Å), and C_1–C_{17} (carboxylate carbonyl carbon) (1.46 Å). The carboxyl proton was placed at 1.45 Å beyond the carboxyl carbon on an extension of the line joining it to C_1.
(8) The dibenzobicyclo[2.2.2]octadiene ring system is extremely rigid. The degree of molecular readjustment from dipole–dipole interactions (and possibly charge–dipole interactions in the anion) via ring deformation involving motions of C_{11} and C_{12} would appear to be minimal.
(9) See C. P. Smyth, "Dielectric Behavior and Structure", McGraw-Hill, New York, N.Y., 1955, pp 237–254.
(10) The tables given by F. H. Westheimer, W. A. Jones, and R. A. Lad [*J. Chem. Phys.*, **10**, 478 (1942)] were used.
(11) C. Tanford, *J. Am. Chem. Soc.*, **79**, 5348 (1957).
(12) The dielectric constant of 50% by volume aqueous ethanol at 25 °C is 53.8 [see M-L. Le Huérou and C-R. Guérillot, *C. R. Acad. Sci.*, **258**, 2549 (1964)]. The calculation of D_E is insensitive to variations in solvent dielectric constant of this magnitude.
(13) If the dominating effect on the ionization were the C–Cl dipole at C_{12}, its angular orientation could induce a reverse substituent effect (acid weakening). However, an anticipated reversed substituent effect in a related acid (the structural isomer of **2b** possessing the carboxyl group at C_2) was not observed.[2a] A possible reason for this was discussed.
(14) Melting points are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 621 spectrophotometer. Nuclear magnetic resonance spectra were determined with a Varian Model A-60 or JEOL Model JNM-PS-100 spectrometer. The mass spectra were obtained on a Hitachi Perkin-Elmer Model RMU-6E mass spectrometer. The pK_a measurements were made using a Beckman research pH meter equipped with a Beckman No. 39000 glass electrode and a Beckman No. 39071-A3U calomel electrode. Elemental analyses were performed by M-H-W Laboratories, Garden City, Mich.
(15) E. A. Coulson, *J. Chem. Soc.*, 1931 (1930). See also S. Akiyama and M. Nakagawa, *Bull. Chem. Soc. Jpn.*, **33**, 1291 (1960).
(16) S. Akiyama, *Bull. Chem. Soc. Jpn.*, **35**, 1826 (1962).
(17) F. Gobert, S. Combrisson, and N. Platzer, *Tetrahedron*, **30**, 2919 (1974).



2a, A = C = F = H; B = D = Cl; E = CO_2Me
3a, B = D = F = H; A = C = Cl; E = CO_2Me
4, A = C = E = H; B = D = Cl; F = CO_2Me
5, B = D = E = H; A = C = Cl; F = CO_2Me
6, A = C = E = F = H; B = D = Cl
7, A = D = E = F = H; B = C = Cl
8, A–F = H
9a, A–D, F = H; E = CO_2Me
10, A–E = H; F = CO_2Me

Electron Impact Behavior of β-Peroxylactones[1]

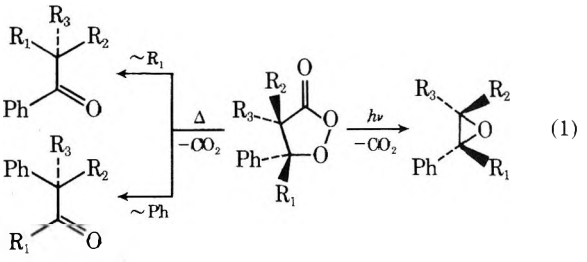
Waldemar Adam[2a] and Robert S.-C. Tsai* [2b]

Department of Chemistry, University of Puerto Rico, Rio Piedras, Puerto Rico 00931, and Research and Development Department, Economic Development Administration, Commonwealth of Puerto Rico, G.P.O. Box 3088, San Juan, Puerto Rico 00936

Received July 20, 1976

Mass spectral study of a series of β-peroxylactones with α-alkyl and β-alkyl or β-phenyl substitution and deuterium labeling was undertaken. By means of metastable ion mass spectra (MIMS), five primary fragmentation processes have been identified, consisting of loss of carbon trioxide, α-lactone, β-alkyl radical, hydroperoxy radical, and carbon dioxide. Except for the β-peroxylactones with β-benzyl substitution, for which the decarboxylation route is the major fragmentation process, the peroxide bond is strengthened on ionization and decarboxylation is significantly suppressed in comparison with photolysis and thermolysis. In all cases studied, employing MIMS, isotopic labeling, and high resolution, the M − CO_2 ions are epoxide-like in structure, as confirmed by their subsequent fragmentations. For example, the β-phenyl migration outweighs the β-alkyl migration. Thus, it is concluded that the electron impact behavior of β-peroxylacetones parallels the photolytic behavior of the compounds. However, in one case the M − CO_2 ion is not the result of a direct decarboxylation, but rather it is produced stepwise by first expelling a carbon monoxide, followed by deoxygenation.

A number of examples have been reported[3] demonstrating a correlation between mass spectral and photochemical behavior of organic compounds. We have observed an unusual energy-dependent decomposition in the thermo- and photodecarboxylation of β-peroxylactones. Thus, while thermolysis[4a] affords predominantly rearrangement ketones (alkyl and phenyl migration), photolysis[4b] leads principally to epoxides (eq 1). It was, therefore, of interest to investigate the



(1)

	1	2	3	4	5	6	7	8
R_1	CH_3	CH_3	CD_3	C_2H_5	*i*-C_3H_7	$C_6H_5CH_2$	Ph	$C_6H_5CH_2$
R_2	H	D	H	H	H	H	CH_3	CH_3
R_3	H	D	H	H	H	H	H	H

electron-impact behavior of β-peroxylactones in order to assess whether the M − CO_2 fragment ion possesses an epoxide-like (photolysis) or a ketone-like (thermolysis) structure. This is particularly relevant since it has been shown[5] that cyclic carbonates, which are structurally isomeric with β-peroxylactones, fragment on electron impact into epoxide-like M − CO_2 ions. We report here our mass spectral study of β-peroxylactones **1–8**, by employing various techniques suitable for a double focusing instrument.

Extensive use of metastable ions has been made since it provides valuable information on ion fragmentation pathways and for ion structure determination.[6] In a decoupled mode operation, a metastable ion not only can be tremendously improved in terms of its intensity, but it also can be continuously scanned to afford either a metastable ion mass spectrum (MIMS) or an ion kinetic energy spectrum (IKES).[7,8] From a MIMS precursors of an ion can be unequivocally identified. Utilization of such metastable transitions, therefore, can provide useful clues for ion structure elucidation. Metastable ion characteristics also show that kinetic energy release in a fragmentation is dependent on the structure of the ion.[9,10]

In addition, the deuterium labeling technique was applied in this study to define the general geometry of the eliminative fragmentations and rearrangement reactions.[11] We also employed high-resolution mass spectrometry to differentiate ions of same nominal mass but different elemental compositions.[12]

Experimental Section

Materials. The β-peroxylactones were prepared according to the published procedures.[13] The deuterated β-peroxylactones **2** and **3** were kindly supplied by Mr. O. Cueto and a complete account of their synthesis and physical and spectral properties is forthcoming.

Spectra. All mass spectra were recorded on a Du Pont 21-492 B double focusing mass spectrometer, equipped with a cooled probe system and MIMS and IKES capabilities. The instrument was operated at 70 eV ionizing electron energy, 2000 eV ion accelerating potential (3.1 kV for high-resolution mass spectrometry), 500 μA ionizing electron emission current, source temperature 20 ± 2 °C, source pressure 1 × 10^{-5} Torr, and analyzer pressure 1 × 10^{-6} Torr.

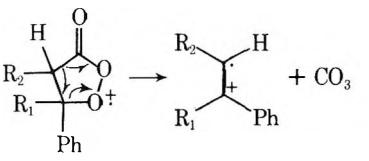
Samples were loaded via a glass capillary tube into the probe and cooled with Freon (R) while being inserted into the ion source. This procedure was followed in order to assure that no thermodecomposition occurred since β-peroxylactones are known to decompose at elevated temperature.[4a]

The IKES and MIMS were recorded on a Hewlett-Packard Model 7001 A X-Y Recorder. The MIMS were recorded by scanning the ion accelerating potential, holding the electric sector voltage constant.

Resolving power as high as 3000 was achieved readily by tuning up the ion source and reducing the β-slit width. Benzaldehyde and *p*-xylene were used as controls in assessing the resolution, showing a doublet at *m/e* 106 (M/AM-2900). For determination of the energy scale in the MIMS, a standard (*n*-decane) was used in the prerun. This exercise was also useful for possible ghost peak identification.

Results and Discussion

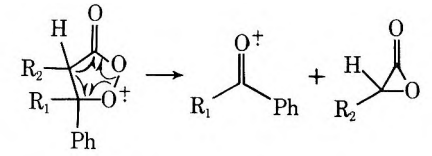
The mass spectra of the β-peroxylactones **1–8** are given in Table I. Except for β-peroxylactone **6**, molecular ions are all present; in some cases such as **2–4** they are abundant. The base peak corresponds to the *m/e* 105 ion ($C_6H_5CO^+$) for all but β-peroxylactone **4**. Contrary to the photolysis and thermolysis, decarboxylation of the molecular ion is greatly decreased. As expected, the fragmentation of the ionized β-peroxylactones in the gas phase is more complex than the decomposition of the neutral molecules in the liquid phase. For example, five major molecular fragmentations have been identified based on the MIMS data (eq 2 and Table II). The effect of substit-

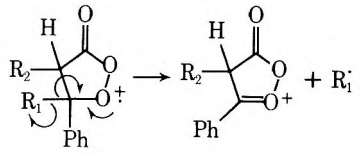


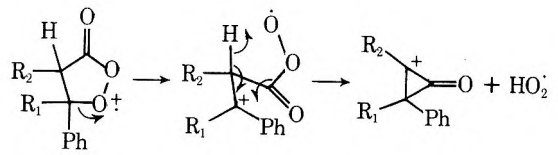
(2a)

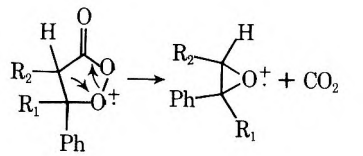
Table I. Ions (*m/e*) and Their Relative Abundances (%) of β-Peroxylactones

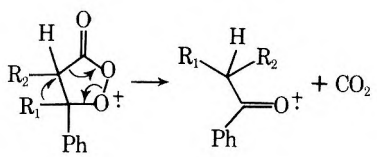
1		2		3		4		5		6		7		8	
m/e	%	*m/e*	%	*m/e*	%	*m/e*	%	*m/e*	%	*m/e*	%	*m/e*	%	*m/e*	%
178	13	180	20	181	25	192	32	206	8	210	20	254	2	268	0.1
163	8	179	6	180	5	163	50	104	15	196	1	210	15	224	16
145	10	178	6	163	14	162	23	163	29	194	0.5	194	4	209	2
134	12	165	14	148	15	148	1	162	57	164	1	182	25	196	0.5
120	28	164	4	137	12	134	3	131	10	163	1	178	1	177	2
119	5	146	11	136	6	132	8	121	8	121	4	163	7	135	14
118	40	145	4	135	4	131	4	120	18	119	12	118	25	108	10
117	13	136	8	134	5	121	15	148	1	108	11	117	25	107	10
106	10	135	4	123	23	117	19	147	2	107	8	116	24	106	13
105	100	121	8	122	6	115	6	146	3	106	10	105	100	105	100
104	5	120	54	121	55	105	34	105	100	105	100	91	15	91	17
103	20	119	25	120	30	92	11	91	85	104	5	77	53	79	13
91	25	118	15	119	10	91	100	78	30	92	6	65	8	78	7
78	15	106	30	118	8	78	23	77	80	91	38	63	5	77	47
77	74	105	100	109	6	77	42	65	12	79	13	51	30	65	4
65	10	104	10	108	45	65	10	51	30	78	10	50	8	63	2
63	7	103	10	106	16	51	25	50	9	77	55	43	5	51	17
51	30	93	20	105	100	39	7	43	90	65	7	39	13	50	5
50	10	92	11	104	5			39	20	63	4			43	2
43	20	91	9	103	13					51	18			39	4
39	15	78	22	95	13					50	7				
		77	88	93	8					43	5				
		65	13	92	7					39	6				
		65	10	91	25										
		63	10	79	13										
		51	35	78	20										
		50	18	77	82										
				66	10										
				65	10										
				51	36										
				50	15										

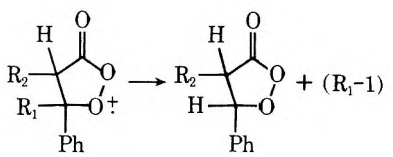

(2b)


(2c)


(2d)


(2e)


(2e′)


(2f)

uents on the fragmentation patterns is summarized in Table III. Apparently, the α-methyl and β-benzyl substituents greatly modify the fragmentation pathways, either by stabilization of the substituents on the product ions or through the availability of a decomposition process requiring low activation energy. The detailed account of each of the five characteristic fragmentations follows.

Loss of Carbon Trioxide (Eq 2a). While direct loss of a CO_3 from $M^{\cdot+}$ has been confirmed by MIMS for β-peroxylactones **2, 3,** and **6,** for the β-peroxylactones **4** and **7** the M − CO_3 fragments arise from an M − CO_2 ion by further loss of an oxygen atom (vide infra). From Table III, the β-benzyl group substantially affects the M − CO_3 ion abundance. The M − CO_3 ion subsequently decomposes via typical mass spectral patterns observed for alkenes, e.g., loss of a neutral alkyl or phenyl radical, as evidenced in the MIMS.

Loss of α-Lactone (Eq 2b). Loss of an α-lactone from $M^{\cdot+}$ is most evident for β-peroxylactone **7**. The driving force lies in the stabilization of the product benzophenone radical cation by the phenyl groups which subsequently decomposes according to its characteristic fragmentation pattern.

Loss of β-Alkyl Radical (Eq 2c). Theoretically, the relative abundance of M − R ion should follow the order of the stability of β-alkyl radical, i.e., $C_6H_5CH_2$ > *i*-Pr > Et > Me. Furthermore, the same β substituents may also kinetically favor reaction pathways such as M → M − CO_2 or M → M − (α-lactone). Consequently, the β-peroxylactones **6–8** show reduced M − R_1 abundance.

The MIMS reveal that M − R_1 ions undergo the subsequent fragmentations illustrated in eq 3. To distinguish between paths a and b (eq 3), the kinetic energy release, as measured from the metastable peak width, was determined for the cations produced in path a and b, and for the phenyl cation which is produced in path d from M − R_1. The kinetic energy release was estimated to be 2.5 times smaller for the phenyl cation than for the cation produced in path a or b. This

Table II. Metastable Ion Mass Spectra (MIMS) of Major Ions of β-Peroxylactones

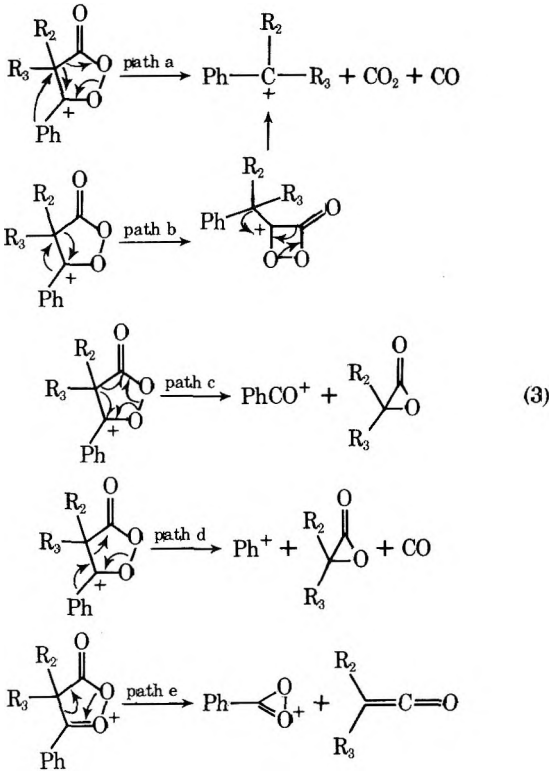
1 (M 178)			2 (M 180)			3 (M 181)			4 (M 192)			5 (M 206)			6 (M 254)			7 (M 254)			8 (M 268)		
m/e	P[a]	NL[a]	*m/e*	P[a]	NL[a]	*m/e*	P[a]	NL[a]	*m/e*	P[a]	NL[a]	*m/e*	P[a]	NL[a]	*m/e*	P[a]	NL[a]	*m/e*	P[a]	NL[a]	*m/e*	P[a]	NL[a]
163	178	CH_3	165	180	CH_3	163	181	CD_3	175	192	OH	163	206	C_3H_7	210	254[d]	CO_2	210	254[d]	CO_2	224	268	CO_2
145	178	O_2H	146	180	O_2D	148	181	O_2H	164	192	CO	162[c]	206	C_3H_8	196	254[d]	$C_2H_2O_2$	194	210	O	209	224	CH_3
134	178[d]	CO_2	136	180[d]	CO_2	137	181[d]	CO_2	159	192	O_2H	162[c]	206	CO_2	194	254[d]	CO_3	182	254	$C_3H_4O_2$	196	224	C_2H_4
120	178[d]	$C_2H_2O_2$	120	180[d]	$C_2D_2O_2$	123	181	$C_2H_2O_2$	163	192	C_2H_5	148	206[d]	$C_2H_2O_2$	181	210[d]	CHO	117	210	C_6H_5O	181	209	CO
118	178[d]	CO_3	120	180	CO_3	121	181	CO_3	162	192	C_2H_6	146	206[d]	CO_3	163	254[d]	C_7H_7		194	C_6H_5		224	C_2H_3O
117	145	CO					163	C_2H_2O	134	192[d]	$C_2H_2O_2$	147	162	CH_3	162	254	C_7H_8	116	117	H	178	268	C_7H_6
105	120	CH_3	105	120	CH_3	120	148	CO	148	164	O	131	147	O	121	162	C_2HO	115	194	C_6H_7	177	268	C_7H_7
	134	CHO		134	C_2H_3D	108	137	CHO	147	164	OH	121	163	C_2H_2O	120	210	C_7H_6	105	182	C_6H_5	135	224	C_7H_5
	134	C_2H_5		136	$C_2H_3D_2$	105	121	CD_2		175	CO	120	162	C_3H_6	119	210	C_7H_7		210	C_8H_9		240	C_7H_5O
	178	*e*		146	C_3H_3D		123	CD_3		148	H	119	146	C_3H_3	105	120	CH_3		210	C_7H_5O		268	*e*
103	118	CH_3		165	$C_2D_2O_2$		137	$C_2H_2D_3$		192	*e*	105	162	C_2HO_2		121	O	91	117	C_2H_2	134	128	CO_2
	105	H_2		180	*e*		147	C_2DO	132	148	O		162	C_4H_9		145	C_2O	77	105	CO	119	224	C_8H_9
91	118	C_2H_3	93	120	C_2H_3		163	$C_2H_2O_2$		160	CO		148	C_3H_7		163	$C_2H_2O_2$		105	C_7H_4	105	224	C_8H_7O
	163	C_2O_3		136	C_2H_3O		181	*e*		192	*e*		146	C_3H_5		196	C_7H_7					224	C_9H_{11}
	178	*e*		165	C_2O_3	103	121	CD_3	131	132	H		120	CH_3		210	C_8H_9					209	C_8H_8
77	105	CO		180	*e*	91	121	C_2D_3		147	O		206	*e*	103	194	C_7H_7					196	C_7H_7
	103	C_2H_2	77	120	$C_3H_3D_2$		137	C_2D_3O		159	CO	103	119	CH_4	91	119	CO					178	$C_9H_6O_2$
	163	$C_3H_2O_3$		105	CO		163	C_2O_3	121	162	C_2HO	91	119	C_2H_4		163	C_2O_3					134	C_2H_5
	178	*e*		165	$C_3D_2O_3$		181	*e*	120	148	C_2H_4		131	C_3H_4		181	C_7H_6					134	CHO
				180	*e*	77	105	CO	117	132	CH_3		146	C_4H_7		210	C_8H_7O					268	*e*
							103	C_2H_3	105	120	CH_3		163	C_2O_3	77	105	CO				91	119	CO
							148	C_4HD_3O		134	C_2H_5	77	105	CO		103	C_8H_7					224	C_9H_9O
							163	$C_3H_2O_3$		147	C_3H_6		103	C_2H_2		120	C_2H_3O				77	105	CO
							181	*e*		148	C_3H_7		120	C_2H_3O		162	C_3HO_3					196	C_8H_7O
										163	$C_2H_2O_2$		163	$C_3H_2O_3$								177	$C_4H_4O_3$
										192	*e*		78	H									
									103	132	C_2H_5												
									91	117	C_2H_2												
										131	C_3H_4												
										163	C_2O_3												
										192	*e*												
										78	H												
										103	C_2H_2												
										105	CO												
										121	CO_2												
										163	$C_3H_2O_3$												
										192													

[a] P = precursor; NL = neutral loss. [b] High resolution of 120 ion shows a doublet, corresponding to $C_9H_8D_2$ and C_8H_6O, with an intensity ratio of 1:3. [c] According to high resolution, 162 ion also shows a doublet which correspond to $M-CO_2$ and $M-C_3H_8$, with an intensity ratio of 1:15. [d] Precursor not observed. [e] Not assigned; may have more than one step fragmentation.

Table III. Molecular Ion Fragmentations of β-Peroxylactones 1–8[a]

Compd	M − CO_3	M − 	M − R_1	M − O_2H	M − CO_2
1	21	48	21	6	4
2	16	48	21	8	7
3	7	47	27	12	7
4	13	7	79		1
5	6	4	70		20
6	1	9	9		81
7	6	60			34
8		38	2		60

[a] Normalized data taken from 15-eV spectra. In those cases in which abundant secondary ions are still present in the 15-eV spectra, corrections were made to convert the secondary ion abundance into pertinent primary ions, based on MIMS.

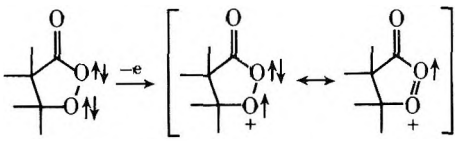


(3)

suggests that the latter cation is formed via a rearranged M − R_1 precursor (path b) rather than M − R_1 directly (path a). Loss of alkane from β-peroxylactones **4** and **5** and elimination of C_7H_6 and C_6H_4 neutrals from β-peroxylactones **6** and **7** are also observed (eq 2f).

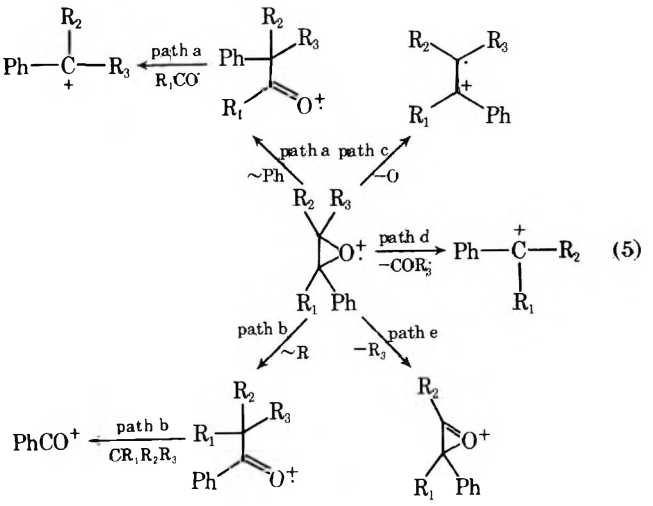
Loss of Hydroperoxy Radical (Eq 2d). On the basis of deuterium labeled β-peroxylactones **2** and **3** and the MIMS for the M − O_2H ion, it is shown that the hydrogen is abstracted from the α carbon (Table III). As indicated in eq 2d, the reaction proceeds via a five-membered ring transition state. Although other hydrogen atoms are available for abstraction, e.g., from the α-methyl substituent in β-peroxylactones **6** and **8** (1,3 elimination), or from the β-methyl group (1,4 elimination) in β-peroxylactone **1**, the 1,2 elimination (eq 2d) is preferred.

Loss of Carbon Dioxide (Eq 2e). A prerequisite for decarboxylation is peroxide bond rupture. The minor M − CO_2 fragments observed in the spectra of β-peroxylactones **1**–**5** suggest that the peroxide bond is strengthened on ionization (eq 4). However, α-methyl and β-$C_6H_5CH_2$ substitution



(4)

change the fragmentation pattern to favor the decarboxylation reaction. The structural assignment of the M − CO_2 ion is scrutinized according to eq 5.



(5)

The skeletal rearrangements, path 5a (Ph migration) and path 5b (R migration), are well established for epoxides.[5,14] However, such evidence is circumstantial and can only support but not prove the epoxide structure of the decarboxylated product ion, M − CO_2. Pertinent information for ion structure identification has been provided through the fragmentations depicted in paths 5c–e, which bespeak an epoxide-like structure for the M − CO_2 ion. Thus, for β-peroxylactone **1** the metastable transition 134 → 105 was observed, which arose either by fragmentation of the M − CO_2 ion via path d (loss of HCO) or via path b from the rearranged M − CO_2 ion (loss of C_2H_5). Indeed, high-resolution data confirm that the 105 ion is a doublet, consisting of the $C_8H_9^+$ and $C_7H_5O^+$ fragments. Also the 106 ion, derived from β-peroxylactone **2**, consists of an analogous C_8H_8D and $C_6C^{13}H_5O$ doublet. Furthermore, from the MIMS of the 106 ion it is concluded that it arises via the consecutive decompositions

$$136 \xrightarrow{-D} 134 \xrightarrow{-CO} 106$$

confirming that the M − CO_2 fragment has an epoxide-like structure.

β-Peroxylactone **2** has also been useful in establishing the migratory aptitude of the phenyl group (path a) and the methyl group (path b) in eq 5. From Table II, the 93 ion arises from the 120, 165, and 136 ions as precursors, while the 105 ion arises from the 120, 134, 136, 145, 165, and 180 ions as precursors. Accordingly, the ion intensity of mass 136 relative to the sum of that of the masses 120, 136, and 165 is a measure of phenyl migration, while the ion intensity of mass 136 relative to the sum of that of the masses 120, 134, 136, 145, 165, and 180 measures the degree of methyl migration. The quotient of these two relative intensity ratios provides an estimate for the methyl to phenyl migratory aptitude, of course keeping in mind that ion intensity data derived from the MIMS gives only approximate values.[15] Our data reveal that phenyl migration outweighs methyl migration by threefold. For the other β-peroxylacetones it is also observed that phenyl migration is preferred over alkyl migration. Again this bears out epoxide-like behavior as established in the mass spectral

fragmentations of epoxides.[14] This migratory aptitude is, however, contrary to the thermal chemistry of β-peroxylactones, in which alkyl migration predominates over phenyl migration,[4a] but coincides with their photochemistry.[4b]

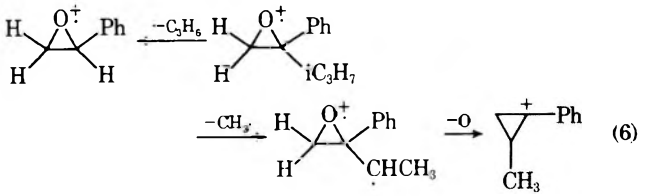
One convincing piece of structural information concerning the M − CO_2 ion comes from β-peroxylactone **3**, in which the abundant 108 ion ($C_6H_5CHCD_3$) derives from eliminating a CHO group from the M − CO_2 ion (Tables II and III and eq 5d). Such a reaction pathway is most characteristic of an epoxide-like M − CO_2 ion.[14]

For β-peroxylactone **4** the M − CO_2 ion (148) is comprised of a complex pathway consisting of decarbonylation, followed by deoxygenation:

$$M \xrightarrow{-CO} M - 28 \xrightarrow{-O} M - 44$$

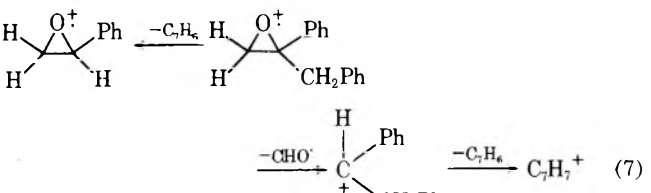
These two steps clearly discount decarboxylation as a source for the M − 44 ion (eq 2e) and render a ketone-like structure for the final M − 44 ion unlikely. Also subsequent deoxygenation of the M − 44 ion, leading to the 132 ion, further supports an epoxide-like structure for the M − CO_2 ion.

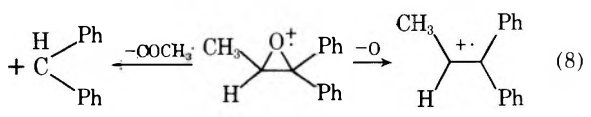
The M − CO_2 ion derived from β-peroxylactone **5** subsequently decomposes according to eq 6. This is indicative of a fragmentation pattern characteristic of an ionized epoxide.

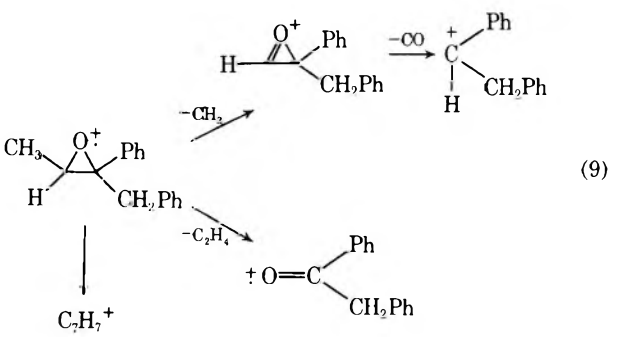

(6)

Decarboxylation becomes the major pathway for the β-peroxylactones **6**–**8** on electron impact. All the M − CO_2 ions undergo typical epoxide-like decomposition patterns, as corroborated by their respective MIMS's (eq 7–9).

In conclusion, electron impact behavior of β-peroxylactones parallels their photochemistry in that an epoxide-like M − CO_2 fragment intervenes. Of course, efficient cooling of the sampling probe is mandatory in avoiding thermal decomposition of the β-peroxylactones prior to electron impact. Unlike the photolysis, decarboxylation is not necessarily the major process on electron impact and depends greatly on the substituent pattern of the β-peroxylactone.


(7)


(8)


(9)

Acknowledgments. Financial support of our work by the National Science Foundation, the National Institutes of Health, and the donors of the Petroleum Research Fund, administered by the American Chemical Society, is gratefully appreciated. We thank Mr. O. Cueto of the Department of Chemistry of the University of Puerto Rico for samples of the deuterated β-peroxylactones.

Registry No.—**1**, 6782-11-2; **2**, 60909-10-6; **3**, 60909-11-7; **4**, 23002-41-7; **5**, 23002-43-9; **6**, 23002-42-8; **7**, 60909-12-8; **8**, 35394-04-8.

References and Notes

(1) Part 44 in the Cyclic Peroxide series.
(2) (a) Department of Chemistry, University of Puerto Rico, Rio Piedras Campus. NIH Research Career Development Awardee (1975–1980) and J. S. Guggenheim Fellow 1972–1973). (b) Department of Chemistry, University of Puerto Rico, Mayagüez Campus, Mayagüez, Puerto Rico 00708.
(3) T. W. Bentley and R. A. W. Johnstone, *Adv. Phys. Org. Chem.*, **8**, 1 (1970); (b) F. W. McLafferty, *Anal. Chem.*, **31**, 82 (1959).
(4) (a) W. Adam and Y. M. Cheng, *J. Am. Chem. Soc.*, **91**, 2109 (1969); (b) W. Adam and G. Santiago, *ibid.*, **93**, 4300 (1971).
(5) P. Brown and C. Djerassi, *Tetrahedron*, **24**, 2949 (1968).
(6) R. G. Cooks, J. H. Beynon, R. M. Caprioli, and G. R. Lester, "Metastable Ions", Elsevier, Amsterdam, 1973.
(7) (a) M. Baber and R. M. Elliot, "Comparison of Metastable Spectra from Single and Double Focusing Mass Spectrometer", 12th Annual Meeting, ASTM Committee E-14 on Mass Spectrometry, Montreal, Canada, June 7–14, 1964; (b) J. H. Beynon, R. A. Saunders, and A. E. Williams, *Nature (London)*, **204**, 67 (1964); (c) J. H. Beynon, R. M. Caprioli, W. E. Baitinger, and J. W. Amy, *Int. J. Mass Spectrom. Ion Phys.*, **3**, 313 (1969); (d) K. Aizawa, S. Yoshida, and N. Takahashi, *Org. Mass Spectrom.*, **9**, 470 (1976); (e) J. L. Holmes and J. K. Terlouw, *ibid.*, **10**, 787 (1975).
(8) (a) M. L. Cross, R. B. Fairweather, W. F. Haddon, F. W. McLafferty, and H. W. Major, "Metastable Ions in Mass Spectra", 16th Annual Meeting, ASTM Committee E-14 on Mass Spectrometry, Pittsburgh, Pa., May 12–17, 1968; (b) R. W. Kisser, R. E. Sullivan, and M. S. Lupin, *Anal. Chem.*, **41**, 1958 (1969).
(9) J. H. Beynon, R. M. Caprioli, and T. W. Shannon, *Org. Mass Spectrom.*, **5**, 967 (1971).
(10) (a) K. R. Jennings, in "Mass Spectrometry: Techniques and Applications", G. W. A. Milne, Ed., Wiley-Interscience, New York, N.Y., 1971; (b) J. H. B. Beynon, M. Bertrand, and R. G. Cooks, *Org. Mass Spectrom.*, **7**, 785 (1974); (c) E. G. Jones, L. E. Bauman, J. H. Beynon, and R. G. Cooks, *ibid.*, **7**, 185 (1974); (d) J. F. Elder, J. H. Beynon, and R. G. Cooks, *ibid.*, **10**, 273 (1975).
(11) (a) F. W. McLafferty and M. C. Hamming, *Chem. Ind. (London)*, 1366 (1958); (b) M. M. Bursey and M. K. Hoffmann in ref 10a.
(12) R. Venkatarghavan, R. J. Klimowski, and F. W. McLafferty, *Acc. Chem. Res.*, **3**, 158 (1970).
(13) (a) F. D. Greene, W. Adam, and G. A. Knudsen, Jr., *J. Org. Chem.*, **31**, 2087 (1966); (b) W. Adam and C. I. Rojas, *Synthesis*, 616 (1972).
(14) (a) H. E. Audier, J. F. Dupin, M. Fétizon, and Y. Hoppilliard, *Tetrahedron Lett.*, 2077 (1966); (b) M. Fétizon, Y. Henry, G. Aranda, H. E. Audier, and H. D. Lutes, *Org. Mass Spectrom.*, **8**, 201 (1974).
(15) Ion intensity measurements are dependent on the ion kinetic energy and thus a function of ion accelerating potential as in the case for MIMS.

Oxidation of 1,2-Diaminobenzimidazoles to 3-Amino-1,2,4-benzotriazines

Alice V. Zeiger and Madeleine M. Joullié*

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104

Received August 9, 1976

Several substituted 1,2-diaminobenzimidazoles were synthesized via the cyclization of *o*-acylhydrazidoanilines with cyanogen bromide. A facile route to 1,2-diaminobenzimidazole and 1,2-diamino-5,6-dimethylbenzimidazole was also devised using the corresponding 2-aminobenzimidazoles and hydroxylamine-*O*-sulfonic acid as the aminating agent. Schiff bases of 1,2-diaminobenzimidazole were also prepared. The reaction of 1,2-diaminobenzimidazole with benzil provided 2,3-diphenyl-*as*-triazino[2,3-*a*]benzimidazole. Oxidation of the 1,2-diaminobenzimidazoles with lead tetraacetate afforded 3-amino-1,2,4-benzotriazines.

The purine antimetabolite behavior of the benzimidazole nucleus[1] coupled with the in vivo[2] and in vitro[3] utilization of preformed purines by malaria parasites prompted us to synthesize substituted 1,2-diaminobenzimidazoles as potential antimalarial agents. The substituents selected for this study, notably trifluoromethyl (−I, −R), chloro (−I, +R), and methyl (+I, +R) groups, represent specific electronic effects important in a wide variety of biologically active drugs.[4]

Synthesis. Our initial approach involved extension of the recent work of Ho and Day[5] to the synthesis of the 1,2-diaminobenzimidazole ring via the cyclization of *o*-acylhydrazidoanilines with cyanogen bromide. The required precursors were prepared from appropriate commercially available para-substituted anilines or o-nitroanilines, respectively. Thus, *p*-aminobenzotrifluoride (1) was acetylated in nearly quantitative yield with acetic anhydride. The resulting product (2) was nitrated with a 60:40 mixture of nitric and sulfuric acids and the intermediate (3) then saponified to give the desired substituted *o*-nitroaniline (**4a**).

Diazotization of *o*-nitroanilines (**4a–c**) followed by a sodium bisulfite reduction resulted in the formation of o-nitrophenylhydrazines (**5a–c**) which, in turn, were treated with acetic acid to afford the corresponding acetylated derivatives (**6a–c**).

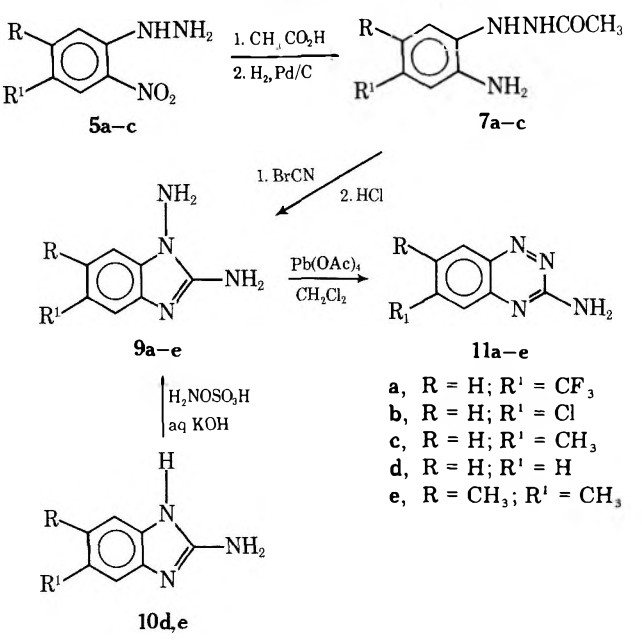
To avoid possible dehalogenation, **6b** was reduced with iron and water. Hydrogenation in a Parr apparatus using a platinum catalyst, although somewhat less effective than iron and water, was significantly faster and was used successfully for both **6a** and **6b.** The reduction of **6c** was accomplished in a Parr apparatus using palladium on carbon as the catalyst.

Cyclization of the reduced compounds was effected by addition of cyanogen bromide to an aqueous suspension of the substituted *o*-acylhydrazidoanilines (**7a–c**). The substituted 1,2-diaminobenzimidazoles (**9a–c**) were obtained by heating the monohydrobromides (**8a–c**) in hydrochloric acid, followed by neutralization with sodium bicarbonate.

Since the above synthesis was rather lengthy, we investigated possible methods of aminating 2-aminobenzimidazoles. After limited success with some of the newer aminating agents such as *O*-(2,4-dinitrophenyl)hydroxylamine,[6] we found hydroxylamine-*O*-sulfonic acid to be useful for this purpose.[7] When the reagent was added to an aqueous suspension of 2-aminobenzimidazole (**10d**) and potassium hydroxide, at ambient temperature, 1,2-diaminobenzimidazole (**9d**) was precipitated after 30 min. 2-Amino-5,6-dimethylbenzimidazole (**10e**) was aminated by the same procedure to afford **9e.** The reactions are summarized in Scheme I.

Reactions. 1,2-Diaminobenzimidazole (**9d**) was found to react preferentially with aldehydes at the 1-amino group. The reaction is catalyzed by a small amount of base. Schiff's bases **12** and **13** could be of considerable interest since the repository activity of antimalarial drugs has often been enhanced by Schiff base formation. Attempts to cyclize **12** to a five-membered ring with copper(II) acetate monohydrate and 2 equiv of hydrochloric acid or dilute sulfuric acid were unsuccessful. Only the corresponding salts were formed. The structures of **12** and **13,** as well as of the salts derived from **12,** were ascertained by infrared, ultraviolet, and nuclear magnetic resonance spectroscopy. ^{13}C nuclear magnetic resonance spectra of these compounds enabled us to unequivocally rule out the formation of a five-membered ring and identify the products of the cyclization attempts as the cited salts.

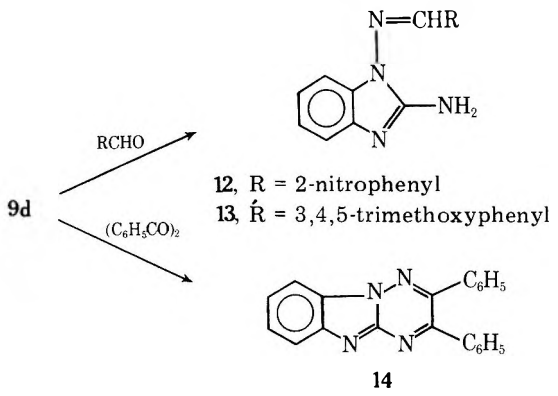
Scheme I



Although it had previously been shown by Ho and Day that 1,2-diaminobenzimidazole (**9d**) reacted with a number of α-dicarbonyl compounds including 2,3-butanedione, 2,3-pentanedione, pyruvic acid and benzoylformic acid, they could not obtain a condensation product with benzil.[8] We found that the desired compound (**14**) could, in fact, be generated in quantitative yield in the presence of potassium hydroxide as a catalyst. These reactions are summarized in Scheme II.

There are several examples in the literature of the synthesis of nitrogen heterocycles via the oxidation of *N*-amino compounds. Baumgarten et al.[9] obtained 3-cinnolinol by the lead tetracetate oxidation of *N*-aminooxindole. Rees et al.[10] synthesized 1,2,3-benzotriazines using either 1- or 2-aminoindazoles. Additional examples involve the formation of pyridazines from 1-amino-2-pyridones, upon loss of carbon monoxide,[11] and the preparation of 1,2,4-benzotriazines from 1-amino-2-quinoxalones.[12] The addition of lead tetraacetate to a solution of each of the 1,2-diaminobenzimidazoles (**9a–e**) in methylene chloride resulted in their oxidative conversion to the appropriately substituted 3-amino-1,2,4-benzotriazines (**11a–e**), thereby illustrating the versatility of the oxidation

Scheme II



of *N*-amino compounds in synthetic heterocyclic chemistry.

3-Amino-6-chloro-1,2,4-benzotriazine (**11b**) was previously reported by Wolf et al.[13] In a subsequent publication,[14] these authors gave the melting point of the compound as 250–251 °C but did not analyze or further characterize their product. We found the melting point of **11b** to be 277.5–279 °C and both our analytical and spectral data support the postulated structure.

Although the reported mechanisms for the lead tetraacetate oxidation of *N*-amino compounds have invoked nitrene formation and subsequent ring expansion, we were unable to trap a nitrene intermediate either with olefins such as cyclohexene or trichloroethylene or with dimethyl sulfoxide.

Experimental Section

General. Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Microanalyses were performed by Midwest Microlab, Ltd., Indianapolis, Ind., and Galbraith Laboratories, Knoxville, Tenn. IR spectra were obtained on a Perkin-Elmer 521 double beam grating spectrophotometer equipped with cesium bromide optics. ^{1}H NMR spectra were recorded with a Varian A-60A or JEOL-JNM-PS 100 instrument. ^{13}C NMR spectra were obtained on a JEOL-JNM-PS 100 spectrometer. Mass spectra were determined on a Perkin-Elmer 270-B, a Consolidated Electrodynamics Corp. CEC-110 (double focusing), and a Varian MAT CH-5 mass spectrometer. UV spectra were obtained on a Beckman DB spectrophotometer.

4-Trifluoromethylacetanilide (2). *p*-Aminobenzotrifluoride (10.0 g, 0.0621 mol) was added to 30 ml of acetic anhydride to give crude 2 which was then purified by recrystallization from benzene–chloroform (12 g, 95% yield): mp 151–152 °C (lit.[15a] mp 152 °C, lit.[15b] 150–151 °C); IR (KBr) 3400, 3375, 3200 (NH), 1670 cm^{-1} (CO); ^{1}H NMR (Me_2CO-d_6) δ 2.17 (s, 3 H, CH_3), 7.61 (d, 2 H, $J_{H\text{-}5,H\text{-}6}$ = 9 Hz, H-3 and H-5), 7.91 (d, 2 H, $J_{H\text{-}5,H\text{-}6}$ = 9 Hz, H-2 and H-6), and 9.55 (broad s, 1 H, NH).

2-Nitro-4-trifluoromethylacetanilide (3). Compound **2** (5.00 g, 0.0246 mol) was nitrated with a 60:40 mixture of nitric and sulfuric acids (50 ml). Recrystallization of the crude product from absolute ethanol gave 5.47 g (90% yield) of **3:** mp 110.5–112 °C (lit.[16] mp 112–113 °C); IR (KBr) 3400, 3300 (NH), 1715 (CO), 1525, and 1365 cm^{-1} (NO_2); ^{1}H NMR (Me_2CO-d_6) δ 2.28 (s, 3 H, CH_3), 7.87–9.10 (m, 3 H, aromatic H), and 10.27 (broad s, 1 H, NH).

2-Nitro-4-trifluoromethylaniline (4a). Compound **3** (5.00 g, 0.002 mol) was heated with potassium hydroxide in a minimum amount of aqueous ethanol for 30 min. The mixture was then added to 75 ml of cold water to afford a bright yellow precipitate. This solid was then chromatographed on silica gel using a 1:1 chloroform–benzene solution to yield 3.89 g (94% yield) of **4a:** mp 105–106.5 °C (lit.[16] mp 106–107 °C); IR (KBr) 3400, 3260, 3100 (NH), 1525, and 1348 cm^{-1} (NO_2); H^1 NMR (Me_2SO-d_6) δ 7.21 (d, 1 H, $J_{H\text{-}5,H\text{-}6}$ = 9 Hz, H-6), 7.54 (dd, 1 H, $J_{H\text{-}2,H\text{-}6}$ = 2 Hz, H-5), 7.72 (broad s, 2 H, NH_2), and 8.27 (broad s, 1 H, H-3).

2-Nitro-4-trifluoromethylphenylhydrazine (5a). A solution of sodium nitrite (13.70 g, 0.198 mol) in 25 ml of water was added dropwise to a stirred mixture of **4a** (31.0 g, 0.150 mol) and 52.5 ml of concentrated hydrochloric acid at −7 °C. The reaction mixture was filtered and the filtrate added to a stirred solution of sodium sulfite (47.5 g, 0.377 mol) and sodium hydroxide (10.0 g, 0.25 mol) in 250 ml of water at −5 °C. Concentrated hydrochloric acid (37.5 ml) was added to the mixture and the temperature of the solution was then raised to 50 °C for 30 min. The yellow solid that formed on cooling was collected, added to 150 ml of concentrated hydrochloric acid, and heated on a steam bath until the yellow solid was converted to a brown precipitate. The brown precipitate was dissolved in a minimum amount of hot water. Insoluble tars were removed by filtration and the filtrate was made basic with a saturated aqueous sodium acetate solution. The free base was collected and recrystallized from benzene to give 13 g (39% yield) of bright orange needles: mp 115–116 °C (lit.[17] mp 112–113 °C); IR (KBr) 3450, 3300 (NH_2), 1560, and 1310 cm^{-1} (NO_2); ^{1}H NMR ($MeNO_2$-d_3) δ 4.28 (s, 2 H, NH_2), 7.66 (dd, 1 H, $J_{H\text{-}5,H\text{-}6}$ = 9.5, $J_{H\text{-}3,H\text{-}5}$ = 2 Hz, H-5), 7.88 (dd, 1 H, $J_{H\text{-}3,H\text{-}6}$ = 1 Hz, H-6), 8.36 (dd, 1 H, H-3), and 9.23 (s, 1 H, NH).

4-Chloro-2-nitrophenylhydrazine (5b). This compound was prepared by the procedure described for **5a** using 25.50 g (0.148 mol) of 4-chloro-2-nitroaniline. The solid obtained was recrystallized from benzene to yield 20.6 g (74.3%) of brownish-red needles: mp 135–136 °C (lit.[18] mp 134 °C); IR (KBr) 3400, 3250 (NH_2), 1550 and 1340 cm^{-1} (NO_2); ^{1}H NMR (Me_2SO-d_6) δ 4.23 (broad s, 2 H, NH_2), 7.53 (dd, 1 H, $J_{H\text{-}5,H\text{-}6}$ = 10, $J_{H\text{-}5,H\text{-}5}$ = 2 Hz, H-5), 7.73 (dd, 1 H, $J_{H\text{-}3,H\text{-}6}$ = 1 Hz, H-6), 7.98 (dd, 1 H, H-3), and 9.18 (broad s, 1 H, NH).

4-Methyl-2-nitrophenylhydrazine (5c). This compound was prepared via the procedure described for **5a** using 10.9 g (0.158 mol) of sodium nitrite in 20 ml of water and 18.0 g (0.118 mol) of 4-methyl-2-nitroaniline. The filtrate was added to a stirred solution of sodium sulfite (38.00 g, 0.3015 mol) and sodium hydroxide (8.0 g, 0.2 mol) in 200 ml of water at −5 °C. The resulting red product was recrystallized from benzene to give 13.0 g of **5c** (66% yield): mp 110–112 °C (lit.[19] mp 110 °C); IR (KBr) 3250 (NH_2), 1550 and 1340 cm^{-1} (NO_2); ^{1}H NMR ($MeNO_2$-d_3) δ 2.24 (s, 3 H, CH_3), 3.95 (broad s, 2 H, NH_2), 7.34 (dd, 1 H, $J_{H\text{-}5,H\text{-}6}$ = 9.5, $J_{H\text{-}3,H\text{-}5}$ = 2 Hz, H-5), 7.58 (dd, 1 H, $J_{H\text{-}3,H\text{-}6}$ = <1 Hz, H-6), 7.86 (dd, 1 H, H-3), and 8.73 (broad s, 1 H, NH).

2-Acethydrazido-5-trifluoromethylnitrobenzene (6a). A solution of **5a** (3.20 g, 0.0145 mol) in 10 ml of glacial acetic acid was heated on a steam bath for 1.5 h. Addition of 50 ml of cold water to this solution induced the precipitation of crude product which was purified by recrystallization from chloroform to give 3.00 g (79% yield) of **6a** as bright yellow needles: mp 186–187 °C; IR (KBr) 3280, 3180 (NH), 1655 (CO), 1535, and 1340 cm^{-1} (NO_2); ^{1}H NMR (Me_2CO-d_6) δ 2.05 (s, 3 H, CH_3), 5.17 (m, 1 H, NH), 7.44 (d, 1 H, $J_{H\text{-}3,H\text{-}4}$ = 9 Hz, H-3), 7.85 (d, 1 H, H-4), 8.48 (s, 1 H, H-6), and 9.43 (broad s, 1 H, NHCO).

Anal. Calcd for $C_9H_8F_3N_3O_3$: C, 41.07; H, 3.06; N, 15.97. Found: C, 40.89; H, 3.11; N, 16.09.

2-Acethydrazido-5-chloronitrobenzene (6b). A solution of **5b** (20.60 g, 0.110 mol) was acetylated with 85 ml of glacial acetic acid as described for **6a.** The product was recrystallized from chloroform to give 18.0 g (71% yield) of **6b** as orange needles: mp 164.5–165.5 °C; IR (KBr) 3280, 3190 (NH), 1650 (CO), 1535 and 1330 cm^{-1} (NO_2); ^{1}H NMR (Me_2SO-d_6) δ 2.00 (s, 3 H, CH_3), 3.51 (broad m, 1 H, NH), 7.20 (d, 1 H, $J_{H\text{-}3,H\text{-}4}$ = 9.5 Hz, H-3), 7.61 (dd, 1 H, $J_{H\text{-}4,H\text{-}6}$ = 2.5 Hz, H-4), 8.11 (d, 1 H, H-6), and 9.29 (broad s, 1 H, NHCO).

Anal. Calcd for $C_8H_8ClN_3O_3$: C, 41.82; H, 3.51; N, 18.31. Found: C, 41.62; H, 3.59; N, 18.21.

2-Acethydrazido-5-methylnitrobenzene (6c). A solution of **5c** (2.5 g, 0.015 mol) was acetylated with 9 ml of glacial acetic acid as described for **6a.** The product was recrystallized from chloroform to give 1.94 g (62% yield) of **6c** as orange needles: mp 168–169.5 °C; IR (KBr) 3250, 3200 (NH), 1650 (CO), 1515 and 1325 cm^{-1} (NO_2); ^{1}H NMR (Me_2SO-d_6) δ 2.00 (s, 3 H, $COCH_3$) 2.28 (s, 3 H, CH_3), 3.37 (broad s, 1 H, NH), 7.07 (d, 1 H, $J_{H\text{-}3,H\text{-}4}$ = 9 Hz, H-3), 7.46 (dd, 1 H, $J_{H\text{-}4,H\text{-}6}$ = 2 Hz, H-4), 7.93 (d, 1 H, H-6), and 9.03 (s, 1 H, NHCO).

Anal. Calcd for $C_9H_{11}N_3O_3$: C, 51.67; H, 5.30; N, 20.09. Found: C, 51.55; H, 5.18; N, 20.14.

2-Acethydrazido-5-trifluoromethylaniline (7a). A solution of **6a** (1.026 g, 0.0039 mol) in 50 ml of absolute ethanol was hydrogenated in a Parr apparatus for 30 min at 50 psi using 0.1 g of 5% platinum on carbon.

The product was recrystallized from ethyl acetate and ether to give 0.86 g (94% yield) of **7a** as a white solid: mp 166–167 °C; IR (KBr) 3300, 3150 (NH), and 1670 cm^{-1} (CO); ^{1}H NMR (Me_2SO-d_6) δ 1.92 (s, 3 H, CH_3), 5.02 (broad s, 2 H, NH_2), 6.50–7.28 (m, 4 H, aromatic H and NH), and 9.70 (s, 1 H, NHCO).

Anal. Calcd for $C_9H_{10}F_3N_3O$: C, 46.35; H, 4.32; N, 18.02. Found: C, 46.51; H, 4.43; N, 18.30.

2-Acethydrazido-5-chloroaniline (7b). This compound was obtained by the hydrogenation of a solution of **6b** (1.0 g, 0.004 mol) in 50 ml of ethanol as described for **7a.** The product was recrystallized

from benzene to give 0.48 g (55% yield) of **7b** as a white solid, mp 124–125 °C. Compound **6b** (7.34 g, 0.032 mol) in 200 ml of benzene was also reduced with activated iron (56.0 g, 1.0 mol) to give 3.9 g (61% yield) of **7b:** IR (KBr) 3300, 3250, 3200, 3175 (NH), and 1650 cm^{-1} (CO); ^1H NMR (Me_2CO-d_6) δ 1.95 (s, 3 H, CH_3), 3.03 (broad s, 1 H, NH_2), 4.58 (broad s, 1 H, NH_2), 6.38 (broad s, 1 H, NH), 6.38–6.95 (m, 3 H, aromatic H), and 9.05 (broad s, 1 H, NHCO).

Anal. Calcd for $C_8H_{10}ClN_3O$: C, 48.11; H, 5.05; N, 21.06. Found: C, 48.37; H, 4.93; N, 21.28.

2-Acethydrazido-5-methylaniline (7c). This compound was prepared by the hydrogenation of **6c** (4.00 g, 0.019 mol) in 150 ml of absolute ethanol using 0.2 g of 10% palladium on carbon (Parr apparatus, 1 h at 60 psi). The product was recrystallized from benzene to give 2.9 g (86% yield) of **7c** as orange-brown needles: mp 117.5–119 °C; IR (KBr) 3375, 3280, 3250, 3180 (NH), and 1650 cm^{-1} (CO); ^1H NMR (Me_2SO-d_6) δ 1.88 (s, 3 H, $COCH_3$), 2.10 (s, 3 H, CH_3), 3.47 (broad s, 2 H, NH_2), 4.48 (broad s, 1 H, NH), 6.13–6.72 (m, 3 H, aromatic H), 9.53 (broad s, 1 H, NHCO).

Anal. Calcd for $C_9H_{13}N_3O$: C, 60.31; H, 7.31; N, 23.45. Found: C, 60.35; H, 7.32; N, 23.19.

1-Acetamido-2-amino-5-trifluoromethyl-1*H*-benzimidazole Hydrobromide Monohydrate (8a). Compound **7a** (0.440 g, 0.0019 mol) in 10 ml of water was added to a solution of cyanogen bromide (1.16 g, 0.011 mol) in 10 ml of water and the mixture stirred at room temperature for 2 h. The water was then removed under reduced pressure and the resulting solid was recrystallized from acetonitrile to give 0.41 g (60% yield) of **8a:** mp 249.5–251 °C; IR (KBr) 3350, 3200, 3125 (NH), and 1725 cm^{-1} (CO); ^1H NMR (Me_2SO-d_6) δ 2.23 (s, 3 H, CH_3), 4.82 (broad s, HBr and H_2O), 7.30–8.00 (m, 3 H, aromatic H), 9.37 (broad s, 2 H, NH_2), and 11.60 (broad s, 1 H, NH).

Anal. Calcd for $C_{10}H_{10}BrF_3N_4O{\cdot}H_2O$: C, 33.63; H, 3.39; N, 15.69. Found: C, 33.24; H, 3.23; N, 15.62.

1-Acetamido-2-amino-5-chloro-1*H*-benzimidazole Hydrobromide (8b). Compound **7b** (0.119 g, 0.0006 mol) in 10 ml of water was mixed with a solution of cyanogen bromide (0.291 g, 0.00275 mol) in 10 ml of water as described for **8a.** The product was recrystallized from absolute ethanol to give 0.16 g (87% yield) of **8b:** mp 306–308 °C; IR (KBr) 3400, 3200, 3150 (NH), and 1740 cm^{-1} (CO); ^1H NMR (Me_2SO-d_6) δ 2.18 (s, 3 H, CH_3), 4.53 (broad s, HBr), 7.17–7.67 (m, 3 H, aromatic H), 9.23 (broad s, 2 H, NH_2), and 11.51 (broad s, 1 H, NH).

Anal. Calcd for $C_9H_{10}BrClN_4O$: C, 35.35; H, 3.30; N, 18.34. Found: C, 35.38; H, 3.58; N, 17.87.

1-Acetamido-2-amino-5-methyl-1*H*-benzimidazole Hydrobromide Monohydrate (8c). Compound **7c** (1.87 g, 0.0104 mol) in 50 ml of water was mixed with a solution of cyanogen bromide (1.10 g, 0.010 mol) in 10 ml of water as described for **8a.** The product was recrystallized from acetonitrile to give 2.17 g (69% yield) of **8c:** mp 254.5–255.5 °C; IR (KBr) 3400, 3350, 3200 (NH), and 1720 cm^{-1} (CO); ^1H NMR (Me_2SO-d_6) δ 2.22 (s, 3 H, $COCH_3$), 2.40 (s, 3 H, CH_3), 5.15 (broad s, HBr and H_2O), 6.72–7.45 (m, 3 H, aromatic H), 8.97 (broad s, 2 H, NH_2), and 11.45 (broad s, 1 H, NH).

Anal. Calcd for $C_{10}H_{13}BrN_4O{\cdot}H_2O$: C, 39.61; H, 4.99; N, 18.48. Found: C, 39.58; H, 4.99; N, 18.37.

1,2-Diamino-5-trifluoromethyl-1*H*-benzimidazole (9a). A solution of **8a** (0.630 g, 0.0018 mol) in 4.5 ml of 4 N hydrochloric acid was refluxed for 1 h. The solution was cooled and then made basic with a saturated sodium bicarbonate solution. The precipitate that formed was recrystallized from absolute ethanol to give 0.35 g (93% yield) of **9a:** mp 250–251 °C; IR (KBr) 3400, 3275, and 3100 cm^{-1} (NH); ^1H NMR (Me_2SO-d_6) δ 5.75 (s, 2 H, NNH_2), 6.67 (s, 2 H, NH_2), 7.30–7.48 (m, 3 H, aromatic H); UV λ_{max} (ethanol) (log ϵ) 285 (3.80), 256 sh (3.50), and 247 nm (3.64); λ_{max} (ethanol, H^+) (log ϵ) 282 (3.82), 276 (3.84), 243 (3.49), and 234 nm (3.75).

Anal. Calcd for $C_8H_7F_3N_4$: C, 44.45; H, 3.22; N, 25.92; F, 26.37. Found: C, 44.19; H, 3.11; N, 25.72; F, 26.59.

1,2-Diamino-5-chloro-1*H*-benzimidazole (9b). A solution of **8b** (0.500 g, 0.0016 mol) in 60 ml of 4 N hydrochloric acid was refluxed for 1 h and then treated as described for **9a.** The product was recrystallized from ethanol–benzene to afford 0.20 g (67% yield) of **9b:** mp 274–275 °C; IR (KBr) 3375, 3240, and 3140 cm^{-1} (NH); ^1H NMR (Me_2SO-d_6) δ 5.55 (s, 2 H, NNH_2), 6.37 (s, 2 H, NH_2), 6.75–7.18 (m, 3 H, aromatic H); UV λ_{max} (ethanol) (log ϵ) 290 (3.53), 254 (3.34), and 249 nm (3.36); λ_{max} (ethanol, H^+) (log ϵ) 289 (3.48), 283 (3.53), 240 sh (3.28) and 232 nm sh (3.53).

Anal. Calcd for $C_7H_7ClN_4$: C, 46.02; H, 3.87; N, 30.69. Found: C, 45.95; H, 4.03; N, 30.48.

1,2-Diamino-5-methyl-1*H*-benzimidazole (9c). A solution of **8c** (1.00 g, 0.0033 mol) in 120 ml of 4 N hydrochloric acid was refluxed for 1 h and then treated as described for **9a.** The product was recrystallized from absolute ethanol to afford 0.50 g (94% yield) of **9c:** mp 296.5–298 °C; IR (KBr) 3340, 3200, and 3050 cm^{-1} (NH); ^1H NMR (Me_2SO-d_6) δ 2.32 (s, 3 H, CH_3), 5.48 (s, 2 H, NNH_2), 6.08 (s, 2 H, NH_2), and 6.67–7.10 (m, 3 H, H-4, aromatic H); UV λ_{max} (ethanol) (log ϵ) 286 (4.18) and 248 nm (4.02); λ_{max} (ethanol, H^+) (log ϵ) 285 (4.17), 279 (4.23), 276 sh (4.18), and 231 nm sh (4.30).

Anal. Calcd for $C_8H_{10}N_4$: C, 59.24; H, 6.21; N, 34.54. Found: C, 59.29; H, 6.01; N, 34.56.

Amination of 2-Aminobenzimidazole (10d). A. With *O*-(2,4-Dinitrophenyl)hydroxylamine. A solution of **10d** (1.33 g, 0.01 mol) in 50 ml of methanol was treated with sodium (0.23 g, 0.01 g-atom) in 30 ml of the same solvent. Evaporation of the solvent afforded a solid which was then dissolved in 100 ml of dry dimethylformamide and mixed with 1 equiv of *O*-(2,4-dinitrophenyl)hydroxylamine (1.99 g, 0.01 mol) at room temperature. After the solvent was removed under reduced pressure, the residue was then triturated with benzene, collected by filtration, and treated with aqueous sodium bicarbonate to afford 1,2-diaminobenzimidazole (**9d**) as an off-white solid (0.52 g, 35% yield), mp 248–252 °C (lit.[5] mp 256–259 °C).

B. With Hydroxylamine-*O*-sulfonic Acid. Hydroxylamine-*O*-sulfonic acid (9.30 g, 0.082 mol) was added to a solution of **10d** (10.0 g, 0.075 mol) and potassium hydroxide (9.82 g, 0.175 mol) in 200 ml of water at 25 °C. The reaction mixture was stirred at ambient temperature for 30 min. The solid that formed was collected and recrystallized from ethanol to afford 5.50 g (49.5% yield) of **9d,** mp 255–258 °C (lit.[5] mp 256–259 °C). The aqueous filtrate was evaporated and the remaining solid extracted with hot ethanol to give 3.5 g of **10d.** Based on recovered starting material, the yield of **9d** was 76%.

Amination of 2-Amino-5,6-dimethylbenzimidazole (10e). A solution of **10e** (1.61 g, 0.01 mol) in 100 ml of 0.85 N potassium hydroxide was treated overnight with hydroxylamine-*O*-sulfonic acid (1.24 g, 0.011 mol). The solid that formed was collected and recrystallized from ethanol to afford 0.44 g (25% yield) of **9e,** mp 292–294 °C. Evaporation of the ethanol filtrate gave 0.57 g (35% recovery) of **10e.** The corrected yield of **9e** was 38.5%: IR (KBr) 3330, 3200, and 3050 cm^{-1} (NH); ^1H NMR (Me_2SO-d_6) δ 2.22 (s, 3 H, CH_3), 2.25 (s, 3 H, CH_3), 5.38 (broad s, 2 H, NNH_2), 5.88 (broad s, 2 H, NH_2), and 6.89 (s, 2 H, aromatic H); UV λ_{max} (ethanol) (log ϵ) 287 (4.01) and 243 nm (3.86); λ_{max} (ethanol, H^+) (log ϵ) 287 (4.03), 282 (4.06), 280 (4.04), and 232 nm (4.09).

Reactions of 1,2-Diaminobenzimidazole (9d). 1. With Aldehydes. 2-Amino-1-[(o-nitrobenzylidene)amino]benzimidazole (12). A mixture of 0.592 g (0.004 mol) of **9d** in 20 ml of ethanol and *o*-nitrobenzaldehyde (0.60 g, 0.004 mol) in 20 ml of ethanol was refluxed for 2 h to yield 0.84 g of **12a** (75% yield) as orange needles, mp 259–260 °C. This reaction was found to be catalyzed by base. When **9d** (1.18 g, 0.008 mol) and *o*-nitrobenzaldehyde (1.21 g, 0.008 mol) were heated in 40 ml of ethanol, addition of 2 drops of 2 N potassium hydroxide induced immediate precipitation of **12** as an orange solid (2.2 g, 98% yield): IR (KBr) 3350 (NH), 3000 (=CH), 1660 (C=C), 1510 (C=N), 1550, and 1360 cm^{-1} (NO_2); ^1H NMR (Me_2SO-d_6) δ 6.85 (s, 2 H, NH_2), 6.93–8.66 (m, 8 H, aromatic H), and 9.45 (s, 1 H, N=CH); ^{13}C NMR 154.1 (C-2), 148.4 (C–NO_2), 144.1 (N=C), 142.5 (C-9), 133.6 (C-5′), 131.1 (C-4′), 129.3 (C-8), 128.9 (C-6′), 128.5 (C-1′), 124.6 (C-3′) 122.8 (C-5), 119.4 (C-6), 116.2 (C-4), and 109.9 ppm (C-7); UV λ_{max} (ethanol) (log ϵ) 332 (3.86), 311 (3.92), 268 (4.32), and 209 nm (4.53); λ_{max} (ethanol, H^+) (log ϵ) 327 (3.79), 260 (4.22), 225 (4.32) and 204 nm (4.72); MS *m/e* (%) 281 (97.5), 132 (100).

Anal. Calcd for $C_{14}H_{11}N_5O_2$: C, 59.78; H, 3.94; N, 24.90. Found: C, 59.98; H, 4.17; N, 24.94.

2-Amino-1-[(3,4,5-trimethoxybenzylidene)amino]benzimidazole (13). A solution of **9d** (1.48 g, 0.01 mol), 3,4,5-trimethoxybenzaldehyde (1.96 g, 0.01 mol), and 1 ml of 1.7 N KOH in 70 ml of ethanol was refluxed for 30 min. Evaporation of the solvent gave a solid which was recrystallized from ethanol to afford 2.9 g (89% yield) of **13:** mp 183–185 °C; IR (KBr) 3350 (NH), 2998 (=CH), 1650 (C=C), 1535 (C=N), 1565 and 1350 cm^{-1} (NO_2); ^1H NMR (Me_2SO-d_6) 3.79 (s, 3 H, *p*-OCH_3), 3.92 (s, 6 H, *m*-OCH_3), 6.88 (broad s, 2 H, NH_2), 6.92–8.03 (m, 6 H, aromatic H), and 9.03 (s, 1 H, =CH); ^{13}C NMR 154.3 (C-2), 153.1 (C-3′ and C-5′), 147.3 (N=C), 142.3 (C-9), 139.5 (C-4′), 129.6 (C-1′). 129.2 (C-8), 122.2 (C-5), 118.9 (C-6), 115.8 (C-4), 110.5 (C-7), 105.3 (C-2′ and C-6′), 60.1 (*p*-OCH_3), and 56.1 ppm (*m*-OCH_3); UV λ_{max} (ethanol) (log ϵ) 320 (4.11), 282 (4.23), and 228 nm (4.22); λ_{max} (ethanol, H^+) (log ϵ) 320 (4.06), 284 (3.87), 278 (3.87), 256 (3.68), and 222 nm (4.20).

Anal. Calcd for $C_{17}H_{18}N_4O_3$: C, 62.57; H, 5.56; N, 17.17. Found: C, 62.38; H, 5.61; N, 16.98.

Attempts to cyclize **12** by a variety of methods were unsuccessful. When **12** (0.50 g, 0.0018 mol) was refluxed in dilute sulfuric acid, a pale yellow solid formed and was recrystallized from ethanol, mp 233.5–235

°C This compound was identified as 2-amino-1-[(o-nitrobenzylidene)amino]benzimidazole sulfate: IR (KBr) 3300 (NH), 3000 (=CH), 1690 (C=C), 1505 (C=N), 1530 and 1330 cm^{-1} (NO_2); ^1H NMR Me_2SO-d_6) δ 5.63 (broad s, 3 H, NH_2 and H_2SO_4), 7.02–8.72 (m, 8 H, aromatic H), and 9.57 (s, 1 H, =CH); ^{13}C NMR 148.8 (C-2, C-NO_2, and N=C), 135.6 (C-9), 133.9 (C-5′), 131.8 (C-4′), 129.2 (C-6′), 127.9 (C-1′), 125.0 (C-8), 124.7 (C-3′), 123.9 (C-5), 121.4 (C-6), 114.5 (C-4), and 110.5 ppm (C-7).

Anal. Calcd for $C_{28}H_{24}N_{10}O_8S$: C, 50.91; H, 3.66; N, 21.21; S, 4.84. Found: C, 50.42; H, 3.61; N, 20.97; S, 4.96.

2. With Benzil. 2,3-Diphenyl-as-triazino[2,3-a]benzimidazole (14). Addition of 3 drops of an aqueous 2 N potassium hydroxide solution to a heated solution of **9d** (0.296 g, 0.002 mol) and benzil (0.420 g, 0.002 mol) in 25 ml of ethanol produced immediate formation of a yellow precipitate. The reaction mixture was refluxed, with stirring, for 30 min to afford 0.64 g (94% yield) of **14**: mp 278–281 °C; IR (KBr) 3000 (=CH), 1540, 1500, and 1475 cm^{-1} (C=C); ^1H NMR δ 7.46 (s, 14 H, aromatic H); MS *m/e* (%) 322 (100); UV λ_{max} (ethanol) (log ϵ) 375 (4.01), 270 (4.38), and 202 nm (4.54).

Anal. Calcd for $C_{21}H_{14}N_4 \cdot H_2O$: C, 74.10; H, 4.74. Found: C, 74.40; H, 4.56.

3. With Lead Tetraacetate. 3-Amino-1,2,4-benzotriazine (11d). Lead tetraacetate (1.42 g, 0.003 mol) was added to a suspension of **9d** (0.30 g, 0.002 mol) in 25 ml of methylene chloride. The reaction mixture turned bright yellow and then brown. After 5 min, 3 ml of ethylene glycol was added to destroy any unreacted lead tetraacetate followed by 100 ml of water. The aqueous layer was extracted with methylene chloride; the extract was reduced in volume and then chromatographed on a silica gel column with methylene chloride–ethyl acetate. Elution of the resulting yellow band afforded 0.23 g (80% yield) of **11d**: mp 206–208 °C (lit.[20] mp 207 °C); IR (KBr) 3200, 3050 (NH), 1660 (C=C), and 1545 cm^{-1} (C=N); MS *m/e* (%) 146 (74) and 118 (100); ^1H NMR (Me_2SO-d_6) δ 7.25–8.45 (m, 6 H, aromatic H and NH_2).

Anal. Calcd for $C_7H_6N_4$: C, 57.53; H, 4.14. Found: C, 57.29; H, 4.22.

3-Amino-6-trifluoromethyl-1,2,4-benzotriazine (11a). This compound was prepared as described for **11d** and isolated directly from the methylene chloride extracts without resort to column chromatography. Recrystallization of **11a** from ethanol afforded 0.10 g (95% yield): mp 230.5–232 °C; IR (KBr) 3240, 3100 (NH), 1650 (C=C), and 1540 cm^{-1} (C=N); UV λ_{max} (ethanol) (log ϵ) 280 (3.33), 252 sh (4.07), 236 (4.38), and 203 nm (4.28); ^1H NMR (Me_2SO-d_6) δ 7.53–8.63 (m, 3 H, aromatic H) and 7.92 (broad s, 2 H, NH_2).

Anal. Calcd for $C_8H_5F_3N_4$: C, 44.87; H, 2.35; N, 26.16. Found: C, 44.67; H, 2.24; N, 26.01.

3-Amino-6-chloro-1,2,4-benzotriazine (11b). Compound **11b** was prepared and purified as described for **11a**. The yield of **11b** was 0.06 g (48%): mp 277.5–279 °C; IR (KBr) 3200, 3095 (NH), 1675 (C=C), and 1550 cm^{-1} (C=N); UV λ_{max} (ethanol) (log ϵ) 303 (3.41), 242 (4.30), and 211 nm (4.25); ^1H NMR (Me_2SO-d_6) δ 7.33–8.35 (m, 3 H, aromatic H) and 7.75 (broad s, 2 H, NH_2).

Anal. Calcd for $C_7H_5ClN_4$: C, 46.55; H, 2.79; Cl, 19.63; N, 31.03. Found: C, 46.22; H, 2.65; Cl, 19.40; N, 30.99.

3-Amino-6-methyl-1,2,4-benzotriazine (11c). This compound was prepared as described for **11d** and purified by chromatography on a silica gel column with a 1:3 mixture of acetonitrile and ethyl acetate. Recrystallization of **11c** from ethanol afforded 0.09 g (57% yield) of a bright yellow solid: mp 242–244 °C; IR (KBr) 3200, 3080 (NH), 1650 (C=C), and 1540 cm^{-1} (C=N); UV λ_{max} (ethanol) (log ϵ) 308 (3.38), 237 (4.24), and 208 nm (4.22); ^1H NMR (Me_2SO-d_6) δ 2.48 (s, 3 H, CH_3), 7.13–8.23 (m, 3 H, aromatic H), and 7.44 (broad s, 2 H, NH_2).

Anal. Calcd for $C_8H_8N_4$: C, 59.99; H, 5.03. Found: C, 59.78; H, 4.70.

3-Amino-6,7-dimethyl-1,2,4-benzotriazine (11e). Compound **11e** was prepared and purified as described for **11a**. The yield of **11e** was 0.06 g (73%): mp 286–288 °C (lit.[21] mp 286 °C); IR (KBr) 3200, 3140 (NH), 1650 (C=C), and 1520 cm^{-1} (C=N); UV λ_{max} (ethanol) (log ϵ) 308 (3.70), 238 (4.61), and 208 nm (4.53); ^1H NMR (Me_2SO-d_6) δ 2.40 (broad s, 6 H, CH_3), 7.28 (s, 1 H, H-5), 7.36 (s, 2 H, NH_2), and 8.78 (s, 1 H, H-8).

Registry No.—**1**, 455-14-1; **2**, 349-97-3; **3**, 396-12-3; **4a**, 400-98-6; **4b**, 89-63-4; **4c**, 89-62-3; **5a**, 1513-50-4; **5b**, 54454-57-8; **5c**, 50707-83-0; **6a**, 60882-61-3; **6b**, 60882-62-4; **6c**, 60882-63-5; **7a**, 60882-64-6; **7b**, 60882-65-7; **7c**, 60882-66-8; **8a**, 60882-67-9; **8b**, 60882-68-0; **8c**, 60882-69-1; **9a**, 60882-70-4; **9b**, 60882-71-5; **9c**, 60882-72-6; **9d**, 29540-87-2; **9e**, 60882-73-7; **10d**, 934-32-7; **10e**, 29096-75-1; **11a**, 60882-74-8; **11b**, 60882-75-9; **11c**, 60882-76-0; **11d**, 20028-80-2; **11e**, 27238-42-2; **12**, 60882-77-1; **12** sulfate, 60882-78-2; **13**, 60882-79-3; **14**, 60882-80-6; cyanogen bromide, 506-68-3; *o*-nitrobenzaldehyde, 552-89-6; 3,4,5-trimethoxybenzaldehyde, 86-81-7; acetic anhydride, 108-24-7; benzil, 134-81-6.

References and Notes

(1) D. W. Wooley, *J. Biol. Chem.*, **152**, 225 (1944).
(2) W. Bungener and G. Nielsen, *Z. Tropenmed. Parasitol.*, **20**, 67 (1969).
(3) C. Walshe and I. W. Sherman *J. Protozool.*, **15**, 763 (1968).
(4) W. A. Sexton, "Chemical Constitution and Biological Activity", 3d ed, Spon, London, 1963.
(5) R. I-Fu Ho and A. R. Day, *J. Org. Chem.*, **38**, 3084 (1973).
(6) T. Sheradsky, G. Salemnick, and Z. Nir, *Tetrahedron*, **28**, 3833 (1972).
(7) M. H. Fisher, B. O. Linn, R. J. Bochis, and C. S. Rooney, German Offen. 2 300 521 (1973); *Chem. Abstr.* **79**, 92229p (1973).
(8) R. I-Fu Ho, Ph.D. Dissertation, University of Pennsylvania, Philadelphia, Pa., 1969, pp 97–98.
(9) H/ E. Baumgarten, P. L. Creger, and R. L. Zey, *J. Am. Chem. Soc.*, **82**, 3977 (1960).
(10) D. J. C. Adams, S. Bradbury, D. C. Horwell, M. Keating, C. W. Rees, and R. C. Storr, *Chem. Commun.*, 828 (1971).
(11) C. W. Rees and M. Yelland, *Chem. Commun.*, 377 (1969).
(12) B. Adger, C. W. Rees, A. A. Sale, and R. C. Storr, *Chem. Commun.*, 695 (1971).
(13) F. J. Wolf and K. Pfister, III, U.S. Patent 2 489 352 (Nov 29, 1949).
(14) F. J. Wolf, K. Pfister, III, R. M. Wilson, Jr., and C. A. Robinson, *J. Am. Chem. Soc.*, **76**, 3551 (1954).
(15) (a) E. Pouterman and A. Girardet, *Helv. Chim. Acta*, **30**, 107 (1947); (b) R. G. Jones, *J. Am. Chem. Soc.*, **69**, 2346 (1947).
(16) M. P. Pettit and J. C. Tatlow, *J. Chem. Soc.*, 3852 (1954).
(17) L. M. Yagupol' skii and B. E. Gruz, *Ukr. Khim. Zh.*, **23**, 634 (1957).
(18) S. G. P. Plant and R. D. J. Rosser, *J. Chem. Soc.*, 2454 (1928).
(19) F. G. Pope and J. M. Hird, *J. Chem. Soc.*, 1141 (1901).
(20) F. Arndt, *Ber.*, **46**, 3522 (1913).
(21) J. C. Mason and G. Tennant, *J. Chem. Soc. B*, 911 (1970).

Syntheses, ^{13}C and ^{1}H Nuclear Magnetic Resonance Spectra of Some 1,2,4-Triazine 1- and 2-Oxides

Robert J. Radel, Brian T. Keen, Cindy Wong, and William W. Paudler*

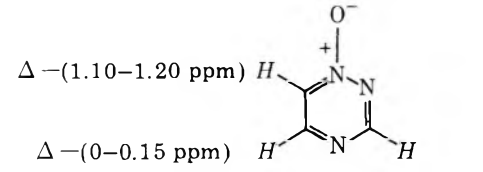
Department of Chemistry, The University of Alabama, University, Alabama 35486

Received June 23, 1976

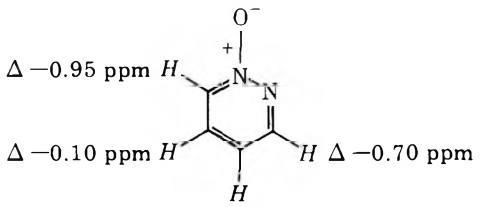
The selective synthesis of 1,2,4-triazine 2-oxide and some of its derivatives is described. The ^{1}H and ^{13}C NMR spectra of these and related compounds are discussed. N-Oxidation of azines causes shielding of the ^{13}C situated ortho and para to the *N*-oxide function and some deshielding of the ^{13}C situated meta to this functional group when viewed *through* an ortho carbon atom. It is suggested that back-donation of the oxide oxygen electrons contributes significantly to the ground state of the 1,2,4-triazine 1- as well as 2-oxides.

Some time ago we described the synthesis of 1,2,4-triazine 1-oxide (**1**) and some of its 3- as well as 5-substituted derivatives, along with structure proofs of 3-amino-5-phenyl- (**2c**) and 3-amino-5,6-diphenyl-1,2,4-triazine 2-oxides.[1]

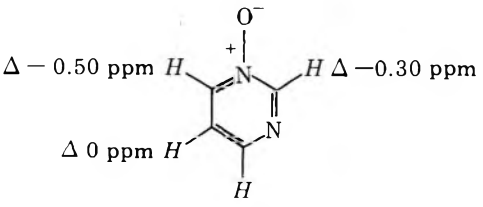
As these studies suggested, substituted 3-amino-1,2,4-triazines afford, as the major N-oxidation products, the 2-oxides. We have now applied this type of oxidation to 3-amino-1,2,4-triazine (**2a**) (cf. Scheme I) and its 5-methyl derivative (**2b**) and have obtained their respective mono-*N*-oxides (**3a** and **3b**). The ^{1}H NMR spectra of these *N*-oxides



1



5



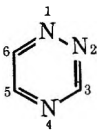
6

($\Delta = \delta_{N\text{-oxide}} - \delta_{\text{non-}N\text{-oxidized azine}}$)

when compared with those of the starting amines (cf. Table I) show that H-6 becomes more shielded upon N-oxidation by 0.65 and 0.62 ppm (cf. Table II), respectively, while H-5 experiences shielding by only 0.34 ppm. In order to establish the site of N-oxidation in these compounds we took recourse to comparing these chemical shift changes with those that occur upon N-oxidation of several other azines:[1-3]

Clearly, the proton situated on the carbon meta to the *N*-oxide function [bonded via another sp^2 nitrogen; H-3 in pyridazine 1-oxide (**5**), and in 1,2,4-triazine 1-oxide (**1**)] becomes more shielded by 0.60–0.70 ppm upon N-oxidation. The proton bonded to the carbon situated para to the *N*-oxide becomes more shielded by 0.30–0.50 ppm [H-4 in pyridazine 1-oxide (**5**) and in pyrimidine 1-oxide (**6**)].

Table I. ^{1}H Chemical Shifts (δ) of Some 1,2,4-Triazine Reference Compounds



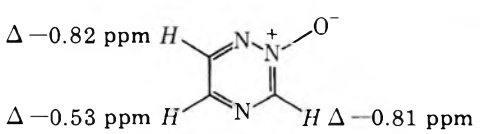
Registry no.	Compd[a]	R_3	R_5	R_6	R_3	R_5	R_6
27531-62-0	1[7]	H	H	H	9.00	8.57	8.04
1120-99-6	**2a**[7]	NH_2	H	H	8.28	8.53	8.88
6302-68-7	**2b**[4]	NH_2	CH_3	H	7.36	8.62	8.80
61108-77-8	**10a**[5]	NHR_3[b]	H	H	3.80	8.12	8.56
61108-78-9	**10b**[5]	NHR_3	CH_3	H	3.83	2.38	8.51
61108-79-0	**10c**[5]	NHR_3	Ph	H	3.88	8.10 7.52	9.09
290-38-0	**25**[1]	H	H	H	9.63	8.53	9.24

[a] Superscript numbers refer to the references describing the syntheses of these compounds. [b] $R_3 = CH_2CH_2Cl$.

Thus, the chemical shift changes in the 3-amino-1,2,4-triazines upon N-oxidation clearly establish these compounds as 2-oxides (**3a–c**) (cf. Scheme I).

When the 3-amino-1,2,4-triazine 2-oxides (**3a–c**) were treated with nitrous acid, in the presence of hydrochloric acid, the respective 3-chloro-1,2,4-triazine 2-oxides (**4a–c**) were obtained, while, with nitrous acid in the presence of hydrobromic acid, the 3-bromo-1,2,4-triazine 2-oxide (**7**) was generated. To assure ourselves that we are indeed dealing with the 3-halo compounds, the 3-chloro derivative **4a** was treated with methanolic ammonia, to regenerate the 3-amino compound **3a**.

In order to prepare 1,2,4-triazine 2-oxide (**9**) itself, the 3-bromo derivative (**7**) was treated with hydrazine to form the 3-hydrazino derivative (**8**), which, when oxidized with activated manganese dioxide, afforded a compound $C_3H_3N_3O$. The ^{1}H NMR spectrum of this substance (**9**) (cf. Table II) shows an ABX pattern ($J_{AB} = 3.0$, $J_{AX} = 0.3$ Hz). The most deshielded proton, a broad singlet approaching a doublet, can be assigned to H-3, while H-5 and H-6 resonate at δ 8.00 and 8.42, respectively. The latter two assignments are established by comparison with the chemical shifts of these protons in compounds **4a,b** and **7**. Thus, the substance is the expected 1,2,4-triazine 2-oxide (**9**). A comparison of these proton chemical shifts with those of the corresponding ones in 1,2,4-triazine (**25**) affords the following proton chemical shift differences ($\Delta = \delta_{N\text{-oxide}} - \delta_{\text{non-N-oxidized compound}}$):



Scheme I

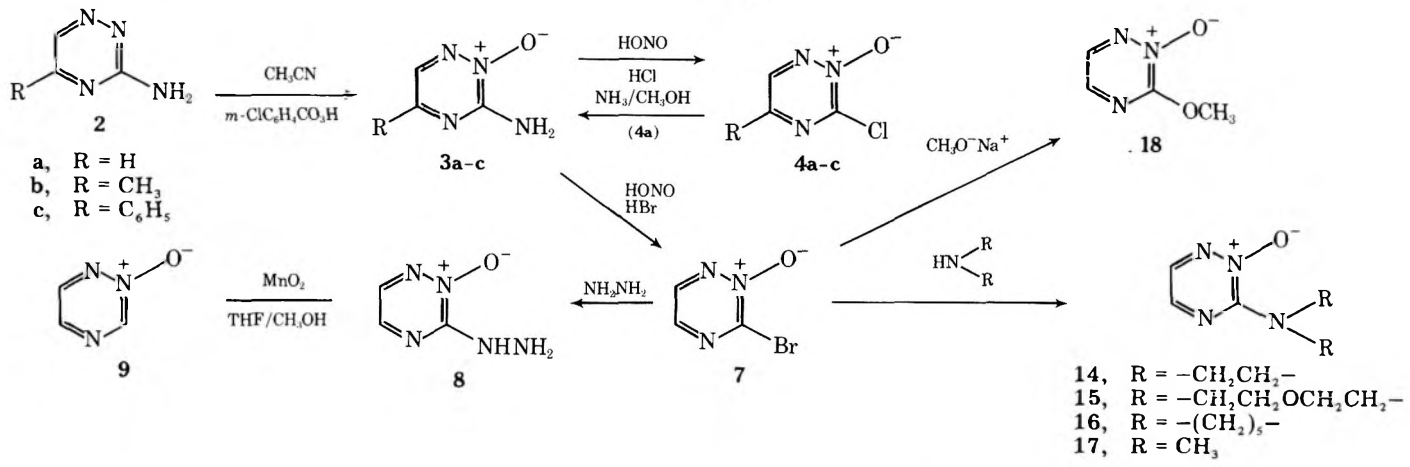
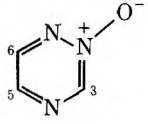


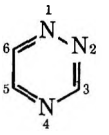
Table II. ^{1}H NMR[a] and Analytical Data of Some 1,2,4-Triazines



Registry no.	Compd	Mol formula	Substituents			^{1}H NMR[a]			Mp, °C	Calcd, %			Found, %		
			R_3	R_5	R_6	R_3	R_5	R_6		C	H	N	C	H	N
61177-95-5	3a	$C_3H_4N_4O$	NH_2	H	H	8.28	8.19	8.23	200–201	32.15	3.16	49.27	31.92	3.34	49.47
61177-96-6	3b	$C_4H_6N_4O$	NH_2	CH_3	H	8.18	2.61	8.18	168–169	38.10	4.80	44.41	38.08	4.89	44.44
61177-97-7	12a	$C_5H_7N_4OCl$	NHR	H	H	3.81	7.23	7.84	106–108	34.40	4.04	37.09	34.31	4.06	32.17
61177-98-8	12b	$C_6H_9N_4OCl$	NHR	CH_3	H	3.81	2.39	7.71	150 dec	38.21	4.81	29.71	38.16	4.82	29.68
61177-99-9	12c	$C_{11}H_{11}N_4OCl$	NHR	Ph	H	3.87	7.98	8.33	165 dec	52.70	4.42		52.89	4.51	
							7.50								
61202-85-5	4a	$C_3H_2N_3OCl$	Cl	H	H		7.98	8.46	84–85	27.39	1.53	31.95	27.68	1.70	31.41
61178-00-5	4b	$C_4H_4N_3OCl$	Cl	CH_3	H		2.55	8.32	72–74	33.01	2.77	28.87	33.01	2.78	28.90
61178-01-6	4c	$C_9H_6N_3OCl$	Cl	Ph	H		8.01	8.88	153–155	52.06	2.91		52.21	3.05	
							7.55								
61178-02-7	7	$C_3H_2N_3OBr$	Br	H	H		7.86	8.45	100–103	27.39	1.53	31.95	27.68	1.70	31.41
61178-03-8	18	$C_4H_5N_3O_2$	OCH_3	H	H	4.24	7.76	8.12	108–110	37.39	3.96	33.07	37.72	4.00	33.10
61178-04-9	17	$C_5H_8N_4O$	NMe_2	H	H	3.30	7.76	7.86	73–75	42.85	5.71	40.00	42.72	5.74	40.14
61178-05-0	15	$C_7H_{10}N_4O_2$	NC_4H_8O	H	H	3.88	7.81	8.02	122–124	46.15	5.49	30.77	46.19	5.53	30.70
61178-06-1	16	$C_8H_{12}N_4O$	NC_5H_{10}	H	H	3.64	7.66	7.79	52–55	53.33	6.66	31.11	53.20	6.54	31.19
						1.59									
61178-12-9	14a	$C_5H_6N_4O$	NC_2H_4	H	H	2.60	7.82	8.16	97–99	43.48	4.38	40.56	43.57	4.42	40.59
61178-08-3	14b	$C_6H_8N_4O$	NC_3H_6	CH_3	H	2.59	2.44	8.02	90–92	47.36	5.30	36.82	47.38	5.31	36.71
61178-09-4	8	$C_3H_5N_5O$	$NHNH_2$	H	H		8.34	8.38	163–164	28.36	3.96	55.10	28.46	3.98	55.38
59323-39-6	9	$C_3H_3N_3O$	H	H	H	8.82	8.00	8.42	82.5–84	37.11	3.09	43.29	37.04	3.17	43.11

[a] Chemical shifts in δ (ppm), dilute solutions in $CDCl_3$, except for the 3-amino derivatives, which are recorded as dilute solutions in CD_3SOCD_3.

Table III. ^{13}C Chemicals Shifts (δ ppm) of Some 1,2,4-Triazines and Their *N*-Oxides[a]

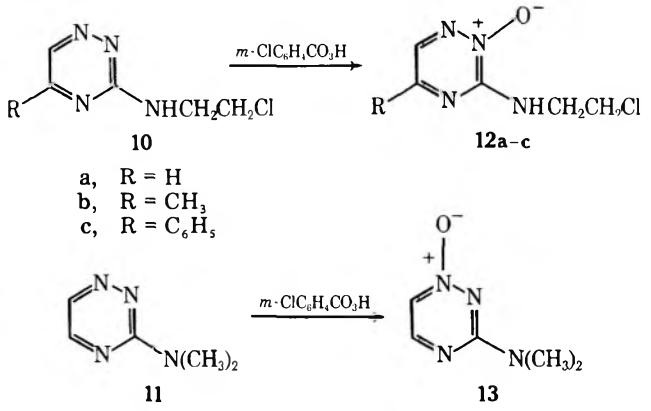


Position of *N*-oxidation — N-ox	Substituents	Registry no.	C_3	C_5	C_6	Substituent carbon
N-2	None (9)		132	143	143	
None	3-OCH_3 (19)	28735-22-0	164	150	143	54
None	3-OCH_3, 6-CH_3 (20)	61178-10-7	163	150	152	54
N-1	3-OCH_3 (21)	27531-67-5	166.5	154	124.5	55.5
N-2	3-OCH_3 (18)		152.5	130	135.5	57
None	3-NH_2 (2a)		161	148	139	
None	3-NH_2, 5-CH_3 (24)	6302-68-7	161	157	139	20
N-1	3-NH_2 (23)	61178-11-8	162	153	119	
N-2	3-NH_2 (3a)		151	132	134	
None	3-NMe_2 (22)	53300-17-7	160	148	138	36
N-1	3-NMe_2 (13)	61178-07-2	161	152	120	36
N-2	3-NMe_2 (17a)		151	132	133	39

[a] ^{13}C spectra were taken with a Hitachi Perkin-Elmer R-26 spectrometer; δ (ppm) from Me_4Si. The spectra of the amino compounds were obtained as 1.5 M solutions in Me_2SO-d_6; all of the others were obrained as 1.5 M solutions in $CDCl_3$. The pulse intervals were 16 s, and a pulse angle of 50° with a total of about 500 scans per spectrum. All spectra were wide-band proton decoupled.

The selective N-2 oxidation of the 3-amino-1,2,4-triazines (**2a–c**) in contrast to the N-1 oxidation of 3-methoxy-1,2,4-triazines prompted us to examine the N-oxidation of some 3-alkylamino- (**10**) and 3-dimethylamino- (**11**) 1,2,4-triazines. In the former instances (cf. Scheme II) the N-oxidation again

Scheme II



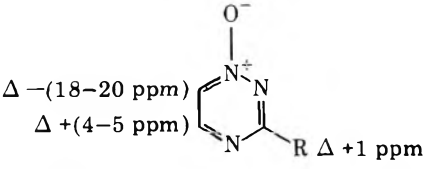
afforded the 2-oxides (**12a–c**) as established by a comparison of the proton chemical shifts with those of the nonoxidized compounds (**10a–c**), while the 1-oxide (**13**) was obtained in the latter instance.[6] Thus, it appears that a *3-amino–3-imino tautomerism* must be possible in order for *N-2 oxidation* to occur on these 1,2,4-triazines, while the absence of this possibility causes N-oxidation to occur at N-1.

That the 3-halo substituents in the 2-oxides (**4a, 7**) are, as expected, subject to facile nucleophilic displacement reactions was shown by their conversion to 3-ethylenimino- (**14a**), 3-morpholino- (**15**), 3-piperidino- (**16**), 3-dimethylamino- (**17**), and 3-methoxy- (**18**) 1,2,4-triazine 2-oxides under very mild conditions (room temperature, 5–10 min).

The ^{13}C chemical shifts of 1,2,4-triazines as well as their 1- and 2-oxides and derivatives have never been examined. To confirm our structural assignments and to develop background information for more detailed studies, we obtained the ^{13}C spectra of some of the compounds (cf. Table III).

3-Methoxy-1,2,4-triazine (**19**) has, as anticipated, four carbon signals. The relaxation time of the most deshielded carbon (164 ppm) is much longer than that of any of the others (relative peak heights 1:4 for C_3 vs. C_5 or C_6 under our experimental conditions) and is, consequently, assigned to C-3, while the most shielded peak (54 ppm) is clearly due to the methoxyl carbon atom. The remaining two peaks (143 and 150 ppm, respectively) must now be assigned. Since it is well known[9] that C-methylation causes deshielding of the methyl group bearing carbon by 8–10 ppm, we examined the ^{13}C spectrum of 3-methoxy-6-methyl-1,2,4-triazine (**20**). The peaks due to C_3 as well as the methoxyl carbon in compound **20** still have the same chemical shift in this derivative as in compound **19**, while the 143-ppm peak is not only shifted to 152 ppm, but its relaxation time is also considerably lengthened (relative peak heights 1:2 for C_6 vs. C_5 under our experimental conditions). Thus, C-6 resonates at 143 ppm and C-5 at 150 ppm in 3-methoxy-1,2,4-triazine (**19**). Similar comparisons of the 3-amino-1,2,4-triazines again show that C-6 is more shielded than C-5. Thus, the shielding sequence of the ^{13}C nuclei in these 1,2,4-triazines is C-3 < C-5 < C-6.

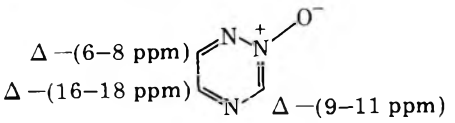
The ^{13}C spectrum of 3-methoxy-1,2,4-triazine 1-oxide (**21**) shows the long relaxation time peak at 166.5 ppm, ascribable to C-3, along with absorptions at 154.0 and 124.5 ppm, respectively. The former is clearly due to C-5 while the latter, with increased relaxation time, must be due to C-6, the carbon ortho to the *N*-oxide function. Thus N-1 oxidation causes shielding (Δ 18 ppm) of C-6, while having little effect (some deshielding, Δ 2–5 ppm) on the other carbon atoms. Similar effects occur in the N-1 oxides of 3-amino- and 3-dimethylamino-1,2,4-triazine. Thus, a composite of the ^{13}C chemical shift effects (Δ) for the 1-oxides vs. the nonoxidized 1,2,4-triazines can be given:



(negative numbers indicate shielding)

The ^{13}C carbons in 3-methoxy-1,2,4-triazine 2-oxide (**18**) in comparison to the non-N-oxidized compound **19** are all more shielded. The lowest intensity peak (longest relaxation time) is again assigned to C-3 (152.5 ppm). This peak has become more shielded by 11 ppm with respect to the non-N-oxidized compound. While the C-5 and C-6 chemical shifts of all of the 2-oxides examined are very similar (Δ 0–5 ppm),

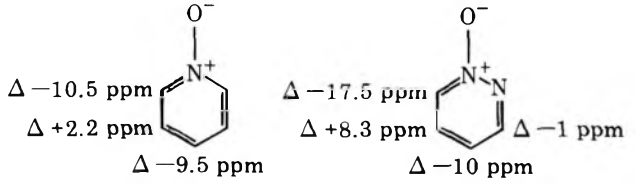
a comparison of these chemical shifts with those of the corresponding non-N-oxidized compounds is nevertheless possible and establishes that C-5, upon 2-oxidation, becomes more shielded by 16–18 ppm, while C-6 experiences a shielding of 6–8 ppm. Thus the following composite can be drawn ($\Delta = \delta_{^{13}C\ N\text{-oxide}} - \delta_{^{13}C\ \text{nonoxidized compound}}$):



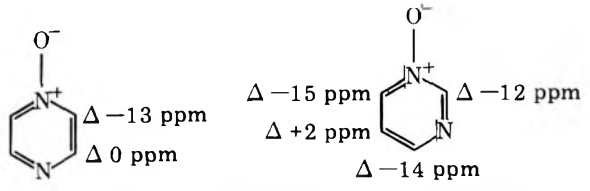
Since the ortho and para positions in the 1- as well as 2-oxides become more shielded in comparison to the nonoxidized compounds, this functional group is increasing the electron density at these positions in the 1,2,4-triazine ring system.[10] Consequently, resonance contributing structures involving back-donation of electrons from the oxygen must contribute significantly to the ground states of these *N*-oxides. Since C-5 in the 2-oxides also experiences shielding upon N-2 oxidation, structure **26** may well best represent the ground-state structure of these 2-oxides while **27** describes the apparent lesser degree of back-donation in the 1-oxides.

26 **27**

The ^{13}C NMR spectra of some pyridine[11] and pyridazine *N*-oxides[12] have also been recently described. In these compounds shielding effects similar to those observed in the 1,2,4-triazine *N*-oxides occur:



In order to complete the "picture" we obtained the ^{13}C spectra of the *N*-oxides of pyrazine (**28**) and pyrimidine (**29**). The differences in the ^{13}C chemical shifts ($\delta_{N\text{-oxide}} - \delta_{\text{non-}N\text{-oxide}}$) of the various ring carbons are as follows.



The chemical shift effect on the carbon atoms in these azines upon N-oxidation can now be summarized. (1) Carbons ortho and para to the *N*-oxide function become more *shielded* (9–20 ppm). (2) Carbons meta to the *N*-oxide *through* a *carbon* bond become slightly *deshielded* (0–8 ppm). (3) Carbons meta to the *N*-oxide *through* a *nitrogen* bond become slightly *shielded* (1–6 ppm). A comparison of these effects with those in the corresponding ^1H NMR spectra points to the interesting difference between the chemical shift changes on the carbon and proton meta to the *N*-oxide through a carbon atom, where in the ^1H NMR none or a small *shielding* effect is observed while in the carbon NMR none or a *deshielding* effect is present.

Conclusion

This study has afforded synthetic means to selectively prepare 1,2,4-triazine 1- and 2-oxides.

The ^{13}C chemical shifts of a series of azine *N*-oxides have been related to their azine precursors. A combination of ^{13}C and ^1H NMR can be employed to unequivocally establish sites of N-oxidation in azines.

Experimental Section[13]

The 3-amino-1,2,4-triazines (**2a–c**) were prepared as described in ref 7, the 3-(2-chloroethylamino)-1,2,4-triazines as described in ref 5. The dimethylamino-1,2,4-triazine 1-oxide was prepared by the method of Paudler and Chen.[6]

Table II lists the necessary analytical data for the new compounds prepared in this study.

Preparation of 3-Amino-1,2,4-triazine 2-Oxides (3a, b). In a typical experiment, 7.00 g (3.40 mmol) of 85% *m*-chloroperbenzoic acid dissolved in 60 ml of reagent grade acetonitrile was added dropwise (10 min) to 2.85 g (26.0 mmol) of 3-amino-1,2,4-triazine (**2a**) in 120 ml of acetonitrile. The reaction mixture was heated at 70–75 °C for 3.0 h and allowed to come to room temperature. The reaction mixture was then evaporated in vacuo and the residue triturated with 100 ml of ether. The suspension was filtered and the solid washed with ether (3 × 20 ml) and benzene (2 × 20 ml) to give 2.63 g (80%) of **3a.** Compounds **3b** could be prepared in 80% yield by a similar procedure. Compounds **3a** and **3b** could be further purified by vacuum sublimation (0.1 Torr, 130 °C) or by recrystallization from acetonitrile.

Preparation of 3-Chloro-1,2,4-triazine 2-Oxides (4a–c). In a typical experiment, 2.76 g (0.04 mol) of $NaNO_2$ in 9 ml of H_2O was added dropwise (20 min) to a solution of 1.12 g (0.01 mol) of compound **3a** in 17 ml (0.10 mol) of 6 N HCl cooled to 0 °C. After the addition was complete, 30 ml of $CHCl_3$ was added and the reaction mixture was allowed to come to room temperature. The $CHCl_3$ was separated and additional $CHCl_3$ (4 × 30 ml) extractions were made. The combined $CHCl_3$ extracts were dried over anhydrous Na_2SO_4, filtered, and evacuated in vacuo. The residue was sublimed at 55–60 °C (0.01 Torr) to give 440 mg (34%) of **4a.** Compounds **4b** and **4c** were prepared by a similar procedure in 32 and 26% yields, respectively.

Preparation of 3-Bromo-1,2,4-triazine 2-Oxide (7). To a solution of 1.12 g (0.01 mol) of 3-amino-1,2,4-triazine 2-oxide (**3a**) in 100 ml of 2 N HBr was added, dropwise, at 0 °C, a solution of 4.14 g (0.12 mol) of $NaNO_2$ in 20 ml of water. The solution was refrigerated overnight and extracted with $CHCl_3$ (5 × 100 ml). The combined extracts were washed with 50 ml of saturated aqueous Na_2CO_3 solution and dried over anhydrous Na_2SO_4. The $CHCl_3$ was evaporated and the residue sublimed at 60 °C (0.05 Torr) to give 1.0 g (47%) of 3-bromo-1,2,4-triazine 2-oxide (**7**).

Preparation of 3-Hydrazino-1,2,4-triazine 2-Oxide (8). To a solution of 1.0 g (5.7 mmol) of 3-bromo-1,2,4-triazine 2-oxide (**7**) in 200 ml of dry tetrahydrofuran was slowly added 0.27 g (0.85 mol) of hydrazine (97%) in 10 ml of dry CH_3OH. The solution was stirred for 30 min and the yellow solid was removed by filtration. Evaporation of the filtrate gave an orange solid which could be recrystallized from CH_3CH_2OH to yield 0.5 (69%) of 3-hydrazino-1,2,4-triazine 2-oxide (**8**).

Preparation of 1,2,4-Triazine 2-Oxide (9). To a solution of 0.2 g (1.4 mmol) of compound **8a** dissolved in 200 ml of dry tetrahydrofuran was added 5 g of activated MnO_2 and the slurry was stirred for 4.5 h. The solution was filtered through Celite and the filtrate was evaporated to dryness to give a yellow-brown oil which crystallized upon standing. Sublimation at room temperature and at 0.1 Torr yielded 40 mg (27%) of 1,2,4-triazine 2-oxide (**9**) as a white solid.

Preparation of 3-(2-Chloroethylamino)-1,2,4-triazine 2-Oxides (12a–c). In a typical experiment, 900 mg (4.4 mmol) of 85% *m*-chloroperbenzoic acid dissolved in 30 ml of anhydrous $CHCl_3$ was added to 640 mg (3.7 mmol) of compound **10b** in 40 ml of anhydrous $CHCl_3$. The reaction mixture was stirred at room temperature overnight and heated at 50–5 °C for 70 min. The cooled $CHCl_3$ solution was washed first with a solution of 0.65 g (4.6 mmol) of K_2CO_3 in 50 ml of H_2O followed by 2 × 20 ml of H_2O. The remaining $CHCl_3$ solution was dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The residue was chromatographed on neutral alumina (grade III) using $CHCl_3$–CH_2Cl_2 (1:1) as eluent to give 530 mg (77%) of **12b.** Compounds **10a** and **10c** were isolated in 51 and 35% yields, respectively, by similar procedures. Analytical samples were obtained by vacuum sublimation.

Preparation of 3-Aziridino-1,2,4-triazine 2-Oxides (14a). In a typical experiment, 0.70 ml (13.0 mmol) of aziridine dissolved in 15 ml of CH_2Cl_2 was added dropwise to 750 mg (5.6 mmol) of compound **7a** in 50 ml of CH_2Cl_2 cooled in an ice bath. After the addition, the ice bath was removed and the reaction mixture was stirred for 0.5 h. The reaction mixture was washed with a solution of 0.79 g (5.6 mmol) of

K_2CO_3 in 10 ml of H_2O. The CH_2Cl_2 was separated and additional CH_2Cl_2 (5 × 25 ml) extracts were made. The combined CH_2Cl_2 extracts were dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo at room temperature. The residue was chromatographed on a short column of neutral alumina (grade III) and eluted with $CHCl_3$ to give 730 mg (95%) of **14a**. An analytical sample was prepared by sublimation at 50 °C (0.01 Torr). A similar procedure gave compound **14b** in 90% yield.

Preparation of 3-Morpholino-1,2,4-triazine 2-Oxide (15). To a solution of 100 mg (5.7 mmol) of 3-bromo-1,2,4-triazine 2-oxide (**7**) in 25 ml of dry tetrahydrofuran was added 99.4 mg (1.14 mmol) of morpholine as a solution in 5 ml of dry tetrahydrofuran. The solution was stirred for 10 min during which time it became bright yellow and the solid which formed was removed by filtration. The filtrate was evaporated to give a yellow solid. This was recrystallized from 50:50 petroleum ether (bp 30–60 °C)–cyclohexane to give 90 mg (93%) of 3-morpholino-1,2,4-triazine 2-oxide (**15**) as yellow needles.

Preparation of 3-Piperidino-1,2,4-triazine 2-Oxide (16). To a solution of 100 mg (0.57 mmol) of 3-bromo 1,2,4-triazine 2-oxide (**7**) in 25 ml of dry tetrahydrofuran was added a solution of 97 mg (1.1 mmol) of piperidine in 5 ml of tetrahydrofuran. The solution was stirred for 10 min during which time it became bright yellow and the solid which formed was removed by filtration. The filtrate was evaporated and the residue was recrystallized from petroleum ether–cyclohexane to give 100 mg (95%) of 3-piperidino-1,2,4-triazine 2-oxide (**16**), as a fluffy, yellow solid.

Preparation of 3-Dimethylamino-1,2,4-triazine 2-Oxide (17). To a solution of 200 mg (1.5 mmol) of 3-bromo-1,2,4-triazine 2-oxide (**7**) in 50 ml of CH_2Cl_2 was bubbled gaseous dimethylamine. The solution became immediately yellow and was stirred for 10 min. The solution was evaporated and the residue sublimed to give a bright yellow solid. This material was recrystallized from tetrahydrofuran to give 200 mg (93%) of 3-dimethylamino-1,2,4-triazine 2-oxide (**17**) as yellow needles.

Preparation of 3-Methoxy-1,2-4-triazine 2-Oxide (18). To a solution of 0.564 g (5.7 mmol) of triethylamine in 25 ml of dry CH_3OH was added 0.5 g (2.85 mmol) of 3-bromo-1,2,4-triazine 2-oxide (**7**). The solution was stirred until TLC (alumina $CHCl_3$) showed that no starting material was left (3 h). The solution was evaporated and the residue, dissolved in 1 ml of $CHCl_3$, was passed through a short column of alumina (15 g) (grade III) and eluted with $CHCl_3$. The solvent was then evaporated below 40 °C and under reduced pressure. The residue was sublimed to yield 60 mg (10%) of 3-methoxy-1,2-4-triazine 2-oxide (**18**).

Acknowledgment. We wish to thank the National Institutes of Health for a Postdoctoral Research Service Award (Fellowship 1 F32CA05065-01) to one of us (B.T.K.).

Registry No.—Aziridine, 151-56-4; morpholine, 110-91-8; piperidine, 110-89-4; dimethylamine, 124-40-3; methanol, 67-56-1.

References and Notes

(1) W. W. Paudler and T. K. Chen, *J. Org. Chem.*, **36**, 787 (1971).
(2) E. Ochiai, "Aromatic Amine Oxides", Elsevier, Amsterdam, 1967, p 101 ff.
(3) W. W. Paudler and S. A. Humphrey, *Org. Magn. Reson.*, **3**, 217 (1971).
(4) J. G. Erickson, *J. Am. Chem. Soc.*, **74**, 4706 (1952).
(5) B. T. Keen, D. J. Krass, and W. W. Paudler, *J. Heterocycl. Chem.*, **13**, 807 (1976).
(6) T. K. Chen, Ph.D. Thesis, Ohio University, 1971; *Diss. Abstr.*, 156 (1971).
(7) W. W. Paudler and J. M. Barton, *J. Org. Chem.*, **31**, 1720 (1966).
(8) (a) H. L. Retcofsky and R. A. Friedel, *J. Phys. Chem.*, **72**, 290, 2619 (1968); (b) *ibid.*, **71**, 3592 (1967).
(9) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists," Wiley-Interscience, New York, N.Y., 1972, pp 83–85.
(10) This comment is not intended to suggest that electron density changes are the sole contributors to ^{13}C chemical shift changes. J. B. Strothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972, pp 106–112.
(11) R. J. Cushley, D. Naugles, and C. Ortiz, *Can. J. Chem.*, **53**, 3419 (1975).
(12) D. F. Klinge, K. C. Van der Plas, and A. Van Veldhuizen, *Recl. Trav. Chim. Pays-Bas*, 21 (1976).
(13) ^1H NMR spectra were obtained with either a Varian HA-100 or a Hitachi Perkin-Elmer R20B NMR spectrometer. ^{13}C NMR spectra were obtained with a Perkin-Elmer Model R-26 spectrometer. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6M instrument equipped with a solid sample injector. The ionizing voltage employed was 70 eV. Elemental analyses were determined by the Analytical Services Laboratory of The University of Alabama Chemistry Department, and Atlantic Microlab, Inc., Atlanta, Ga. Melting points are corrected.

Catalytic Reduction. 4. Hydrogenation of Aldehydes over Borohydride Reduced Nickel and Palladium[1,2]

Thomas W. Russell,* David M. Duncan, and Steven C. Hansen

Division of Natural Sciences, Eastern New Mexico University, Portales, New Mexico 88130

Received May 4, 1976

The hydrogenation of unsaturated aldehydes, over any of a myriad of catalysts, gives a wide variety of products depending on the reaction conditions employed. The case of cinnamaldehyde (I) exemplifies well this problem. Using the "same" catalyst, colloidial palladium, to effect hydrogenation of I, Skita in 1915 found only the saturated aldehyde II.[3] However, Straus and Grindel in 1924 found the saturated alcohol III and hydrocarbon IV, and no aldehyde.[4] Bogert and Powell in 1931 obtained only the aldehyde II.[5] Rylander in 1967 was able to obtain either the aldehyde II or the unsaturated alcohol V just by varying the amount of colloidial palladium used.[6]

$$\underset{\text{I}}{PhCH{=}CHCHO} \rightarrow \underset{\text{II}}{PhCH_2CH_2CHO}, \underset{\text{III}}{PhCH_2CH_2CH_2OH},$$

$$\underset{\text{IV}}{PhCH_2CH_2CH_3}, \underset{\text{V}}{PhCH{=}CHCH_2OH}$$

In a review of the subject, Rylander lists some of the variables with known effects on the catalytic hydrogenation of aldehydes.[6] These include the method of catalyst preparation, source of metal used, solvents used in catalyst preparation and catalyst use, catalyst support, additives (both known and impurities), and amount of catalyst used. Hence, a desired monoreduction of a di- or polyfunctional compound can make the choice of catalyst a rather lengthy decision.

These uncertainties encountered in the hydrogenations of unsaturated aldehydes over many catalysts are not extant when borohydride-reduced nickel or palladium is the catalyst. And, when combined with previous results,[7] the utility of borohydride-reduced metals as hydrogenation catalysts becomes obvious. Work by this laboratory, the Browns, Strohmeier, and others, has indicated that borohydride-reduced nickel and palladium exhibit an almost perfect selectivity for only one of several potentially reducible groups in a molecule.

Borohydride-reduced palladium does not affect the carbonyl π bond of aldehydes; only carbon–carbon π bonds are reduced. A representative selection of aldehydes studied is listed in Table I. In all cases studied, only the saturated aldehyde was obtained. No other products, such as alcohols or hydrocarbons, were detected.

It is especially noteworthy to point out the failure of borohydride-reduced palladium to effect the hydrogenation of benzaldehyde. One might perceive the rapid formation of the dimethyl acetal of benzaldehyde preventing a carbonyl group from being exposed to hydrogenation. However, this possibility cannot be the reason as the IR spectrum of the final reaction product depicts a strong carbonyl absorption at 5.8 μ. Further, no peaks attributable to compounds other than methanol or the saturated aldehyde were observed in the IR spectra or gas chromatograms of the reaction mixtures.

In contrast to the single site affected by palladium, borohydride-reduced nickel does effect hydrogenation of both carbon–oxygen and carbon–carbon π bonds in unsaturated aldehydes. Table II lists a representative selection of the aldehydes studied.

Table I. Aldehydes Treated with Hydrogen over Borohydride-Reduced Palladium[a]

Reactant	Product	Pd, mmol	Time, h
Crotonaldehyde	Butyraldehyde	2.5	0.25[b]
Butyraldehyde	N.R.	20	27
Cinnamaldehyde	Hydrocinnamaldehyde	2.5	3.5[b]
Benzaldehyde	N.R.	2.5	48

[a] 100 mmol of reactant, 30 psi H_2 initial pressure, ambient temperature, in 40 ml of methanol. [b] Hours for uptake of 100 mmol of H_2, reaction continued for an additional 24 h with no additional uptake of H_2.

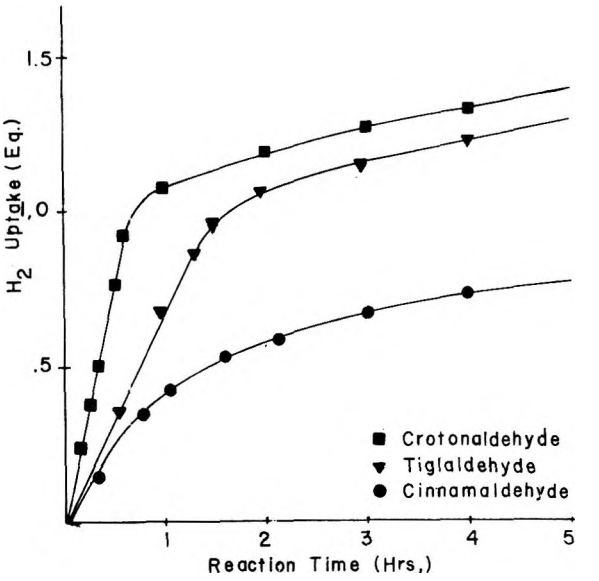


Figure 1. Hydrogenation velocities for 100 mmol of α,β-unsaturated aldehydes over 5 mmol of Ni.

As can be seen from the data in Table II, the carbonyl group is hydrogenated more slowly than the olefinic group over the nickel catalyst. Figure 1 depicts the relative velocities of these two competing reactions for several aldehydes.

The borohydride-reduced palladium effects hydrogenation in a wide variety of solvents. Table III lists hydrogenation times for crotonaldehyde in several solvents. The change in solvent does not change the specificity of the hydrogenation, as no products other than the saturated aldehydes were detected.

The differences between nickel and palladium hydrogenation catalysts produced by borohydride reduction of the metal salts and those "same" metallic catalysts prepared by other reductive methods are clearly apparent. Work is continuing on the elucidation of the properties of these and other borohydride-reduced transition metal catalysts.

Experimental Section

Chemicals. The aldehydes used were extracted with aqueous sodium bicarbonate, dried, and distilled prior to use. Solvents used were

Table II. Aldehydes Treated with Hydrogen over Borohydride-Reduced Nickel[a]

Registry no.	Reactant	Product	Ni, mmol	Time,[b] h
107-02-8	Acrolein	Propionaldehyde	5	0.5
4170-30-3	Crotonaldehyde	Butyraldehyde	5	8
	Crotonaldehyde	Butyraldehyde	20	0.75
104-55-2	Cinnamaldehyde	Hydrocinnamaldehyde	20	1
497-03-0	Tiglaldehyde	α-Methylbutyraldehyde	20	1
123-38-6	Propionaldehyde	Propyl alcohol	50	15
123-72-8	Butyraldehyde	Butyl alcohol	50	21
104-53-0	Hydrocinnamaldehyde	3-Phenylpropanol	20	4
96-17-3	α-Methylbutyraldehyde	2-Methylbutanol	20	7.5
100-52-7	Benzaldehyde	Benzyl alcohol	10	48
98-01-1	Furfural	Furfuryl alcohol	5	12

[a] 100 mmol of reactant, 30 psi initial H_2 pressure, ambient temperature, in 50 ml of 95% ethanol. [b] Hours for uptake of 100 mmol of H_2.

Table III. Hydrogenation Times for Crotonaldehyde in Various Solvents[a]

Solvent	Time,[b] min
Cyclohexane	35
1,2-Dimethoxyethane	20
Dimethylformamide[c]	55
Methanol	15
Toluene	40

[a] 100 mmol of reactant, 2.5 mmol of Pd, 40 ml of solvent, 30 psi H_2 initial pressure, ambient temperature. [b] Minutes for uptake of 100 mmol of H_2. [c] Catalyst prepared in methanol. Black material prepared in DMF did not effect hydrogenation in DMF.

lower grade chemicals and were used directly from the bottles without further purification. Palladium chloride was from Research Organic Chemicals; nickel acetate was from Fisher Scientific. All organic chemicals were analyzed for purity by gas chromatography prior to use. Liquid phases for GC analyses included XF-1150, SE-30, QF-10065, Carbowax 20M, and SF-96.

Catalyst Preparation. Nickel. To a stirred suspension of 1.24 g (5 mmol) of powdered nickel acetate in 50 ml of 95% ethanol was added 5 ml of 1.0 M sodium borohydride in 95% ethanol at room temperature. (Other amounts of catalyst were prepared by using multiples of the amounts of reactants.) Stirring was continued until the evolution of a gas had ceased, usually within 30 min. The black colloidal material was used directly.

Palladium. To a stirred suspension of 0.443 g (2.5 mmol) of powdered palladium chloride in 40 ml of absolute methanol, or other liquid, at room temperature was added 0.19 g (5 mmol) of powdered sodium borohydride over a 5–10-min period. (Other amounts of the catalyst were prepared by using multiples of the amounts of reactants.) Stirring was continued until the evolution of a gas had ceased, usually within 20 min. The black catalyst settled rapidly when stirring was stopped. The solvent is changed readily by decanting and washing two or three times.

Hydrogenation Procedure. To the desired amount of catalyst and solvent in a hydrogenation flask was added 100 mmol of purified aldehyde. The flask was flushed with hydrogen, connected to a Parr low-pressure hydrogenator, and pressurized to 30 psi. Time and pressure were monitored. Reactions were begun at room temperature and conducted under ambient conditions.

The nickel catalyst was removed by centrifugation prior to product analysis. The palladium catalyst settled rapidly upon cessation of shaking.

Product Analysis. Infrared spectra of reaction mixtures were taken prior to gas chromatographic analyses to enable detection of unexpected thermal reactions and incomplete elutions. All reaction mixtures were analyzed directly, after removal of the catalyst, with the exception of those in dimethylformamide. These reaction mixtures were extracted with water and ethyl ether prior to analysis to avoid adverse effects on the GC columns by DMF. The ethereal layer was dried over $CaCl_2$ prior to analysis.

The GC liquid phases used were those aforementioned. Samples of all effluent components were isolated and identified by comparison of IR spectra with those of authentic samples or those in the "Aldrich Library of Infrared Spectra".[8] A comparison was also made of all absorptions of the components of the reaction mixture. No extraneous absorptions were detected.

Acknowledgments. Support of this work by the National Science Foundation (Grants GY-7101 and GU-3431) and Eastern New Mexico University is gratefully acknowledged.

Registry No.—Nickel, 7440-02-0; sodium borohydride, 16940-66-2; palladium, 7440-05-3.

References and Notes

(1) Part 3: T. W. Russell and D. M. Duncan, *J. Org. Chem.*, **39**, 3050 (1974).
(2) Taken in part from the Masters Thesis of D.M.D. Presented in part at the Second Rocky Mountain Regional Meeting of the American Chemical Society, Albuquerque, N.M., July 1974.
(3) A. Skita, *Chem. Ber.*, **48**, 1685 (1915).
(4) F. Straus and H. Grindel, *Justus Liebigs Ann. Chem.*, **439**, 276 (1924).
(5) M. T. Bogert and C. Powell, *J. Am. Chem. Soc.*, **53**, 2747 (1931).
(6) P. N. Rylander, "Catalytic Hydrogenation over Platinum Metals", Academic Press, New York, N.Y., 1967.
(7) see, inter alia, ref 1; H. C. Brown and C. A. Brown, *Tetrahedron, Suppl. 8, Part 1*, 149 (1966); W. Strohmeier and H. Steigerwald, *Z. Naturforsch. B*, **30**, 643 (1975); R. Paul, P. Buisson, and N. Joseph, *Ind. Eng. Chem.*, **44**, 1006 (1952); and references cited therein.
(8) C. Pouchert, Ed., "The Aldrich Library of Infrared Spectra", Aldrich Chemical Co., Milwaukee, Wis., 1970.

Nucleophilic Cleavage Reactions of Cyclic and Acyclic α-Diazo-β-ketophosphoryl Compounds

Hideo Tomioka, Naoki Toriyama, and Yasuji Izawa*

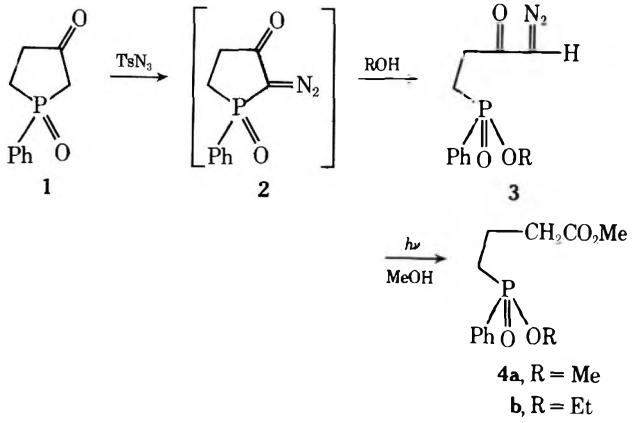
Department of Industrial Chemistry, Faculty of Engineering, Mie University, Tsu, Mie, Japan

Received June 8, 1976

Acyl cleavage reactions of diazocarbonyl compounds have only recently achieved a measure of preparative importance, although they have long been known. The reaction has been shown to be useful for the preparation of α-diazocarboxylates,[1] α-diazo ketones,[2] and α-diazo sulfones[3] from the corresponding acyl derivatives which are readily available via the diazo transfer reaction. In the course of our studies on cyclic phosphorus compounds, we became interested in the five-membered cyclic diazoketophosphoryl compound (**2**) which might be converted to the phosphetane system via photochemical ring contraction. Thus, we attempted to prepare 2-diazo-3-phospholanone oxide (**2**) and found that the ring system in **2** was unstable, leading to ring cleavage exclusively at the P–C bond when treated with an alcohol containing amine.

For comparative purposes, we also examined the reaction of acyclic diazoketophosphoryl compounds under similar conditions.

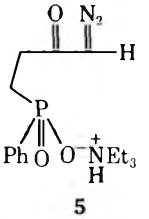
Treatment of a methanol solution of 1-phenyl-3-phospholanone oxide (1) containing a slight excess of triethylamine



with tosyl azide at 0 °C gave a yellow solution. After standing overnight at room temperature, the mixture was freed of solvent. Column chromatography on neutral alumina with chloroform gave acyclic diazo compound (**3a**) and tosyl amide in 81 and 78% yields, respectively, indicating that ring opening at P–C occurred during the reaction. The identity of **3** was confirmed on the basis of spectral data. The infrared spectrum of **3a** showed a prominent diazo absorption at 2140 cm^{-1} and a carbonyl at 1640 cm^{-1}, characteristic of simple acyclic diazo ketone.[2b] The NMR spectrum of **3a** showed a sharp 3 H doublet at δ 3.59 ppm with J_{PH} = 11.2 Hz, characteristic of $POCH_3$, and singlet at δ 5.27 ppm due to the $COCH{=}N_2$ proton. Further evidence concerning the acyclic structure of **3a** was derived from its efficient conversion to methyl carboxylate (**4**) via a photochemical Wolff rearrangement in methanol.

Ethyl phosphinate (**3b**) was similarly obtained by similar treatment in ethanol. In no case did we detect any product derived from an acyl cleavage reaction.

In an attempt to isolate cyclic diazo compound (**2**), the reaction was carried out in aprotic solvents, e.g., dry acetonitrile, acetone, or chloroform. However, in all cases the only neutral product isolable by column chromatography was tosyl amide (80–85% yield); no trace of cyclic diazo compound (**2**) could be isolated. Yellow material at the top of the column was extractable only with alkaline solution, e.g., a methanol solution of triethylamine. The extract was allowed to evaporate to dryness, leaving a yellow, viscous oil, which was tentatively assigned as the triethylamine salt of diazoketophosphinic acid (**5**) from its spectral data.



5

When the reaction was carried out in acetonitrile followed by addition of excess methanol after all tosyl azide had reacted, a 23% yield of **3** was obtained by column chromatography, indicating the transient presence of **2** in solution.

In connection with the observed exclusive phosphoryl cleavage of cyclic system **2** in alcohol with weak base, it is of special interest to examine the behavior of acyclic α-diazo-β-ketophosphonates under similar conditions. Regitz et al.[4] have obtained benzoyldiazomethane as a by-product in the diazo transfer reaction of benzoylphosphonylmethane in the presence of phenyllithium, presumably arising from a phosphoryl cleavage of diazoketophosphonate during aqueous workup. Therefore, **6a** was stirred in methanol containing triethylamine overnight at room temperature. Contrary to the results of Regitz, we found that methyl benzoate and diazomethylphosphonate (**7**) derived from an acyl cleavage were formed in 80 and 78% yields, respectively. Neither phosphate (**8a**) nor benzoyldiazomethane could be isolated even though careful GC analysis of the crude reaction mixtures showed the presence of a trace amount (<1%) of phosphate. The present reaction affords a more convenient method for the preparation of the parent diazophosphonate compared to the reported[5] procedure in which direct diazotization of the corresponding amine was used because of the nonexistence and presumed instability of the required carbonyl precursor [$HCOP(O)(OR)_2 \rightarrow HP(O)(OR)_2 + CO$].

The reaction using acetyl derivative (**6b**) was much more convenient since the cleavage fragment (methyl acetate) was easily removable by evaporation under reduced pressure, leaving diazo compound (**7**) in a relatively uncontaminated state.

In order to clarify whether the observed difference in the cleavage positions between **2** and **6** is due to the phosphine oxide vs. phosphonyl functionality or to the cyclic vs. acyclic system, we also treated α-diazobenzylphosphine oxide (**6c**) with methanol containing amine. Methyl benzoate and diazomethylphosphine oxide (**7c**) were isolated again as main products in 88 and 86% yields, respectively, along with small amounts of phosphinate (**8c**) and benzoyldiazomethane, suggesting an obvious preference for acyl cleavage in the acyclic system. The noted increase in the yield of the phosphoryl cleavage is consistent with the fact that phosphinate is hydrolyzed by hydroxide more easily than phosphate.[6]

Experimental Section

General. Infrared spectra were determined on a JASCO IR-G recording spectrometer. Proton magnetic resonance spectra were determined on a JEOL JNM-MH-100 NMR spectrometer: chemical shifts are reported in units of δ (parts per million) downfield from Me_4Si. Mass spectra were obtained on a Shimadzu GC-MS 1000 spectrometer. GC analysis was performed on a Yanagimoto instrument Model G-80 using a column consisting of 10% SE-30 on Diasolid L (5.0 mm × 2.0 m). Woelm neutral alumina (activity III) was always used for column chromatography.

Starting Materials. Tosyl azide,[1] diazoketophosphonate,[4] and diazoketophosphine oxide[7] were prepared by literature procedures.

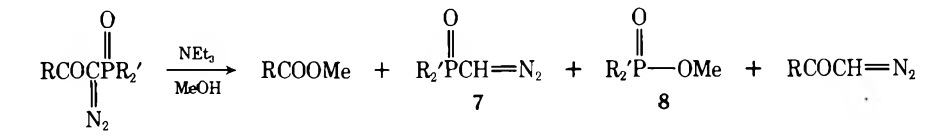
Phenylphospholanone oxide (**1**) was prepared from chloroprene and phenylphosphonous dichloride according to the literature[8] procedure for *P*-methyl derivative and recrystallized from dry benzene: mp 159–161 °C; IR ($CHCl_3$) ν 3380 (OH), 1738 (C=O), 1590 (C=C), and 1180 cm^{-1} (P=O); NMR ($CDCl_3$) δ 1.86–3.24 (m, $-CH_2-$), 4.89 (d, J = 18.8 Hz, C=CH of enol form), and 7.18–7.80 (m, C_6H_5).

Anal. Calcd for $C_{10}H_{11}O_2P$: C, 61.86; H, 5.71. Found: C, 62.03; H, 5.74.

Methyl Phenyl-4-diazo-3-ketobutylphosphinate (3a). To a cooled solution of 97 mg (0.5 mmol) of 1-phenylphospholanone oxide (**1**) and 70 mg (0.68 mmol) of triethylamine in 1.0 ml of dry methanol was added 99 mg (0.5 mmol) of tosyl azide with vigorous stirring over 10–15 min at 0 °C. The addition causes the reaction mixture to warm and assume a yellow color. The mixture was allowed to stand overnight at room temperature, and then all volatile components were evaporated at 20 °C under reduced pressure on a rotary evaporator. The resulting residue was chromatographed over neutral alumina using chloroform as the eluent.

The first fraction obtained, yellowish liquid (103 mg, 81%), was identified as phosphinate (**3**): IR ($CHCl_3$) ν 2140 (C=N_2), 1640 (C=O), 1195 (P=O), and 1040 cm^{-1} (POC); NMR ($CDCl_3$) 2.13–2.73 (m, 4 H, $-CH_2-$), 3.59 (d, 3 H, J = 11.2 Hz, POMe), 5.27 (s, 1 H, CH=N_2), and 7.37–7.91 (m, 5 H, C_6H_5); mass spectrum m/e 224 (M^+ − 28), 196, 168.

The second fraction, obtained as white crystals (130 mg, 76%), was



6a, R = Ph; R′ = OEt	80%	78%	<1%	
b, R = Me; R′ = OEt		90%		
c, R = R′ = Ph	88%	86%	12%	10%

identified as tosyl amide by comparison of its IR and NMR spectra with those of an authentic sample.

Ethyl Phosphinate (3b). Using ethanol as solvent in the above procedure gave a 78% yield of **3b**: IR ($CHCl_3$) ν 2140 (C=N_2), 1640 (C=O), 1193 (P=O), and 1035 cm^{-1} (POC); NMR ($CDCl_3$) δ 1.28 (t, J = 7.0 Hz, 3 H, CH_2CH_3), 2.16–2.82 (m, 4 H, $-CH_2-$), 3.86 (d, J_{PH} = 7.0 Hz, of q, J_{HH} = 7.0 Hz, 2 H, $POCH_2CH_3$), 5.24 (s, 1 H, CH=N_2), and 7.26–7.80 (m, 5 H, C_6H_5); mass spectrum *m/e* 238 ($M^+ - 28$), 210, 182.

Attempt to Isolate 2-Diazo-3-phospholanone Oxide (2). To a solution of 194 mg (1.0 mmol) of phospholanone oxide (**1**) and 140 mg of triethylamine in 2.0 ml of dry acetonitrile was added 198 mg (1.0 mmol) of tosyl azide and the mixture was kept overnight at room temperature. TLC analysis of the reaction mixture showed that no tosyl azide was present at the end of this time.

To one-half of the solution was added 1.0 ml of dry methanol and the resulting solution was allowed to stir overnight. The solvent was removed under reduced pressure and the residue was chromatographed in the usual way. The foreband gave acyclic diazophosphinate (**3a**) (28 mg, 23%); further elution with chloroform afforded tosyl amide (66 mg, 77%).

The second half of the reaction mixture was evaporated under reduced pressure, followed by chromatography. Only tosyl amide (70 mg, 82%) was eluted from the column. The yellow material adsorbed on the alumina at the top of the column was extracted with 10% triethylamine in methanol and the extract was evaporated to dryness under vacuum to give **5** as a sticky yellow oil, which failed to crystallize upon standing: IR ($CHCl_3$) ν 2400, 2250 (N^+H), 2140 (C=N_2), 1640 (C=O), 1190 cm^{-1} (P=O); NMR ($CDCl_3$) δ 1.10 (t, J = 8 Hz, 9 H, CH_2CH_3), 1.75–2.68 (m, 4 H, $-CH_2-$), 2.95 (q, J = 8 Hz, 6 H, CH_2CH_3), 3.41 (s, 1 H, ^+NH), 5.33 (s, 1 H, CH=N_2), and 7.20–7.95 (m, 5 H, C_6H_5).

Photolysis of 3 in Methanol. A solution of 56 mg of **3a** in 1 ml of methanol was placed in a quartz tube and irradiated for 5 h at 12 °C with a 300-W medium-pressure mercury lamp. After removal of solvent under vacuum, the residue was chromatographed on alumina using chloroform to afford 26.7 mg (80%) of methyl carboxylate **4a** as a colorless liquid: ir ($CHCl_3$) ν 1730 (C=O), 1179 (P=O), and 1040 cm^{-1} (POC); NMR ($CDCl_3$) δ 1.65–2.57 (m, 6 H, $-CH_2-$), 3.63 (d, J = 11.3 Hz, 3 H, POMe), 3.65 (s, 3 H, COOMe), and 7.38–8.18 (m, 5 H, C_6H_5); mass spectrum *m/e* 256 (M^+), 225, 197.

Anal. Calcd for $C_{12}H_{17}O_4P$: C, 56.25; H, 6.69; P, 12.09. Found: C, 56.12; H, 6.70; P, 11.96.

Using **3b** in the above procedure gave **4b** in 63% yield: IR ($CHCl_3$) ν 1730 (C=O), 1190 (P=O), and 1036 cm^{-1} (POC); NMR ($CDCl_3$) δ 1.30 (t, J = 6.6 Hz, 3 H, $POCH_2CH_3$), 1.71–2.55 (m, 6 H, $-CH_2-$), 3.46 (s, 3 H, OMe), 4.02 (d, J_{PH} = 6.6 Hz, of q, J_{HH} = 6.6 Hz, 2 H, $POCH_2CH_3$), and 7.37–7.95 (m, 5 H, C_6H_5); mass spectrum *m/e* 270 (M^+), 239, 211.

Anal. Calcd for $C_{13}H_{19}O_4P$: C, 57.77; H, 7.09; P, 11.46. Found: C, 57.60; H, 7.13; P, 11.10.

Diethyl Diazomethylphosphonate (7). A. From Benzoyl Derivative (6a). To a solution of 84 mg (0.3 mmol) of diethyl α-diazophenacylphosphonate (**6a**) in 0.5 ml of dry methanol was added 33 mg (0.32 mmol) of triethylamine in 0.5 ml of methanol at room temperature. The solution was stirred vigorously overnight at the same temperature. GC analysis of the reaction mixture at the end of this time indicated the presence of methyl benzoate and a trace amount of methyl diethyl phosphate. Volatile components were removed from the resulting red solution under reduced pressure at 20 °C and the residue was chromatographed on alumina.

The first fraction was methyl benzoate (33 mg, 80%), identified by IR and NMR comparison with an authentic sample.

The second fraction was diazomethylphosphonate (**7a**, 42 mg, 78%), yellow liquid: IR ($CHCl_3$) ν 2142 (C=N_2), 1250 (P=O), and 1024 cm^{-1} (POC); NMR ($CDCl_3$) δ 1.37 (t, J = 7.2 Hz, 6 H, $POCH_2CH_3$), 3.68 (d, J = 10.8 Hz, 1 H, CH=N_2), and 4.08 (d, J_{PH} = 7.2 Hz, of q, J_{HH} = 7.2 Hz, 4 H, $POCH_2$).

B. From Acetyl Derivative (6b). To a solution of 137 mg (0.62 mmol) of **6b** in 1.0 ml of methanol was added 80 mg of triethylamine. After stirring overnight at room temperature, all volatile components were rigorously evaporated under reduced pressure at 30 °C to give yellow liquid (101 mg, 90%), which showed essentially identical NMR and IR spectra with those of **7** obtained above.

Diphenyldiazomethylphosphine Oxide (7c). Treatment of a suspension of 208 mg (0.6 mmol) of **6c** in 1.0 ml of methanol with 80 mg (0.8 mmol) of triethylamine as above resulted in a clear solution. Chromatography of the reaction mixture as usual manner gave the following products in their order of separation. Methyl benzoate (71.8 mg, 88%); benzoyldiazomethane [8.9 mg, 10%; IR ($CHCl_3$) ν 2125 (C=N_2) and 1612 cm^{-1} (C=O); NMR ($CDCl_3$) δ 5.92 (s, 1 H, CH=N_2) and 7.35–7.84 (m, 5 H, C_6H_5)]; **8c** [17.4 mg, 12%; NMR ($CDCl_3$) 3.67 (d, J_{PH} = 12.0 Hz, 3 H, POMe) and 7.28–7.92 (m, 5 H, C_6H_5)]; **7c** [124.5 mg, 86%; IR ($CHCl_3$) ν 2120 (C=N_2) and 1282 cm^{-1} (P=O); NMR ($CDCl_3$) 4.20 (d, J_{PH} = 12.1 Hz, 1 H, CH=N_2) and 7.34–7.81 (m, 5 H, C_6H_5)].

Acknowledgments. The authors wish to thank Denki Kagaku Kogyo Co. for providing us with chloroprene used in the preparation of the phospholanone.

Registry No.—**1**, 60705-77-3; **3a**, 60705-78-4; **3b**, 60705-79-5; **4a**, 60705-80-8; **4b**, 60705-81-9; **5**, 60705-83-1; **6a**, 19734-16-8; **6b**, 21047-57-4; **6c**, 17507-54-9; **7a**, 25411-73-8; **7c**, 5353-66-2; **8a**, 867-17-4; **8c**, 1706-90-7; PhCOOMe, 93-58-3; $PhCOCH=N_2$, 3282-32-4; tosyl azide, 941-55-9; tosyl amide, 70-55-3.

References and Notes

(1) M. Regitz, J. Hocker, and A. Liedhegener, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 179; *Org. Prep. Proced.*, **1**, 99 (1969).
(2) (a) P. Yates and B. L. Shapiro, *J. Org. Chem.*, **23**, 759 (1958); (b) J. B. Hendrickson and W. A. Wolf, *ibid.*, **33**, 3610 (1968).
(3) D. Hodson, G. Holt, and D. K. Wall, *J. Chem. Soc. C*, 2201 (1968).
(4) M. Regitz, W. Anschütz, and A. Liedhegener, *Chem. Ber.*, **101**, 3734 (1968).
(5) D. Seyferth, R. S. Marmor, and P. Hilbert, *J. Org. Chem.*, **36**, 1379 (1971).
(6) R. F. Hudson and L. Keay, *J. Chem. Soc.*, 1859 (1960).
(7) M. Regitz and W. Anshütz, *Chem. Ber.*, **102**, 2216 (1969).
(8) L. D. Quin and R. C. Stocks, *J. Org. Chem.*, **39**, 686 (1974).

A Simple, High Yield Method for the Nucleophilic Substitution of Halonitrobenzenes by Thiols

Elijah H. Gold,* Victor Piotrowski, and Ben Zion Weiner

Schering Corporation, Chemical Research—Medicinals, Bloomfield, New Jersey 07003

Received July 12, 1976

Although the use of direct thioalkylation of halonitrobenzenes is often a convenient route to the corresponding thioanisoles,[1] the desired reaction can be almost completely precluded by reduction of the nitro group.[2] During the course of other work, we required thioanisole **2b** (R = CH_3) as an intermediate. In attempting to prepare this compound by the method of Hodgson and Handley,[1,2] we obtained **2b** (R = CH_3) in only 18% yield, the remainder consisting of the three possible azoxybenzenes **3b–d** (R = CH_3).[3]

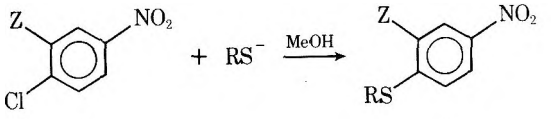
It occurred to us that this problem might be readily overcome by forming the thiolate anion in the presence of both excess thiol[4] and aromatic substrate. This was readily carried out by the dropwise addition of methanolic KOH to **1b** in the

Table I

Reactants	Solvent	Method[a]	Product(s)[b]	Registry no.	% yield[c]	Mp, °C[d]
1. **1a**[r] + CH_3SH[t]	MeOH	A	**2a** (R = methyl)	701-57-5	92[e]	67[f]
2. **1b**[s] + CH_3SH	MeOH	B	**3b**	60789-46-0		144–144.5[h]
			3c (R = methyl)	60789-47-1	81[e,g]	124.5–125[h]
			3d (R = methyl)	60789-48-2		168.5–169
			2b (R = methyl)	60789-49-3	18[e]	
3. **1b** + CH_3SH	MeOH	A	**2b** (R = methyl)		95[e]	54–54.5[h]
4. **1b** + $(CH_3)_2CHSH$[u]	MeOH	B	2-Methoxy-5-nitro-(α,α,α-trifluoro)-toluene	654-76-2	92[e]	79.5–80[i]
5. **1b** + $(CH_3)_2CHSH$	MeOH	A	**3b**		87[e]	
6. **1a** + $(CH_3)_2CHSH$	MeOH	A	**2a** (R = 2-propyl)	7205-63-2	93[e]	45.5[j]
7. **1b** + $(CH_3)_2CHSH$	DMF	B	**2b** (R = 2-propyl)	60789-50-6	34[e,l]	48[k]
8. **1b** + $(CH_3)_2CHSH$	DMF	A	**2b** (R = 2-propyl)		92[e]	
9. **1a** + $PHCH_2SH$[v]	MeOH	B	**2a** (R = benzyl)	27691-43-6	~70[m]	
			3a	614-26-6	6[e]	150.5[n]
			4-Nitroanisole	100-17-4	~23[m]	
10. **1a** + $PhCH_2SH$	MeOH	A	**2a** (R = benzyl)		98[e]	122°
11. **1b** + $PhCH_2SH$	MeOH	B	**2b** (R = benzyl)	60789-51-7	~75[m]	
			2-Methoxy-5-nitro-(α,α,α-trifluoro)-toluene		~19[m]	
12. **1b** + $PhCH_2SH$	MeOH	A	**2b** (R = benzyl)		93[e]	83.5[p]
13. **1b** + $PhCH_2SH$	DMF	B	**2b** (R = benzyl)		~35[m]	
			3b		~60[m]	
14. **1b** + $PhCH_2SH$	DMF	A	**2b** (R = benzyl)		96[e]	
15. **1b** + PhSH[w]	MeOH	B	**2b** (R = phenyl)	3833-18-9	92[e]	51.5[q]
16. **1b** + PhSH	MeOH	A	**2b** (R = phenyl)		95[e]	

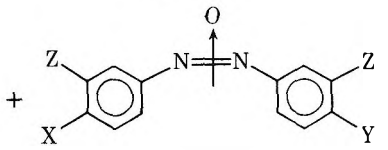
[a] A = new procedure, see Experimental Section; B = literature method, see Experimental Section. [b] Satisfactory IR, NMR, and MS data were obtained for all new compounds in table. [c] No special effort was made to optimize isolated yields. [d] Melting points were determined in capillary tubes using a Thomas-Hoover apparatus, and are corrected. [e] Isolated yield. [f] Reference 7, 66–67 °C. [g] As a mixture. [h] See Experimental Section. [i] Reference 3, 79–79.5 °C. [j] Reference 8, 44.5 °C. [k] Recrystallized from hexane. Anal. Calcd: C, 45.28; H, 3.80; N, 5.28; F, 21.49; S, 12.09. Found: C, 45.44; H, 3.51; N, 5.10; F, 21.42; S, 12.23. [l] The remaining three products (TLC, not isolated) are presumably **3b–d** (R = 2-propyl). [m] Not isolated; yields approximated by NMR. [n] Reference 1, 150–151 °C. [o] Reference 7, 120–122.5 °C; ref 8, 123 °C. [p] Recrystallized from hexane. Anal. Calcd: C, 53.67; H, 3.22; N, 4.47; F, 18.19; S, 10.23. Found: C, 53.64; H, 3.51; N, 4.33; F, 17.95; S, 10.32. [q] Recrystallized from hexane. Anal. Calcd: C, 52.17; H, 2.69; N, 4.68; F, 19.04; S, 10.71. Found: C, 51.90; H, 2.93; N, 4.69; F, 19.03; S, 10.85. [r] Registry no., 100-00-5. [s] Registry no., 777-37-7. [t] Registry no., 74-93-1. [u] Registry no., 75-33-2. [v] Registry no., 100-53-8. [w] Registry no., 108-98-5.

presence of a small stoichiometric excess of methanethiol which, indeed, afforded only the desired substitution product **2b** (R = CH_3); none of the azoxy compounds **3b–d** (R = CH_3)



1
a, Z = H
b, Z = CF_3

2
a, Z = H
b, Z = CF_3



3
a, Z = H; X = Y = Cl
b, Z = CF_3; X = Y = Cl
c, Z = CF_3; X = Cl; Y = RS
d, Z = CF_3; X = Y = RS

were present, as evidenced by TLC. A further significant improvement in this approach was made by the use of dimethylformamide (DMF)[5] instead of methanol, which virtually eliminated other side reactions.[6]

A comparison of the general efficacy of this method vs. the literature procedure was made by reacting the readily reducible substrates **1a** and **1b** with several representative thiols, and the results are summarized in Table I.

The effectiveness of DMF vs. an alcoholic solvent such as methanol is probably due both to its nonnucleophilicity as well as to the approximately 10^5-fold rate enhancement for the desired nucleophilic substitution reaction.[9] This latter point is evidenced by comparison of the reaction of sodium 2-propanethiolate under various conditions with **1a** and **1b**.[10] In methanol, even under the excess thiol conditions of this work, **1b** essentially afforded only reduction product **3b** whereas, under the same conditions, **1a** yielded mainly addition product **2a** (R = 2-propyl). Apparently, in the case of **1b**, steric hindrance caused by the combination of an ortho substituent (CF_3) and a secondary thiol (i.e., 2-propyl vs. methyl) is great enough to retard the rate of substitution relative to the redox reaction. In DMF, however, the rate of the desired substitution reaction is enhanced to the point where it now proceeds faster than the redox process.

In summary, the use of this simple modification, along with the change of solvent to DMF, should greatly increase the versatility of this often unpredictable chemical reaction.

Experimental Section

General New Procedure for Thiolation. To a cold (ca. 0 °C), stirred solution (under nitrogen) of 0.07 mol of thiol and 0.040 mol of 1 in 30 ml of DMF (or 30 ml of MeOH), 3.1 g (0.055 mol) of KOH, dissolved in a mixture of 20 ml of DMF (or 20 ml of MeOH) and 1.5 ml of H_2O, was added dropwise (ca. 40 min), maintaining the temperature at ca. 0 °C. Following addition, the mixture was heated at

80 °C for 1 h (or refluxed when MeOH was used) and poured onto 200 ml of ice–water, and the solid product(s) was filtered. It was subsequently determined that the use of 0.045 mol (1.1 equiv) of thiol gave comparable results.

General Literature[1] Thiolation Method. The thiol (0.05 mol) was added to a cold (ca. 0 °C), stirred solution of 2.8 g (0.05 mol) of KOH in 50 ml of MeOH (or 50 ml of DMF), followed by dropwise addition (ca. 15 min) of 0.04 mol of 1 in 30 ml of MeOH (or 30 ml of DMF), maintaining the temperature at ca. 0 °C. The mixture was refluxed (or heated at 80 °C when DMF was used) for 40 min and poured onto 200 ml of ice-cold 10% HCl, and the solid product(s) was filtered.

Separation of 2b and 3b–d. A portion of the crude solid (7.1 g) obtained from the reaction of CH_3SNa with **1b** was chromatographed on 350 g of silica gel (J. T. Baker Chemical Co., no. 5-3405) in a 5-cm column. After elution of **3b** with CH_2Cl_2–hexane (1:9), the solvent ratio was changed to 3:20 and the remaining compounds were eluted in the order **3c, 2b, 3d.** Azoxybenzenes **3b–d** were recrystallized from ethanol and **2b** was recrystallized from hexane: UV[11] λ_{max} (log ϵ), **3b** 230 (4.07), 268 (4.01), 330 (4.35); **3c** 240 (4.01), 364 (4.38); **3d** 247 (4.09), 380 (4.52); **2b,** 225 (3.84), 334 (4.18). Anal. **3b.** Calcd: C, 41.71; H, 1.50; N, 6.95, Cl, 17.59. Found: C, 41.73; H, 1.75; N, 6.69; Cl, 17.50. **3c.** Calcd: C, 43.43; H, 2.19; N, 6.55; Cl, 8.55; S, 7.73. Found: C, 43.36, H, 2.38; N, 6.66; Cl, 8.71; S, 7.97. **3d.** Calcd: C, 45.06; H, 2.84; N, 6.57; S, 15.04. Found: C, 44.70; H, 3.00; N, 6.45; S, 15.50. **2b.** Calcd: C, 40.50; H, 2.55; N, 5.91; S, 13.52. Found: C, 40.73; H, 2.68; N, 5.87; S, 13.51.

References and Notes

(1) H. H. Hodgson and F. W. Handley, *J. Soc. Chem. Ind., London,* **46,** 435T (1927).
(2) For example, in ref 1, the addition of *p*-chloronitrobenzene (**1a**) to a methanolic solution of sodium methanethiolate affords mainly 4,4-dichloroazoxybenzene (**3a**) and only a "very small amount" of the desired thioanisole (**2a**, R = CH_3).
(3) This is in contrast to the analogous substitution of **1a** by methoxide, which proceeds readily in good yield: R. Filler and H. Novar, *J. Org. Chem.,* **26,** 2707 (1961).
(4) It was expected that the buffering effect of the excess thiol would slow the rate of reduction, presumably by lowering the effective reduction potential of the system.
(5) The success with DMF obviated studies with other potentially useful solvents [e.g., Me_2SO, see R. L. Jacobs, *J. Org. Chem.,* **36,** 242 (1971)].
(6) For example, the addition of solvent (see Table I, entries 4, 9, 11).
(7) W. R. Waldron and E. E. Reid, *J. Am. Chem. Soc.,* **45,** 2399 (1923).
(8) R. H. Baker, R. M. Dodson, and B. Riegel, *J. Am. Chem. Soc.,* **68,** 2636 (1946).
(9) J. Miller and A. J. Parker, *J. Am. Chem. Soc.,* **83,** 117 (1961).
(10) Table I, entries 4–8.
(11) UV spectra were taken in ethanol on a Cary 14 instrument.

Thermolysis of 4,4,10β-Trimethyl-*trans*-decal-3β-ol Azidoformate

Michael R. Czarny, Barrett W. Benson,[1] and Thomas A. Spencer*

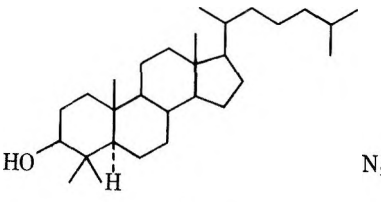
Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755

Received July 27, 1976

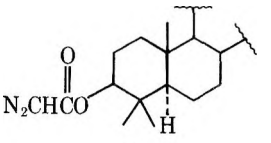
A recent report[2,23] of thermolysis of the azidoformate derived from lanostanol prompts us to describe the results of an analogous experiment in the decalin series.[3] Our aim, like that of Jones, Alewood, Benn, and Wong,[2] was to see if functionalization of one or both of the C-4 methyl groups of a compound like 4,4-dimethylcholestan-3β-ol (1) could be achieved by intramolecular insertion of the nitrene formed from an azidoformate derivative of the C-3 β-hydroxyl group. Although such insertion would lead to a six-membered ring carbamate, rather than the usually predominant[4,5] five-membered ring carbamate which would result from nitrene attack at C-2, molecular models indicate that insertion into either C-4 methyl group is relatively favorable geometrically. Because we had previously succeeded in functionalizing the C-4 β-methyl group via photolysis of a doxyl derivative of 4,4-dimethylcholestan-3-one,[6] our hope was that insertion would occur at the equatorial, 4α-methyl group. As indicated below, this hope was realized in the conversion of **5** to **8**, although in lower yield than in the comparable conversion in the lanostanol series.[2]

Initially, we explored decomposition of diazoacetate **2,** derived from **1** by the method of House,[7] to see if carbenoid insertion at a C-4 methyl group would occur. However, the products from thermolysis or photolysis of **2** were very complex mixtures, which contained predominantly material which afforded **1** upon treatment with $LiAlH_4$. Since these facts indicated that a useful amount of intramolecular insertion had not occurred, we turned to azidoformate decomposition.

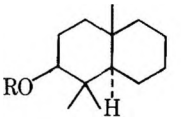
The azidoformate selected for thermolysis was **5,** derived from 4,4,10β-trimethyl-*trans*-decal-3β-ol (**3**).[8,9] Preparation



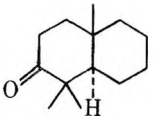
1



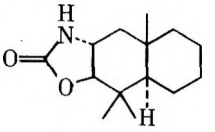
2



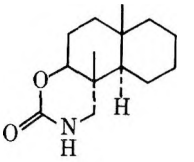
3, R = H
4, R = COCl
5, R = CON_3



6



7



8

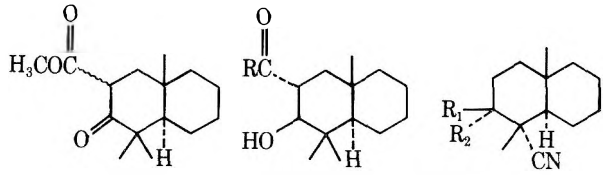
of **5,** mp 55–57 °C, was accomplished in excellent yield by treatment of **3** with phosgene to afford **4,** which was readily converted to **5** with sodium azide. When a vacuum degassed CCl_4 solution of **5** was heated at 180 °C for 3 h, a much simpler product mixture was formed than from **2,** and the three principal products were easily separated by chromatography. One was readily identified, by comparison with an authentic sample,[10] as 4,4,10β-trimethyl-*trans*-decal-3-one (**6,** 14%), a type of product, like the other two described below, which has previously been obtained from azidoformate decompositions.[2,5]

The other two products both had molecular formula $C_{14}H_{23}NO_2$, consistent with their being intramolecular nitrene insertion products. The major product, mp 185–186 °C (51%), had ν_{max} 1740 cm^{-1} and three methyl peaks in its NMR spectrum suggesting that it was an oxazolidinone formed by insertion at C-2. The third product, mp 164–166 °C (14%), had ν_{max} 1715 cm^{-1} and only two methyl peaks plus a new two-proton signal at ~3 ppm in its ^1H NMR spectrum, suggesting that it was the desired type of product resulting from insertion at a C-4 methyl group. These inferences were confirmed by identification of the two substances as **7** and **8,** respectively, by comparison with authentic samples of **7** and **8** synthesized by the alternate pathways delineated below.

These results are very similar to those obtained in the thermolysis of lanostanyl azidoformate,[2] which afforded ca. 15% of lanostanone, ca. 30% of an oxazolidinone of unassigned stereochemistry at C-2, and ca. 35% of the product analogous to **8.** Assignment of structure to the latter two insertion

products was based on analysis of their ^{13}C NMR spectra,[2] as opposed to the chemical means utilized in this study. The only apparent difference between the two sets of results is the greater proportion of insertion at the C-4 α-methyl in the steroidal case. The reason for this difference is not obvious from examination of molecular models.

The decision to synthesize **7** rather than its C-2 epimer was based on the report by Edwards and Paryzek[5] that the trans-fused oxazolidinone formed by insertion at the 6α position is the predominant product from thermolysis of 3β-acetoxy-11-oxolanostan-7β-yl azidoformate. Work of Pavia, Winternitz, and Wylde[11] suggested the pathway we used to prepare **7**, through the sequence **6** → **9** → **10** → **11** → **7**. The



9 **10**, R = OCH_3 **11**, R = $NHNH_2$ **12**, R_1, R_2 = O **13**, R_1 = OH, R_2 = H

conversion of ketone **6** to β-keto ester **9** was accomplished in 92% yield using methylmagnesium carbonate.[12] This method for introducing the carbomethoxyl function at C-2 was impressively superior to several others, including the recent procedure employing NaH–KH and dimethyl carbonate in tetrahydrofuran,[13] all of which gave only very low yields of the largely enolic **9**.

The next step, reduction of **9** to **10**, proved to be the most troublesome conversion in the sequence. A wide variety of reducing agents gave only low yields of what was eventually identified as the desired 3β-hydroxy 2α-carbomethoxy compound. A good yield (67%) of **10** was finally obtained using $NaBH_4$ as reductant in isopropyl alcohol–water at −50 °C. The stereochemistry of **10** was determined from its ^1H NMR spectrum, which showed (in the presence of D_2O to eliminate coupling to the hydroxyl proton) a doublet at 3.42 ppm with J = 11 Hz for the C-3 H, and a triplet of doublets at 2.65 ppm with J = 11, 11, and 4 Hz for the C-2 H, a pattern consistent only with both protons being axially disposed.[14,15]

Conversion of **10** to hydrazide **11** with hydrazine in methanol was essentially quantiative, and diazotization of **11**, inducing migration of C-2 to nitrogen with retention of configuration,[16] afforded **7** in 91% yield. This product was identical in all respects with the oxazolidinone obtained by thermolysis of **5**.

Synthesis of **8** was accomplished using the known 4α-cyano-4β-methyldecal-3-one **12**, which was prepared from the readily accessible 4,10-dimethyl-$\Delta^{4,5}$-octal-3-one[18] in a somewhat better yield (44%) by a modification of the venturesome reductive cyanation procedure of Kuehne and Nelson.[17] Reduction of **12** with $NaBH_4$ afforded **13** in essentially quantitative yield. Hydrogenation of the nitrile function of **13** proved more effective than $LiAlH_4$ reduction for generation of the presumed 4α-aminomethyl-3β-hydroxy intermediate, which, without purification, was converted by treatment with phosgene to **8** in excellent overall yield from **13**. The **8** thus prepared was identical with the third product from thermolysis of **5**, establishing conclusively that functionalization of the 4α-methyl group had been achieved, albeit in low yield.

Experimental Section

Melting points were determined in open capillaries using a Thomas-Hoover apparatus and are uncorrected. Unless otherwise specified, IR spectra of solids were obtained as KBr pellets and of liquids as neat films on a Perkin-Elmer 137 spectrophotometer. Unless otherwise specified, NMR spectra were determined in $CDCl_3$ on a Perkin-Elmer R-24 spectrometer with Me_4Si as an internal standard. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Mass spectra were determined by Dr. Catherine Costello at the MIT Mass Spectrometry Facility, sponsored by the USPHS Division of Research Resources through Grant RR00317. Preparative TLC was performed on 20 × 20 cm plates coated with 1.45-mm thick layers of silica gel $PF_{254+366}$ (Brinkmann Instruments, Inc., Westbury, N.Y.) which had been mixed with 0.002% Rhodamine 6G dye (Eastman Kodak Co., Rochester, N.Y.). UV light was used to visualize TLC plates. Brine refers to saturated aqueous sodium chloride solution.

4,4-Dimethyl-3β-diazoacetoxycholestane (2). 4,4-Dimethylcholestan-3β-ol (**1**) was prepared in 74% yield with mp 155–156 °C by $LiAlH_4$ reduction of 4,4-dimethylcholestan-3-one.[19] The tosylhydrazone of glyoxylic acid and its acid chloride were prepared according to the procedure of House.[20] To a stirred solution of 3.00 g (7.19 mmol) of **1** in 40 ml of distilled CH_2Cl_2 was added 1.90 g (7.28 mmol) of the acid chloride at room temperature. Triethylamine, 0.74 g (7.32 mmol), which had been purified by successive distillations from phthalic anhydride and potassium hydroxide, was added dropwise with stirring over 10 min, while the solution was maintained at 25–30 °C. Over the next hour additional half equivalents of acid chloride and triethylamine were sequentially added to the solution, followed by dropwise addition of a further 1.15 g of triethylamine. After a further 1.5 h at room temperature, TLC analysis of a sample of the yellow-orange solution showed almost no **1**. The reaction mixture was evaporated to a solid residue which was partitioned between ether and brine. The aqueous layer was extracted with two 50-ml portions of ether. The combined ether extracts were washed with dilute $NaHCO_3$ solution and water, dried over Na_2SO_4, and evaporated to afford 3.9 g of yellow solid which was recrystallized in two crops from benzene–methanol to yield 2.03 g (58%) of **2**, which TLC analysis showed to contain a small amount of unidentified impurity. Preparative TLC (1:9 ether–hexane), followed by recrystallization from benzene–methanol, gave pure **2**: mp 156–157 °C dec (sealed tube); IR 2100 and 1700 cm^{-1}; UV λ_{max} (hexane) 245 nm (ϵ 12 500); NMR (C_6D_6) δ 4.1 (s, 1, HC=N) and 4.5–4.8 ppm (m, 1, HCO–).

Anal. Calcd for $C_{31}H_{52}N_2O_2$: C, 76.81; H, 10.81; N, 5.78. Found: C, 76.89; H, 10.82; N, 5.71.

4,4,10β-Trimethyl-*trans*-decal-3β-ol Chloroformate (4). Through a solution of 1.00 g (5.10 mmol) of 4,4,10β-trimethyl-*trans*-decal-3β-ol (**3**)[9] and 0.67 ml (4.9 mmol) of triethylamine in 100 ml of anhydrous benzene was bubbled a gentle stream of phosgene (Matheson) for 10 min, causing formation of a white precipitate. The mixture was stirred for 1 h at room temperature, treated with phosgene for an additional 10 min, stirred for another 1 h at room temperature, washed with two 50-ml portions of brine, dried ($MgSO_4$), and evaporated to afford 1.258 g (96%) of **4** as an oil which was homogeneous by TLC (hexane, twice): IR 1760 cm^{-1}; NMR δ 0.89 (s, 3), 0.97 (s, 6) and 4.55 ppm (dd, 1, J = 5 and 9 Hz, 3α H); M^+ m/e 258.1413 (calcd for $C_{14}H_{23}O_2Cl$, 258.1387).

4,4,10β-Trimethyl-*trans*-decal-3β-ol Azidoformate (5). A solution of 1.160 g (4.49 mmol) of **4** in 50 ml of dry dimethylformamide was added to a flask containing 1.20 g (18.5 mmol) of sodium azide. The resulting suspension was stirred for 1 h at room temperature, after which 150 ml of ether and 50 ml of water were added. The aqueous layer was separated and extracted with 50 ml of ether, and the combined organic layers were washed with two 50-ml portions of brine, dried ($MgSO_4$), and evaporated to afford 1.179 g of a colorless oil, which was chromatographed on 30 g of silica gel. Elution with hexane afforded 1.019 g (92%) of **5**. Elution with 1:9 ether–hexane gave 0.030 g of **3**. The oily **5** was purified by sublimation at 60 °C (0.05 mm) to afford 0.902 g (77%) of pure **5**: mp 55–57 °C; IR 2190, 2120, and 1730 cm^{-1}; NMR δ 0.83 (s, 3), 0.90 (s, 3), 0.94 (s, 3) and 4.49 ppm (dd, 1, J = 5 and 9 Hz, 3α H).

Anal. Calcd for $C_{14}H_{23}N_3O_2$: C, 63.37; H, 8.74; N, 15.84. Found: C, 63.48; H, 8.67; N, 15.85.

Thermolysis of 5. A vacuum degassed solution of 0.200 g (0.754 mmol) of **5** in 10 ml of CCl_4 was heated at 180 °C in a sealed tube for 3 h. The resulting light yellow solution was evaporated to afford 0.196 g of oil, which was separated by preparative TLC using ether into three principal fractions. The band with the highest R_f value afforded 0.021 g (14%) of 4,4,10β-trimethyl-*trans*-decal-3-one (**6**), identified by comparison of its IR and NMR spectra and TLC mobility with those of an authentic sample.[10] The second band afforded 0.090 g (51%) of **7** as a white, oily solid, which was recrystallized from 1:1 methylene chloride–hexane to give 0.063 g (36%) of **7**: mp 185–186 °C; IR 3400 and 1740 cm^{-1}; NMR δ 0.95 (s, 3, 10β H_3C–), 1.05 (s, 3), 1.09 (s, 3), 3.5–4.0 (bm, 2, 2β H and 3α H), and 6.2 ppm (bs, 1, HN); M^+ m/e 237.1729 (calcd for $C_{14}H_{23}NO_2$, 237.1729).

The third band afforded 0.024 g (14%) of **8** as a white solid which

was recrystallized from 1:1 methylene chloride–hexane to afford 0.014 g (8%) of pure **8**: mp 164–166 °C; IR 3350, 3150, and 1715 cm^{-1}; NMR δ 0.97 (s, 3, 10β H_3C–), 1.01 (s, 3, 4β H_3C–), 2.85–3.1 (m, 2, H_2CNH), 3.85 (bt, 1, J = 6 Hz, 3α H), and 6.5 ppm (bs, 1-HN); M^+ *m/e* 237.1742 (calcd for $C_{14}H_{23}NO_2$, 237.1729).

2-Carbomethoxy-4,4,10-trimethyl-*trans*-decal-3-one (9). A solution of 2.30 g (11.85 mmol) of **6**[10] in 10 ml of dimethylformamide was added to 60 ml of a freshly prepared solution of methylmagnesium carbonate[12] in dimethylformamide (~2 mmol/ml). The resulting solution was heated at 110–115 °C for 15 h under a slow stream of CO_2. The solution was cooled to 5 °C and brought to pH ~2 with 175 ml of 10% H_2SO_4. The solution was extracted with 300- and 100-ml portions of ether, and the combined ether layers were washed with 3 × 100 ml of water and then dripped into an ethereal solution of diazomethane, freshly prepared from EXR-101.[21] After 1 h the mixture was evaporated to afford 2.953 g of colorless oil, which TLC (7:1 hexane–ether) indicated to be **9** containing a small amount of **6**. The latter was removed by chromatography on 30 g of Florisil. Elution with hexane gave 2.756 g (92%) of pure **9** as a clear, colorless oil: IR 1760, 1715, 1660, and 1610 cm^{-1}; NMR δ 0.91 (s, 3), 1.07 (s, 3), 1.16 (s, 3), 3.73 (s, H_3COOC–), and 12.67 (s, 1, HOC=); M^+ *m/e* 252.1732 (calcd for $C_{15}H_{24}O_3$, 252.1725).

2α-Carbomethoxy-4,4,10β-trimethyl-*trans*-decal-3β-ol (10). To a solution of 1.862 g (7.38 mmol) of **9** in 75 ml of isopropyl alcohol, cooled to −50 °C, was added 8 ml of an aqueous $NaBH_4$ solution (0.5 mmol/ml). The resulting slurry was stirred for 1 h at −50 °C, then an additional 3 ml of the $NaBH_4$ solution was added and the viscous reaction mixture was allowed to warm to room temperature and stirred for 6 h. After being stored at −10 °C for 12 h, the reaction mixture was evaporated to a white solid residue. This was dissolved in a mixture of 50 ml of ether and 30 ml of 10% H_2SO_4, which was then added to 200 ml of ether and 100 ml of H_2O. The aqueous layer was extracted with 100 ml of ether and the combined ether layers were washed with 2 × 100 ml of H_2O, dried ($MgSO_4$), and evaporated to give 1.86 g of oily solid. Preparative TLC (3:2 hexane–ether, twice) afforded five fractions. The first was 0.015 g of **9**. The second was 0.102 g of a hydroxy ester (2α-carbomethoxy-4,4,10β-trimethyl-*trans*-decal-3α-ol?[14]): NMR δ 0.86 (s, 3), 0.88 (s, 3), 1.01 (s, 3), 2.8–3.1 (m, 1), 3.71 (s, 3, H_3COOC–), and 4.11 ppm (d, 1, J = 10 Hz). The third was 0.177 g, tentatively identified as another hydroxy ester of unknown stereochemistry: NMR δ 0.84 (s, 3), 1.0 (s, 6), 2.7–3.1 (complex m), and 3.75 ppm (s, 3, H_3COOC–). The fourth fraction was 1.254 g (67%) of **10**, which was purified by sublimation at 85–90 °C (0.25 mm) to afford 1.081 g (58%) of pure, white flakes of **10**: mp 71–73 °C; IR 3600 and 1715 cm^{-1}; NMR δ 0.75 (s, 3), 0.94 (s, 3), 0.96 (s, 3), 2.5–2.8 (complex m, 2), 3.42 (dd, J = 11 and 5 Hz, 1, 3α H), and 3.70 ppm (s, 3, H_3COOC–). Upon addition of a drop of D_2O the following changes in the spectrum were observed: δ 2.65 (dt, 1, J = 11, 11, and 4 Hz, 2β H) and 3.42 ppm (d, 1, J = 11 Hz, 3α H). M^+ *m/e* 254.1908 (calcd for $C_{15}H_{26}O_3$, 254.1882).

The fifth fraction was 0.183 g of a mixture of two compounds which showed no H_3COOC– peak in its NMR spectrum.

Hydrazide 11. A mixture of 0.500 g (1.96 mmol) of **10**, 5 ml of 98% hydrazine, and 20 ml of methanol was stirred at room temperature for 18 h, concentrated in vacuo, and partitioned between CH_2Cl_2 and H_2O. Evaporation of the organic layer yielded 0.500 g (100%) of white, solid **11**. Recrystallization from ether–dimethoxyethane afforded 0.385 g (77%) of pure **11**: mp 200–202 °C; IR 3350 and 1600 cm^{-1}; NMR δ 0.76 (s, 3), 0.97 (bs, 6), 2.7–3.25 (bm), and 3.5 ppm (d, 1, J = 12 Hz, 3α H); M^+ *m/e* 254.2006 (calcd for $C_{14}H_{26}N_2O_2$, 254.1994).

Conversion of 11 to 7. To a stirred suspension of 0.100 g (0.39 mmol) of **11** in 4 ml of 0.5 N HCl, cooled to 10 °C, was added a solution of 0.050 g (0.72 mmol) of $NaNO_2$ in 2 ml of H_2O. The resulting gummy suspension was stirred for 1 h at 10 °C and extracted with ether, which was evaporated to afford 0.104 g of gum. This was dissolved in 5 ml of ethanol, which was heated at reflux for 90 min and then evaporated to give 0.091 g (98%) of crude, gummy **7**. Preparative TLC (ether) afforded 0.083 g (91%) of **7** as a colorless solid, which was recrystallized from CH_2Cl_2–hexane to give 0.064 g (69%) of **7**: mp 186–187 °C; IR 3400 and 1740 cm^{-1}; NMR δ 0.95 (s, 3), 1.05 (s, 3), 1.09 (s, 3), 3.5–4.0 (bm, 2, 2β H and 3α H), and 6.17 ppm (bs, 1, HN); mmp with **7** from **5** 185–186 °C; M^+ *m/e* 237.1752 (calcd for $C_{14}H_{23}NO_2$, 237.1729).

4α-Cyano-4β,10β-dimethyl-*trans*-decal-3-one (12). The following modification of the procedure of Kuehne and Nelson[17] was employed for reductive cyanation of 4,10-dimethyl-$\Delta^{4,5}$-octal-3-one.[18] Liquid ammonia (150 ml) was placed into an oven-dried apparatus consisting of a 500-ml three-necked round-bottomed flask, a Dewar condenser, and a mechanical stirrer equipped with a glass paddle. Lithium wire (250 mg, 35.7 mmol), freshly cleaned by wiping with a hexane-soaked cloth, was added to the liquid ammonia and the resulting blue solution was stirred for 30 min. A solution of 2.287 g (12.84 mmol) of enone in 20 ml of dry tetrahydrofuran was added as rapidly as possible. The resulting mixture was stirred for 20 min, and then an additional 20 ml of tetrahydrofuran containing 1 ml of isoprene was added to destroy excess lithium. A heating mantle was placed under the flask and the tetrahydrofuran suspension was refluxed until all the ammonia had evaporated and for 45 min further. The suspension was cooled to 0 °C and a solution of 4.5 g (73 mmol) of cyanogen chloride, prepared by the method of Coleman, Leeper, and Schulze,[22] and freshly distilled, in 20 ml of tetrahydrofuran was added. The solution was stirred overnight, and then was concentrated in vacuo to a brown oil. This oil was partitioned between 200 ml of ether and 100 ml of 10% H_2SO_4. The aqueous layer was extracted with an additional 200 ml of ether, and the combined organic layers were washed with 100 ml of water, dried ($MgSO_4$), and evaporated to afford 2.583 g of brown oil. This was chromatographed on 60 g of Florisil, and 1.4 g (51%) of crude cyano ketone **12**, contaminated with starting material, was eluted with 4:1 ether–hexane. Preparative TLC of this oily solid (1:1 ether–hexane, twice) afforded 1.158 g (44%) of crystalline **12**. Two recrystallizations from hexane afforded 0.766 g (29%) of pure **12** as white prisms: mp 84–86 °C (lit.[17] mp 82–83 °C); IR 2250 and 1715 cm^{-1}; NMR δ 1.16 (s, 3) and 1.46 ppm (s, 3).

4α-Cyano-4β,10β-dimethyl-*trans*-decal-3β-ol (13). To a solution of 0.455 g (2.21 mmol) of **12** in 25 ml of methanol, cooled to 10 °C, was added 0.060 g (1.5 mmol) of $NaBH_4$. The resulting soltuion was stirred at room temperature for 3 h, and then concentrated in vacuo. The residual oil was partitioned between ether and 10% H_2SO_4. Standard ether extraction and workup afforded 0.470 g of oil. Preparative TLC (3:2 hexane–ether) gave 0.411 g (98%) of **13** as a colorless oil: IR 3450 and 2250 cm^{-1}; NMR δ 0.91 (s, 3), 1.22 (s, 3), and 3.89 ppm (bt, 1, 3α H); M^+ *m/e* 207.1615 (calcd for $C_{13}H_{21}NO$, 207.1623).

Conversion of 13 to 8. A solution of 0.264 g (1.27 mmol) of **13** in 25 ml of ethyl acetate containing 1 drop of acetic acid was hydrogenated over PtO_2 at atmospheric pressure for 4 h. The mixture was filtered and concentrated in vacuo to afford 0.280 g of oil which was dissolved in 10 ml of $CHCl_3$, washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$), and evaporated to yield 0.224 g (83%) of crude 4α-aminomethyl-4β,10β-methyl-*trans*-decal-3β-ol as a colorless oil: IR 3400 cm^{-1}; NMR δ 0.82 (s, 3), 0.93 (s, 3), and 2.8–3.7 ppm (bm). Without purification, this oil was dissolved in 30 ml of ether containing 1 drop of triethylamine. Through this solution was bubbled a slow stream of phosgene until cloudiness developed, and the resulting mixture was stirred at room temperature for 2 h. The mixture was washed with $NaHCO_3$ solution, dried ($MgSO_4$), and evaporated to afford 0.245 g (98%) of **8**, which was purified by preparative TLC (ether, twice) to yield 0.205 g (81%) of pure **8**, which was recrystallized from CH_2Cl_2–hexane to afford 0.175 g (69%) of **8**: mp 165–166 °C; IR 3350, 3170, and 1715 cm^{-1}; NMR δ 0.97 (s, 3), 1.01 (s, 3), 2.85–3.1 (m, 2, H_2CN), 3.85 (bt, 1, J = 6 Hz, 3α H), and 6.1 ppm (bs, 1, HN); mmp with **8** from **5** 164–165 °C; M^+ *m/e* 237.1761 (calcd for $C_{14}H_{23}NO_2$, 237.1729).

Acknowledgment. This research was generously supported by USPHS Research Grant AM 12855. The authors are grateful to Dr. James A. Nelson for extensive advice and assistance, particularly in the preparation of cyanogen chloride.

Registry No.—**1**, 2550-84-7; **2**, 60705-86-4; **3**, 60761-10-6; **4**, 60705-87-5; **5**, 60705-88-6; **6**, 775-54-2; **7**, 60705-89-7; **8**, 60705-90-0; **9**, 60705-91-1; **10**, 60705-92-2; **11**, 60705-93-3; **12**, 60761-11-7; **13**, 60705-94-4; phosgene, 75-44-5; sodium azide, 26628-22-8; methylmagnesium carbonate, 14171-36-9; hydazine, 302-01-2; 4,10-dimethyl-$\Delta^{4,5}$-octal-3-one, 878-55-7; 4α-aminomethyl-4β,10β-methyl-*trans*-decal-3β-ol, 60705-95-5.

References and Notes

(1) On leave from Bloomsburg State College, Bloomsburg, Pa. 17815.
(2) A. J. Jones, P. F. Alewood, M. Benn, and J. Wong, *Tetrahedron Lett.*, 1655 (1976).
(3) Jones et al. state in ref 2, without any elaboration, that they have applied their steroidal functionalization procedure "to a series of analogous decalin derivatives".
(4) P. F. Alewood, M. Benn, and R. Reinfried, *Can. J. Chem.*, **52**, 4083 (1974).
(5) O. E. Edwards and Z. Paryzek, *Can. J. Chem.*, **51**, 3866 (1973).
(6) J. A. Nelson, S. Chou, and T. A. Spencer, *J. Am. Chem. Soc.*, **97**, 648 (1975).
(7) H. O. House and C. J. Blankley, *J. Org. Chem.*, **33**, 53 (1968).
(8) Steroid numbering is used for all decalin derivatives in this paper in order to have internal consistency with the steroids described [cf. M. R. Czarny,

K. K. Maheshwari, J. A. Nelson, and T. A. Spencer, *J. Org. Chem.*, **40**, 2079 (1975)].
(9) Compound **3**, mp 61–62 °C, originally reported with mp 60–65 °C by B. Gaspert, T. G. Halsall, and D. Willis, *J. Chem. Soc.*, 624 (1958), was prepared in 92% yield by catalytic hydrogenation (10% Pd/C in hexane) of 4,4,10β-trimethyldecal-5-en-3β-ol prepared by the method of H. W. Whitlock and A. H. Olson, *J. Am. Chem. Soc.*, **92**, 5383 (1970).
(10) Compound **6**, originally reported with mp 25–28 °C by Gaspert, Halsall, and Willis (reference in footnote 9), was prepared as an oil in like manner by Jones oxidation of **3**.
(11) A. Pavia, F. Winternitz, and R. Wylde, *Bull. Soc. Chim. Fr.*, 2506 (1966).
(12) H. L. Finkbeiner and G. W. Wagner, *J. Org. Chem.*, **28**, 215 (1963).
(13) L. Ruest, G. Blouin, and P. Deslongchamps, *Synth. Commun.*, 6, 169 (1976).
(14) A. Pavia and F. Winternitz, *Bull. Soc. Chim. Fr.*, 3104 (1969).
(15) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry. Illustrations from the Steroid Field", Holden-Day, San Francisco, Calif., 1964, Chapter 3.
(16) P. A. S. Smith in "Molecular Rearrangements", Vol. 1, P. de Mayo, Ed., Wiley, New York, N.Y., 1963, p 530.
(17) M. E. Kuehne and J. A. Nelson, *J. Org. Chem.*, **35**, 161 (1970).
(18) This compound, originally reported by M. Yanagita and R. Futaki, *J. Org. Chem.*, **21**, 949 (1956), was prepared by the procedure of N. C. Ross and R. Levine, *ibid.*, **29**, 2341 (1964).
(19) 4,4-Dimethylcholestan-3-one was prepared by hydrogenation of 4,4-dimethylcholest-5-en-3-one [prepared by the method of H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, **22**, 602 (1957) for the preparation of 4,4-dimethylandrost-5-en-17β-ol-3-one] according to our revised procedure: J. A. Nelson, S. Kahn, T. A. Spencer, K. B. Sharpless, and R. B. Clayton, *Bioorg. Chem.*, **4**, 363 (1975).
(20) C. J. Blankley, F. J. Sauter, and H. O. House, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 258.
(21) J. A. Moore and D. E. Reed, ref 20, p 351.
(22) G. H. Coleman, R. W. Leeper, and C. C. Schulze, *Inorg. Synth.*, **2**, 90 (1946).
(23) **Note Added in Proof.** J. J. Wright and J. B. Morton, *Chem. Commun.*, 688 (1976), have recently published an analogous study with similar results of the thermolysis of 3β-lanost-8-enyl azidoformate. We thank Dr. Wright for informing us of his results prior to publication.

1,3-Dipolar Cycloaddition Reactions with Isatin-*N*-acetic Acids. Synthesis of Dimethyl 9-Oxo-9*H*-pyrrolo[1,2-*a*]indole-1,2-dicarboxylates

Wayne K. Anderson* and Paul F. Corey

Department of Medicinal Chemistry, School of Pharmacy, State University of New York at Buffalo, Buffalo, New York 14214

Received August 16, 1976

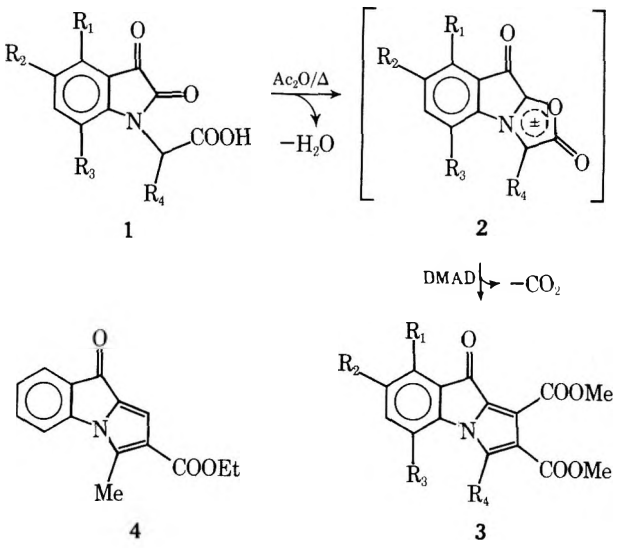
The 9*H*-pyrrolo[1,2-*a*]indole skeleton, first recognized in 1955,[1] has been encountered during the course of investigations directed toward the synthesis of the antitumor agent mitomycin.[2-5] More recently, derivatives of 9-oxo-9*H*-pyrrolo[1,2-*a*]indole have been shown to possess hypoglycemic[6] and anticancer[7] activities. The most commonly applied synthesis of 9-oxo-9*H*-pyrrolo[1,2-*a*]indoles involves an intramolecular Friedel–Crafts acylation of an appropriately substituted *N*-phenylpyrrole, generating the central ring through formation of a second bridge between the two aromatic moieties.[5,8,9]

Current work in our laboratory required a versatile synthesis of dimethyl 9-oxo-9*H*-pyrrolo[1,2-*a*]indole-1,2-dicarboxylates (**3**) which would allow for the incorporation of a variety of substituents in the six-membered ring. We now wish to report a facile synthesis of **3** which involves a 1,3-dipolar cycloaddition of a mesoionic intermediate, **2**, derived from substituted isatin-*N*-acetic acids (**1**), with dimethyl acetylenedicarboxylate (DMAD). This approach affords some considerable versatility in that the starting isatins are available with a broad range of substituents.

The starting isatin was converted to the sodium salt by treatment with NaH in HMPA; the salt was alkylated, without isolation, with ethyl 2-bromopropionate and the resulting ester was saponified to give the corresponding isatin-*N*-(α-methyl) acetic acids (**1c–g**). The acids **1a** and **1b** were prepared according to previously described procedures.[10-12] The method we used to prepare **1** is both simple and mild, and makes possible N-alkylation of isatins labile to more vigorous conditions.

N-Acyl-α-amino acids, under dehydrating conditions, cyclize to mesoionic oxazolones which react as 1,3 dipoles with acetylenic compounds to give pyrroles.[13-16] Analogously, isatin-*N*-acetic acids (**1**) form mesoionic derivatives, **2**, that undergo 1,3-dipolar cycloaddition reactions in situ with DMAD to give **3**. This reaction (Scheme I) requires more

Scheme I



1 **2** **4** **3**

a, $R_1 = R_2 = R_3 = R_4 = H$
b, $R_1 = R_2 = R_3 = H$; $R_4 = Me$
c, $R_1 = R_3 = H$; $R_2 = Br$; $R_4 = Me$
d, $R_1 = R_3 = H$; $R_2 = R_4 = Me$
e, $R_1 = R_3 = Cl$; $R_2 = H$; $R_4 = Me$
f, $R_1 = H$; $R_2 = R_3 = Cl$; $R_4 = Me$
g, $R_1 = Cl$; $R_2 = H$; $R_3 = OMe$; $R_4 = Me$

vigorous conditions and gives lower yields than the comparable reaction of *N*-phenyl-*N*-acetylalanine with DMAD.[15] The lower reactivity may be due to decreased reactivity of the mesoionic intermediate, due to charge delocalization in **2** through the C-3 carbonyl of isatin, or it may be associated with an increased difficulty to form **2**. The increased strain introduced by the rigid isatin molecule or the development of a positively charged imminium group adjacent to an electron-withdrawing carbonyl could retard the formation of **2**.

The alkyl group α to the carboxylic acid moiety (i.e., R_4) of **1b–g** considerably increased reactivity over that observed for **1a**, where R_4 = H. Thus, **1b** reacts with acetic anhydride–DMAD to give **3b** in 62% yield whereas **1a** reacted to give only 20% yield of **3a**. Ethyl propiolate, a less reactive dipolarophile, gave **4** in 50% yield from **1b**; **1a** failed to react.

A cycloaddition reaction of this type involving an unsymmetrical dipolarophile is complicated by the possibility of two isomeric products, a problem recently discussed by Huisgen.[17] The reaction of **1b** with ethyl propiolate yielded only **4**, with no evidence of the other possible isomer. The direction of the cycloaddition was confirmed by x-ray crystallography.[18]

In summary, the 1,3-dipolar cycloaddition reaction affords a very simple approach to dimethyl 9-oxo-9*H*-pyrrolo[1,2-*a*]indole-1,2-dicarboxylates. Each crystallized spontaneously from the cooling reaction mixture and, although no attempt was made to optimize conditions, the yields were good. Substituents R_1, R_2, and R_3 were chosen to illustrate the general applicability of this reaction to the large class of polysubstituted isatins.

Experimental Section

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer Model 237 infrared spectrophotometer in KBr wafers. NMR spectra were obtained with a Varian Model T-60 spectrometer using $CDCl_3$ as solvent (unless otherwise specified) and Me_4Si as an internal reference. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Ga. All starting materials and reagents were used as received from the manufacturer without additional purification. No attempt was made to optimize yields in these reactions.

4,7-Dichloroisatin-*N*-(α-methyl)acetic Acid (1e). A stirred solution of 4,7-dichloroisatin (21.6 g, 0.10 mol) in hexamethylphosphoramide (100 ml) (*Caution:* hexamethylphosphoramide is a potent carcinogen; handle with care!) was cooled to 0 °C, treated portionwise with NaH (5.3 g of a 50% oil dispersion, 1.1 equiv), and allowed to warm to room temperature and stirred for 18 h. Ethyl 2-bromopropionate (14.28 ml, 1.1 equiv) was added and the mixture was stirred at room temperature for an additional 18 h. The reaction mixture was poured into Et_2O (500 ml) and extracted with 200-ml portions of H_2O until the aqueous extracts were essentially colorless. The combined aqueous extracts were washed with Et_2O (2 × 200 ml) and the combined ethereal solution was freed of solvent under reduced pressure. The residue was saponified by treatment with a solution of sodium hydroxide (8.0 g, 2 equiv) in 50% aqueous ethanol (400 ml) heated under reflux for 1 h. The mixture was cooled, diluted with H_2O (300 ml), and extracted with Et_2O (2 × 150 ml). The aqueous phase was acidified with concentrated aqueous HCl and extracted with $CHCl_3$ (3 × 150 ml). The combined $CHCl_3$ extracts were dried (Na_2SO_4), concentrated under reduced pressure to 100 ml, and diluted with 100 ml of cyclohexane to yield **1e** (15.57 g, 55%) as an orange powder: mp 180–182 °C dec; IR 3061, 1767, and 1736 (C=O), 1467, 1255, 1110 cm^{-1}; NMR (Me_2SO-d_6–acetone-d_6) δ 1.73 (d, J = 7 Hz, 3 H), 5.42 (q, J = 7 Hz, 1 H), 7.20 (d, $|J_{AB}|$ = 8.8 Hz, 1 H), 7.66 (d, $|J_{AB}|$ = 8.8 Hz, 1 H), 10.33 (br s, 1 H).

Anal. Calcd for $C_{11}H_7NO_4Cl_2$: C, 45.86; H, 2.45; N, 4.86. Found: C, 45.82; H, 2.49; N, 4.93.

5-Bromoisatin-*N*-(α-methyl)acetic Acid (1c). This acid was obtained from 5-bromoisatin as described for **1e,** yield 55% (orange solid), mp 218–220 °C (lit.[12] 219–225 °C).

5-Methylisatin-*N*-(α-methyl)acetic Acid (1d). This acid was obtained from 5-methylisatin as described for **1e,** yield 53% (orange solid), mp 180–183 °C (lit.[12] 180–184 °C).

5,7-Dichloroisatin-*N*-(α-methyl)acetic Acid (1f). This acid was obtained from 5,7-dichloroisatin as described for **1e,** yield 46% (orange solid): mp 217–221 °C dec; IR 3053, 1744, and 1721 (C=O), 1456, 1242, 1118 cm^{-1}; NMR (Me_2SO-d_6–acetone-d_6) δ 1.72 (d, J = 7 Hz, 3 H), 5.5 (q, J = 7 Hz, 1 H), 7.67 (d, $|J_{AB}|$ = 1.55 Hz, 1 H), 7.83 (d, $|J_{AB}|$ = 1.55 Hz, 1 H), 7.67 (br s, 1 H).

Anal. Calcd for $C_{11}H_9NO_4Cl_2$: C, 45.86; H, 2.45; N, 4.86. Found: C, 45.98; H, 2.49; N, 4.78.

4-Chloro-7-methoxyisatin-*N*-(α-methyl)acetic Acid (1g). This acid was obtained from 4-chloro-7-methoxyisatin as described for **1e,** yield 45% (red solid): mp 229–230 °C dec; IR 2938, 1743, and 1720 (C=O), 1497, 1290, 1121 cm^{-1}; NMR (Me_2SO-d_6–acetone-d_6) δ 1.65 (d, J = 7 Hz, 3 H), 3.95 (s, 3 H), 5.42 (q, J = 7 Hz, 1 H), 7.17 (d, $|J_{AB}|$ = 8.5 Hz, 1 H), 7.48 (d, $|J_{AB}|$ = 8.5 Hz, 1 H), 7.83 (br s, 1 H).

Anal. Calcd for $C_{12}H_{10}NO_5Cl$: C, 50.81; H, 3.55; N, 4.94. Found: C, 50.88; H, 3.56; N, 4.94.

Dimethyl 9-Oxo-9*H*-pyrrolo[1,2-*a*]indole-1,2-dicarboxylate (3a). A solution of isatin-*N*-acetic acid (**1a,**[10] 2.05 g, 0.01 mol) in *n*-butyric anhydride (20 ml) was treated with DMAD (10 ml, 8 equiv) and heated under reflux (200 °C bath) for 6 h. Volatile reaction components were removed under reduced pressure (1 Torr, 130 °C bath) leaving a black tar which was dissolved in hot methanol (40 ml); on extended standing at −20 °C. **3a** (0.56 g, 20%) precipitated as dark red crystals. One recrystallization from $CHCl_3$–cyclohexane afforded the analytical sample as a pale orange wool: mp 178–179 °C; IR 3100, 1739, 1719, and 1706 (C=O), 1498, 1208, 1091 cm^{-1}; NMR δ 3.89 (s, 3 H), 4.03 (s, 3 H), 7.18–7.85 (m, 4 H), 7.72 (s, 1 H).

Anal. Calcd for $C_{15}H_{11}NO_5$: C, 63.16; H, 3.89; N, 4.91. Found: C, 63.20; H, 3.92; N, 4.93.

Dimethyl 9-Oxo-3-methyl-9*H*-pyrrolo[1,2-*a*]indole-1,2-dicarboxylate (3b). A solution of isatin-*N*-(α-methyl)acetic acid (**1b,**[12] 10.56 g, 0.05 mol) in *n*-butyric anhydride (50 ml) was treated with DMAD (25 ml, 4 equiv) and heated under reflux (200 °C bath) for 6 h. Volatile reaction components were removed under reduced pressure (1 Torr, 150 °C bath) leaving a brown tar which was dissolved in 125 ml of hot methanol; **3b** (9.21 g, 62%) precipitated on cooling. One recrystallization from methanol afforded the analytical sample as orange needles: mp 201.5–202.5 °C; IR 2962, 1744, and 1706 (C=O), 1481, 1206, 1114 cm^{-1}; NMR δ 2.79 (s, 3 H), 3.84 (s, 3 H), 3.97 (s, 3 H), 7.03–7.73 (m, 4 H).

Anal. Calcd for $C_{16}H_{13}NO_5$: C, 64.21; H, 4.38; N, 4.68. Found: C, 64.02; H, 4.38; N, 4.70.

Dimethyl 9-Oxo-7-bromo-3-methyl-9*H*-pyrrolo[1,2-*a*]indole-1,2-dicarboxylate (3c). A solution of 5-bromoisatin-*N*-(α-methyl)acetic acid (**1c,** 11.92 g, 0.04 mol) in acetic anhydride (40 ml) was treated with DMAD (20 ml, 4.1 equiv) and heated under reflux (155 °C bath) for 6 h. On cooling crystals of **3c** (9.623 g, 64%) spontaneously precipitated. One recrystallization from 1,2-dichloroethane–cyclohexane (1:1) afforded the analytical sample as orange whiskers: mp 235.5–236.5 °C; IR 2935, 1739, 1721, and 1706 (C=O), 1478, 1211, 1121 cm^{-1}; NMR δ 2.84 (s, 3 H), 3.92 (s, 3 H), 4.03 (s, 3 H), 7.33–8.00 (m, 3 H).

Anal. Calcd for $C_{16}H_{12}NO_5Br$: C, 50.82; H, 3.20; N, 3.70. Found: C, 50.94; H, 3.23; N, 3.72.

Dimethyl 9-Oxo-3,7-dimethyl-9*H*-pyrrolo[1,2-*a*]indole-1,2-dicarboxylate (3d). This pyrrolo[1,2-*a*]indole was obtained from 5-methylisatin-*N*-(α-methyl)acetic acid (**1d**) as described for **3c,** but with a 36-h reflux period, yield 70% (orange needles from 1,2-dichloroethane): mp 132.5–133.5 °C; IR 2960, 1747, and 1732 (C=O), 1489, 1214, 1123 cm^{-1}; NMR δ 2.36 (s, 3 H), 2.75 (s, 3 H), 3.83 (s, 3 H), 3.96 (s, 3 H), 7.17–7.43 (m, 3 H).

Anal. Calcd for $C_{17}H_{15}NO_5$: C, 65.17; H, 4.83; N, 4.47. Found: C, 65.14; H, 4.84; N, 4.44.

Dimethyl 9-Oxo-5,8-dichloro-3-methyl-9*H*-pyrrolo[1,2-*a*]indole-1,2-dicarboxylate (3e). This pyrrolo[1,2-*a*]indole was obtained from 4,7-dichloroisatin-*N*-(α-methyl)acetic acid (**1e**) as described for **3c,** but with a 33-h reflux period, yield 51% [yellow-orange, chunky prisms from 1,2-dichloroethane–cyclohexane (1:1)]: mp 199.5–200.5 °C; IR 3066, 1739, 1710, and 1717 (C=O), 1456, 1221, 1112 cm^{-1}; NMR δ 3.02 (s, 3 H), 3.83 (s, 3 H), 3.95 (s, 3 H), 7.11 (d, $|J_{AB}|$ = 8.25 Hz, 1 H), 7.36 (d, $|J_{AB}|$ = 8.25 Hz, 1 H).

Anal. Calcd for $C_{16}H_{11}NO_5Cl_2$: C, 52.20; H, 3.01; N, 3.80. Found: C, 52.14; H, 3.04; N, 3.78.

Dimethyl 9-Oxo-5,7-dichloro-3-methyl-9*H*-pyrrolo[1,2-*a*]indole-1,2-dicarboxylate (3f). This pyrrol[1,2-*a*]indole was obtained from 5,7-dichloroisatin-*N*-(α-methyl)acetic acid (**1f**) as described for **3c,** but with a 13.5-h reflux period, yield 47% [red-orange, chunky prisms from 1,2-dichloroethane–cyclohexane (1:1)]: mp 200.5–201.5 °C; IR 3064, 1750, and 1712 (C=O), 1447, 1233, 1110 cm^{-1}; NMR δ 3.01 (s, 3 H), 3.84 (s, 3 H), 3.94 (s, 3 H), 7.50 (s, 2 H).

Anal. Calcd for $C_{16}H_{11}NO_5Cl_2$: C, 52.20; H, 3.01; N, 3.80. Found: C, 52.04; H, 3.01; N, 3.76.

Dimethyl 9-Oxo-8-chloro-5-methoxy-3-methyl-9*H*-pyrrolo[1,2-*a*]indole-1,2-dicarboxylate (3g). This pyrrolo[1,2-*a*]indole was obtained from 4-chloro-7-methoxyisatin-*N*-(α-methyl)acetic acid (**1g**) as described for **3c,** but with a 35-h reflux period, yield 29% [bright yellow wool from 1,2-dichloroethane–cyclohexane (1:1)]: mp 209–210 °C; IR 2949, 1736, and 1711 (C=O), 1458, 1226, 1129 cm^{-1}; NMR δ 2.72 (s, 3 H), 3.83 (s, 3 H), 3.89 (s, 3 H), 3.93 (s, 3 H), 6.95 (s, 2 H).

Anal. Calcd for $C_{17}H_{14}NO_6Cl$: C, 56.13; H, 3.88; N, 3.85. Found: C, 56.01; H, 3.87; N, 3.85.

Ethyl 9-Oxo-3-methyl-9*H*-pyrrolo[1,2-*a*]indole-2-carboxylate (4). A solution of isatin-*N*-(α-methyl)acetic acid (**1b,**[12] 12.0 g, 0.055 mol) in *n*-butyric anhydride (60 ml) was treated with ethyl propiolate (25.0 g, 4.66 equiv) heated under reflux (170 °C bath) for 6.5 h. Volatile reaction components were removed under reduced pressure (1 Torr, 130 °C bath). The maroon-colored syrup residue was dissolved in $CHCl_3$ and eluted through a 150-g alumina (neutral, Brockman III) dry column with the same solvent. The mobile band was collected, freed of solvent under reduced pressure, and crystallized from $CHCl_3$–petroleum ether (1:2) to give 4 (6.94 g, 49%). One recrystallization from methanol afforded the analytical sample as yellow needles: mp 168–169 °C; IR 3984, 1691 (C=O), 1477, 1227, 1097 cm^{-1}; NMR δ 1.35 (t, J = 7 Hz, 3 H), 2.76 (s, 3 H), 4.28 (q, J = 7 Hz, 2 H), 7.02 (s, 1 H), 7.08–7.62 (m, 4 H). The attachment of the carboxylate ester to C-2 was determined by x-ray crystallography.[18]

Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.56; H, 5.17; N, 5.51.

Acknowledgment. The authors wish to thank the National Institutes of Health, National Institute of General Medical Science, Grant 5T1GM55, for partial financial support of this work.

Registry No.—**1a,** 60705-96-6; **1b,** 19612-69-2; **1c,** 19612-71-6; **1d,** 19612-73-8; **1e,** 60705-97-7; **1f,** 60705-98-8; **1g,** 60705-99-9; **3a,**

60706-00-5; **3b**, 60706-01-6; **3c**, 60706-02-7; **3d**, 60706-03-8; **3e**, 60706-04-9; **3f**, 60734-17-0; **3g**, 60706-05-0; **4**, 60706-06-1; 4,7-dichloroisatin, 18711-13-2; ethyl 2-bromopropionate, 535-11-5; 5-bromoisatin, 87-48-9; 5-methylisatin, 608-05-9; 5,7-dichloroisatin, 6374-92-1; 4-chloro-7-methoxyisatin, 60706-07-2; DMAD, 23055-10-9; ethyl propiolate, 105-37-3.

References and Notes

(1) D. A. Shirley, B. H. Gross, and P. A. Roussel, *J. Org. Chem.*, **20**, 225 (1955).
(2) R. W. Franck and J. Auerbach, *J. Org. Chem.*, **36**, 31 (1971).
(3) Y. Yamada, T. Hirata, and M. Matsui, *Tetrahedron Lett.*, 101 (1969).
(4) T. Hirata, Y. Yamada, and M. Matsui, *Tetrahedron Lett.*, 4107 (1969).
(5) V. J. Mazzola, K. F. Bernady, and R. W. Franck, *J. Org. Chem.*, **32**, 486 (1967).
(6) H. Sugihara, N. Matsumoto, Y. Hamuro, and Y. Kawamatsu, *Arzneim.-Forsch.*, **24**, 1560 (1974).
(7) R. Giuliano, G. C. Porretta, M. Scalzo, F. Chimenti, M. Artico, E. Dolfini, and L. Morasca, *Farmaco, Ed. Sci.*, **27**, 1091 (1972).
(8) E. Laschtuvka and R. Huisgen, *Chem. Ber.*, **93**, 81 (1960).
(9) A. D. Josey and E. L. Jenner, *J. Org. Chem.*, **27**, 2466 (1962).
(10) W. Langenbeck, *Chem. Ber.*, **61**, 942 (1928).
(11) A. D. Ainley and R. Robinson, *J. Chem. Soc.*, 1508 (1934).
(12) F. Gapp, J. Margreiter, and E. Schmid, U.S. Patent 3 383 383 (1968).
(13) R. Huisgen, H. Gotthardt, H. O. Bayer, and F. C. Schaefer, *Angew. Chem., Int. Ed. Engl.*, **3**, 136 (1964).
(14) H. O. Bayer, H. Gotthardt, and R. Huisgen, *Chem. Ber.*, **103**, 2356 (1970).
(15) R. Huisgen, H. Gotthardt, H. O. Bayer, and F. C. Schaefer, *Chem. Ber.*, **103**, 2611 (1970).
(16) H. Gotthardt, R. Huisgen, and H. O. Bayer, *J. Am. Chem. Soc.*, **92**, 4340 (1970).
(17) R. Huisgen, *J. Org. Chem.*, **41**, 403 (1976).
(18) W. L. Duax, personal communication.

Ion Radicals. 37. Preparation and Isolation of Cation Radical Tetrafluoroborates by the Use of Nitrosonium Tetrafluoroborate[1,2]

B. K. Bandlish and H. J. Shine*

Department of Chemistry, Texas Tech University, Lubbock, Texas 79409

Received May 21, 1976

During the last several years we have reported the preparation of a number of heteroaromatic and aromatic cation radical perchlorates. Methods of oxidation of the organic substrates have varied, e.g., by using $I_2/AgClO_4$, perchloric acid itself, and anodic oxidation in the presence of a perchlorate salt electrolyte. In the case of phenothiazine and 10-methylphenothiazine we have also used disproportionation of the parent heterocycle and its 5-oxide in perchloric acid solution.[3] The preparation of perchlorate salts has been useful not only because of the relative ease of isolating them, but also because the perchlorate ion is an innocuous nucleophile, a desirable feature for our interest in mapping out the reactions of these cation radicals with nucleophilic agents. A hazard that is always present with the cation radical perchlorates (and some of the perchlorate salt products of reaction) is their potential explosiveness,[4] so that their use has always been limited to small amounts. The isolation of solid salts other than perchlorates is attractive, but we have not until now been successful in easily preparing usable ones. Cation radical hexachloroantimonates are very easily obtained,[5] but, in our admittedly limited use of them, they have been troublesome both in interference by chloride ion in nucleophilic reactions and inclusion of antimony in products of reaction.[6] Tetrafluoroborates appear to be attractive alternates to perchlorates. Thianthrene cation radical tetrafluoroborate was prepared by Rundel and Scheffler from the disproportionation reaction in fluoroboric acid,[7] but this preparation requires the use of dry $HF{\cdot}BF_3$. Oxidation by $I_2/AgBF_4$ is suitable in principle, but we have not had encouraging success with this method ourselves.

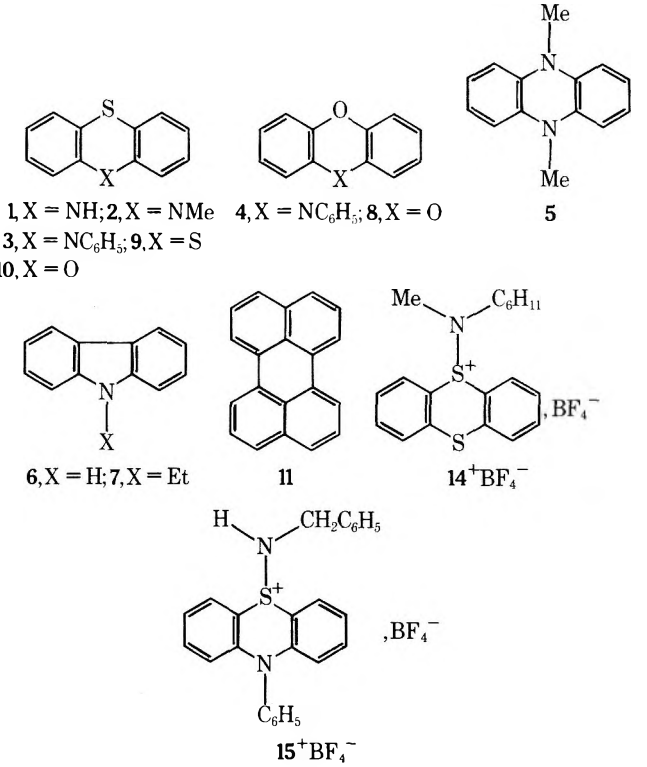
We have found recently that commercially available nitrosonium tetrafluoroborate ($NOBF_4$)[8] is very useful in cleanly oxidizing a number of aromatics and heteroaromatics to the cation radicals (eq 1), and we have isolated a number of crystalline tetrafluoroborates of high purity. Our practice is to carry out the oxidation in, e.g., acetonitrile solution after purging with N_2 and keeping a stream of N_2 bubbling through the solution to carry out the NO that is formed. Unless this is done, complications can arise from the formation of, and subsequent reactions with, NO_2.

$$Ar + NO^+BF_4^- \rightarrow Ar^+{\cdot}BF_4^- + NO \qquad (1)$$

Nitrosonium salts have been used recently by others. Connelly and co-workers, for example, have pointed out that among the several reactions that are known to occur between $NOPF_6$ and transition-metal complexes are nitrosation and one-electron oxidation.[9] Musker and Wolford have used $NOBF_4$ in making solutions of the cation radical tetrafluoroborates of 1,5-dithiacyclooctane and thianthrene; the salts were not isolated.[10] In our own work, use of $NOBF_4$ has given the solid tetrafluoroborates of phenothiazine (**1**), 10-methylphenothiazine (**2**), 10-phenylphenothiazine (**3**), 10-phenylphenoxazine (**4**), and 5,10-dimethyl-5,10-dihydrophenazine (**5**). The yields varied from 45% (**2**) to 69% (**3** and **5**), while the cation-radical content determined iodimetrically (except with **5**) was 95–99%. No attempts were made to optimize yields. Carbazole (**6**) and *N*-ethylcarbazole (**7**) gave the cation radicals of their dimers, namely 3,3′-dicarbazolyl- and 9,9′-diethyl-3,3′-dicarbazolyl tetrafluoroborates, in 97–98% yield. In contrast, the latter's perchlorate was obtained in 48% yield in solution with $I_2/AgClO_4$.[11] Oxidation of **5** was controlled by the use of less than the stoichiometrically required amount of $NOBF_4$ (i.e., 0.85 equiv), because **5** is easily oxidized also to the dication. Since $5^+{\cdot}$ is not reduced by iodide, the purity of $5^+{\cdot}BF_4^-$ was not assayed; the cation radical was identified by its visible spectrum. Use of an appropriate amount of $NOBF_4$ gave $5^{2+}{\cdot}2BF_4^-$.

Several compounds were easily oxidized to their cation radicals but we could not isolate the solid tetrafluoroborates

Chart of Compounds



without serious loss in purity. Thus, dibenzodioxin (**8**), thianthrene (**9**), phenoxathiin (**10**), and perylene (**11**) gave clean solutions of their cation radicals. Attempts to remove the solvent from $8^{+}\cdot BF_4^-$ and $9^{+}\cdot BF_4^-$, or to precipitate the latter, gave products with poor cation-radical content. We believe that the use of the solutions themselves should be suitable, though, for carrying out cation-radical reactions and have shown that this is so with $9^{+}\cdot BF_4^-$ solution. An example of the use of an isolated cation radical tetrafluoroborate ($3^{+}\cdot BF_4^-$ reacting with benzylamine) is also given.

It may be pertinent to comment briefly at this stage on the competition between one-electron oxidation and nitrosation. One might have anticipated that the electron-rich aromatics which we have used would undergo electrophilic nitrosation rather than one-electron oxidation. In particular, carbazole is easily N-nitrosated with nitrous acid; and, indeed, in aqueous acetonitrile carbazole and $NOBF_4$ gave *N*-nitrosocarbazole (32% yield). Nitrosation appears to occur here through the agency of $H_2{}^+ONO$. One might also wonder if there are connections between nitrosation and one-electron oxidation reactions. For example, where nitrosation does occur with NO^+ is it possible that it is preceded by electron exchange, that is, that a cation radical and NO are formed in close proximity and then unite? This type of question is not new in electrophilic substitutions, and recently proposals for its validity in the alkylation and other reactions of alkyl-substituted phenols have been made.[12] Whether or not nitrosations via this route may be validated too will become a matter of interest. In this connection, too, we note the recent reports that the reaction between nitrous acid and urea in aqueous perchloric acid leads rapidly to the formation of the *S*-nitrosourea cation $[(NH_2)_2CSNO]^+$ (**12**), and this is followed by the slow formation of NO and $[(NH_2)_2CSSC(NH_2)_2]^{2+}$ (**13**), i.e., what is, in principle, the dimer of the urea cation radical.[13] A similar behavior was observed with *N,N'*-tetramethylurea. Precisely how **13** is formed from **12** appears not to be known, but the possibility that the urea cation radical may be involved is intriguing.

Experimental Section

Oxidations with $NOBF_4$. The general procedure is illustrated with **phenothiazine** (**1**). Nitrogen was bubbled vigorously into a solution of 466 mg (2.34 mmol) of **1** in 15 ml of dry CH_3CN for 30 min. To this was added next, dropwise, a solution of 279 mg (2.38 mmol) of $NOBF_4$ in 20 ml of CH_3CN. After addition, N_2 bubbling was continued for 15 min, and the solution was poured into 500 ml of ether. The precipitated $1^{+}\cdot BF_4^-$ was filtered, washed with ether, and dried under vacuum to give 370 mg (1.29 mmol, 55%). Iodimetric assay showed the product to have 98.2% of $1^{+}\cdot$.

From 426 mg (2.00 mmol) of **10-methylphenothiazine** (**2**) in 20 ml of CH_3CN and 234 mg (2.00 mmol) of $NOBF_4$ in 20 ml of CH_3CN was obtained 270 mg (0.90 mmol, 45%) of $2^{+}\cdot BF_4^-$, 99.6% assay. From 450 mg (1.63 mmol) of **10-phenylphenothiazine** (**3**) and 190 mg (1.62 mmol) of $NOBF_4$ was obtained 405 mg (1.12 mmol, 68.7%) of $3^{+}\cdot BF_4^-$, 99.9% assay. From 225 mg (0.868 mmol) of **10-phenylphenoxazine** (**4**) in 10 ml of CH_2Cl_2 and 112 mg (0.96 mmol) of $NOBF_4$ in 8 ml of CH_2Cl_2 was obtained by pouring into 100 ml of dry petroleum ether, bp 30–60 °C, 180 mg (0.52 mmol, 60%) of $4^{+}\cdot BF_4^-$, 97% assay. From 420 mg (2.0 mmol) of **5,10-dimethyl-5,10-dihydrophenazine** (**5**) in 40 ml of dry CH_3CN and 198 mg (1.69 mmol) of $NOBF_4$ in 20 ml of CH_3CN was obtained 410 mg (1.38 mmol, 69%) of $5^{+}\cdot BF_4^-$, λ_{max} (CH_3CN) and $10^{-3}\,\epsilon$ 446 nm, 7.0; 454 nm, 7.0; 601 nm, 1.25; 649 nm, 1.82; and 719 nm, 1.63. From 504 mg (3.02 mmol) of **carbazole** (**6**) in 40 ml of CH_3CN and 576 mg (4.92 mmol) of $NOBF_4$ in 20 ml of CH_3CN was obtained 542 mg (1.29 mmol, 86%) of **3,3'-dicarbazolyl cation radical tetrafluoroborate,** assay 97.3%, mass spectrum parent peak 332.1 (calcd for the cation radical, $6^{+}\cdot$, 332.1). From 1.04 g (5.33 mmol) of ***N*-ethylcarbazole** (**7**) in 30 ml of CH_3CN and 1.0 g (8.54 mmol) of $NOBF_4$ in 30 ml of CH_3CN was obtained by pouring into 600 ml of dry ether 1.24 g (2.6 mmol, 98%) of **9,9'-diethyl-3,3'-dicarbazolyl cation radical tetrafluoroborate,** 94.5% assay.

Preparation of $5^{2+}\cdot 2BF_4^-$. From a solution of 420 mg (2.0 mmol) of **5** in 30 ml of dry CH_3CN and 579 mg (4.95 mmol) of $NOBF_4$ in 40 ml of CH_3CN was obtained by pouring into 500 ml of dry ether 625 mg (1.63 mmol, 81.5%) of $5^{2+}v12BF_4^-$. Iodimetric assay constituted reduction to $5^{+}\cdot$ and showed 84% content of 5^{2+}.

Preparation of *N*-Nitrosocarbazole. To a solution of 2.0 g (17.1 mmol) of $NOBF_4$ in 19 ml of CH_3CN, containing 1 ml of water, was added a solution of 500 mg (3.00 mmol) of carbazole. After 2 h of stirring the solution was concentrated and poured into 300 ml of water. Following extraction with 3 × 75 ml of CH_2Cl_2, concentration, and preparative scale TLC of the CH_2Cl_2 solution, with petroleum ether (bp 30–60 °C) as developer, there was obtained 185 mg (0.944 mmol, 31.4%) of *N*-nitrosocarbazole, mp 79–80.5 °C (from petroleum ether), lit. mp 82 °C.[14] Five other bands were removed from the TLC plates, giving 283 mg of products which were not investigated further.

Reaction of Thianthrene$^{+}\cdot BF_4^-$ with Cyclohexylmethylamine. To a solution of 927 mg (7.92 mmol) of $NOBF_4$ in 30 ml of dry CH_3CN was added a solution of 1.9 g (8.79 mmol) of thianthrene, while N_2 was bubbled vigorously continuously. After 1 h of standing the purple solution was added to a stirred solution of 3 ml (~23.0 mmol) of cyclohexylmethylamine in 10 ml of CH_3CN. Reaction was immediate. The solution was concentrated, poured into 300 ml of water, and extracted with CH_2Cl_2, and the dried, concentrated CH_2Cl_2 solution was chromatographed on a column of silica gel (Merck, 30–70 mesh). Benzene elution gave 1.07 g (4.95 mmol, 56% conversion) of thianthrene; ether elution gave 234 mg (1.01 mmol, 11%) of thianthrene 5-oxide; acetone elution gave 540 mg (1.31 mmol, 15%) of 5-(cyclohexylmethylamino)thianthrenium tetrafluoroborate ($14^{+}BF_4^-$), mp 183–184.5 °C (from CH_2Cl_2–ether).

Conversion of $14^{+}BF_4^-$ into $14^{+}ClO_4^-$. A solution of 340 mg (0.82 mmol) of $14^{+}BF_4^-$ and 2.0 g (18.8 mmol) of $LiClO_4$ in 75 ml of CH_3CN was stirred overnight, concentrated, and poured into 300 ml of water. Extraction with CH_2Cl_2 gave 272 mg (0.64 mmol, 78%) of $14^{+}ClO_4^-$, mp 170–172 °C (from CH_2Cl_2–ether). Authentic $14^{+}ClO_4^-$ prepared by the reaction of $9\cdot{}^{+}ClO_4^-$ with cyclohexylmethylamine had mp 170–172 °C.

Reaction of $3^{+}\cdot BF_4^-$ with Benzylamine. Benzylamine was added dropwise to a solution of 2.0 g (5.52 mmol) of $3^{+}\cdot BF_4^-$ in 30 ml of dry CH_3CN until reaction was complete (disappearance of $3^{+}\cdot$ color). After stirring for 10 min the solution was poured into 400 ml of water. Extraction with 5 × 75 ml of petroleum ether (bp 30–60 °C) gave 778 mg (2.83 mmol, 102% yield) of **3.** Extraction with 3 × 75 ml of CH_2Cl_2 gave 610 mg (1.30 mmol, 47%) of 5-(benzylimino)-5,5-dihydro-10-phenylphenothiazine tetrafluoroborate ($15^{+}BF_4^-$), mp 166–168 °C (from CH_2Cl_2–ether).

Reaction of 5-Benzylimino-5,5-dihydro-10-phenylphenothiazine with Methyl Iodide. A solution of 345 mg (0.737 mmol) of $15^{+}BF_4^-$ in 20 ml of ethanol was made alkaline with a few drops of 50% aqueous NaOH. The solution was concentrated at room temperature and water was added. The precipitated solid [5-(benzylimino)-5,5-dihydro-10-phenylphenothiazine] was extracted with ether and to this were added several milliliters of methyl iodide. The solution was evaporated after 1 h and the residue was crystallized from CH_2Cl_2–ether, giving 334 mg (0.692 mmol, 94%) of (5-benzylmethylimino)-5,5-dihydro-10-phenylphenothiazine iodide (**16**), mp 149–150 °C, lit. mp 149–150 °C.[3a]

Elemental Analyses. Although iodimetric titrations were in agreement with the anticipated structures of the solid cation radical fluoroborates, two were selected as representative for elemental analysis.

Anal. Calcd for $C_{13}H_{11}NSBF_4(2^{+}\cdot BF_4^-)$: C, 52.0; H, 3.70; F, 25.3. Found: C, 52.7; H, 3.78; F, 24.9.

Anal. Calcd for $C_{18}H_{13}NSBF_4(3^{+}\cdot BF_4^-)$: C, 59.7; H, 3.62; N, 3.87; S, 8.84; F, 21.0. Found: C, 60.0; H, 4.31; N, 3.77; S, 8.59; F, 20.8.

It was found that if the solid fluoroborates were heated (boiling benzene) under vacuum or pumped under vacuum for long periods for preanalysis drying they tended to lose BF_3. Analyses were carried out, therefore, on solids which were dried under vacuum for a short time only.

Registry No.—**1,** 92-84-2; $1^{+}\cdot BF_4^-$, 60896-29-9; **2,** 1207-72-3; $2^{+}\cdot BF_4^-$, 54014-68-5; **3,** 7152-42-3; $3^{+}\cdot BF_4^-$, 60896-30-2; **4,** 37832-25-0; $4^{+}\cdot BF_4^-$, 60896-31-3; **5,** 15546-75-5; $5^{+}\cdot BF_4^-$, 60896-32-4; $5^{2+}\cdot 2BF_4^-$, 60896-33-5; **6,** 86-74-8; **7,** 86-28-2; **9,** 92-85-3; $9^{+}\cdot BF_4^-$, 60896-34-6; $9\cdot{}^{+}ClO_4^-$, 35787-71-4; $14^{+}BF_4^-$, 60896-36-8; $14^{+}ClO_4^-$, 60896-37-9; $15^{+}BF_4^-$, 60920-64-1; **16,** 55223-15-9; $NOBF_4$, 14635-75-7; 3,3'-dicarbazolyl$^{+}\cdot BF_4^-$, 60896-39-1; 9,9'-diethyl-3,3'-dicarbazolyl$^{+}\cdot BF_4^-$, 60920-63-0; *N*-nitrosocarbazole, 2788-23-0; cyclohexylmethylamine, 100-60-7; benzylamine, 100-46-9.

References and Notes

(1) Part 36: A. G. Padilla, S. M. Wu, and H. J. Shine, *J. Chem. Soc., Chem Commun.*, 236 (1976).

(2) Supported by the National Science Foundation, Grant MPS 75-02794, and the Robert A. Welch Foundation, Grant D-028.
(3) For details see (a) B. K. Bandlish, A. G. Padilla, and H. J. Shine, *J. Org. Chem.*, **40**, 2590 (1975); (b) S. R. Mani and H. J. Shine, *ibid.*, **40**, 2756 (1975), and earlier references cited therein.
(4) J. J. Silber and H. J. Shine, *J. Org. Chem.*, **36**, 2923 (1971).
(5) For example, see Y. Sato, S. Kinoshita, M. Sano, and H. Akamatu, *Bull. Chem. Soc. Jpn.*, **40**, 2539 (1967); **42**, 548 (1969); I. C. Lewis and L. S. Singer, *J. Chem. Phys.*, **43**, 2712 (1965).
(6) Unpublished work of Dr. T. Okuyama.
(7) W. Rundel and K. Scheffler, *Tetrahedron Lett.*, 993 (1963).
(8) Aldrich Chemical Co., Inc.
(9) N. G. Donnelly, Z. Demidowicz, and R. L. Kelly, *J. Chem. Soc., Dalton Trans.*, 2335 (1975).
(10) W. L. Musker and T. L. Wolford, *J. Am. Chem. Soc.*, **98**, 3055 (1976). We thank Professor Musker for additional information.
(11) B. K. Bandlish and H. J. Shine, *J. Heterocycl. Chem.*, **12**, 287 (1975).
(12) V. D. Pokhdenko, V. A. Khizhnyi, V. G. Koshechko, and I. Shkrebtii, *J. Org. Chem. USSR (Engl. Transl.)*, **11**, 1883 (1975).
(13) P. Collings, K. Al-Mallah, and G. Stedman, *J. Chem. Soc., Perkin Trans. 2*, 1734 (1975); K. Y. Al-Mallah, P. Collings, and G. Stedman, *J. Chem. Soc., Dalton Trans.*, 2469 (1974).
(14) A. V. Blom, *J. Prakt. Chem.*, **94**, 77 (1916).

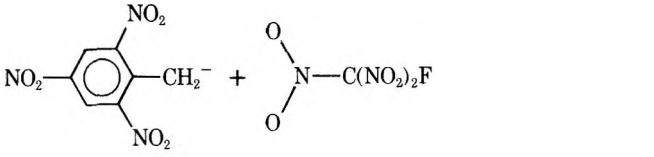
Fluorotrinitromethane as an Alkaline Nitrating Agent. Preparation of α,2,4,6-Tetranitrotoluene from 2,4,6-Trinitrotoluene

Michael E. Sitzmann,* Lloyd A. Kaplan,[1a] and Isaac Angres[1b]

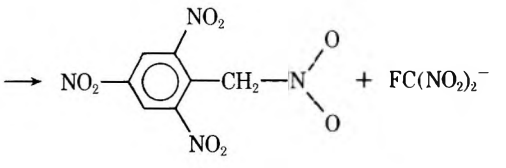
Naval Surface Weapons Center, White Oak, Silver Spring, Maryland 20910

Received August 4, 1976

Although alternative synthetic methods for α,2,4,6-tetranitrotoluene (1) have been reported,[2,3] they are relatively cumbersome. We have therefore investigated the possibility that alkaline nitration of 2,4,6-trinitrotoluene (2) might offer a more convenient route to 1. In contrast with more usual alkaline nitrating agents (alkyl nitrates, tetranitromethane), which did not give the desired tetranitrotoluene, we found that 1 can be prepared in excellent yield by the reaction of 2 with fluorotrinitromethane in alkaline THF–methanol.



3



1

Alkaline nitration of 2 with fluorotrinitromethane apparently proceeds by nucleophilic attack of 2,4,6-trinitrobenzyl anion 3[4] on a nitro nitrogen, resulting in displacement of fluorodinitromethide carbanion; the latter, however, was not isolated.[5] This is in marked contrast to the manner in which certain other nucleophiles ($OC_2H_5^-$, $OCH_2CF_3^-$, N_3^-, F^-) attack fluorotrinitromethane resulting in formal substitution on carbon, with displacement of one of the nitro groups.[6]

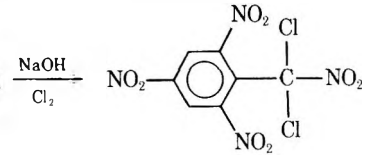
$$B^- + FC(NO_2)_3 \rightarrow FC(NO_2)_2B + NO_2^-$$

The fact that 3 attacks fluorotrinitromethane on nitrogen rather than carbon is probably due to the greater steric requirements of 3 over the other nucleophiles. The nitrogen atoms in fluorotrinitromethane are sterically more accessible than the carbon atom.

The reasons for failure with alkyl nitrates and tetranitromethane are not clear and cannot be rationalized on the basis of the relative stabilities of the leaving groups since fluorodinitromethide carbanion is very much less stable than trinitromethide carbanion.[6] Other factors to be considered are the relative rates of the competing reactions of tetranitromethane with 3 and the excess of hydroxide ion used to convert 2 to 3. Another possibility is O-nitration as a competing reaction. However, by TLC analysis we detected no trinitrobenzyl alcohol, trinitrobenzyl nitrite, or trinitrobenzaldehyde, which would be likely products of O-nitration.

The pK_a of 1 in methanol–water (75:25) was found to be 5.93 (the midpoint in the titration with sodium hydroxide). The potassium salt of 1 can be formed from 1 and potassium hydroxide in tetrahydrofuran–methanol solution and precipitated by the addition of ether (Caution! The potassium salt is highly sensitive to impact and heat.) Addition of the deep red potassium salt to aqueous acid regenerates 1.

Chlorination of 1 in the presence of sodium hydroxide yields α,α-dichloro-α,2,4,6-tetranitrotoluene (4).



4

Experimental Section[7]

General. (Caution!) The compounds described herein are explosives and should be handled with care. Fluorodinitro compounds show varying degrees of toxicity and may cause painful burns when brought into contact with the skin.

α,2,4,6-Tetranitrotoluene. A well-stirred solution of 11.5 g (0.05 mol) of 2,4,6-trinitrotoluene and 17 g (0.1 mol) of fluorotrinitromethane[8] in 150 ml of tetrahydrofuran and 75 ml of methanol was immersed in a dry ice–acetone bath. When the temperature of the solution reached 0 °C, an ice-cold solution of 9.6 g (0.15 mol) of potassium hydroxide (87%) in 50 ml of water and 75 ml of methanol was quickly added. The temperature immediately rose to about 5 °C and then began to fall. When the temperature of the deep red solution again reached 0 °C, the reaction was quenched by pouring the solution into 1500 ml of water containing 25 ml of concentrated hydrochloric acid. The total reaction time was approximately 1.5 min. The precipitated yellow solid was removed by filtration, washed well with water, and dried. The yellow solid (12.0 g, 89%) showed only one spot on a thin layer chromatogram (no starting TNT remained). Crystallization from benzene–hexane gave 10.0 g, mp 114–116 °C. An additional crystallization from methanol–water raised the melting point to 116.5–118 °C; NMR (CD_3COCD_3) δ 9.24 (s, 2, aromatic H), 6.30 (s, 2, CH_2); mass spectrum *m/e* 226 ($M^+ - NO_2$); mol wt calcd 272, found 270.

Anal. Calcd for $C_7H_4N_4O_8$: C, 30.89; H, 1.48; N, 20.58. Found: C, 30.76; H, 1.26; N, 20.45.

α,α-Dichloro-α,2,4,6-tetranitrotoluene. To a solution of 0.54 g (0.002 mol) of α,2,4,6-tetranitrotoluene in 15 ml of tetrahydrofuran and 5 ml of water was added 0.4 ml of 5 N sodium hydroxide. Chlorine gas was bubbled into the red solution until the solution was light yellow in color and then 50 ml of water containing 5 ml of concentrated hydrochloric acid was added. A yellow oil separated which solidified upon standing to give 0.65 g, mp 126–129 °C dec. Crystallization from methanol–water gave 0.5 g of pale yellow needles: mp 133–134 °C dec; NMR (CD_3COCD_3) δ 9.18 (s); mass spectrum *m/e* 294, 296, 298 ($M^+ - NO_2$, chlorine isotopes).

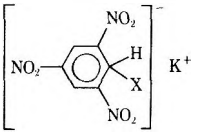
Anal. Calcd for $C_7H_2N_4O_8Cl_2$: C, 24.65; H, 0.59; N, 16.43; Cl, 20.79. Found: C, 24.45; H, 0.48; N, 16.25; Cl, 20.41.

Acknowledgment. This work was supported by NSWC Task IR-144. The authors are grateful to Dr. Mortimer J. Kamlet for his helpful suggestions and to Mr. Donald J. Glover for the pK_a determination. I.A. would like to thank the National Research Council and the Naval Surface Weapons Center for a postdoctoral associateship.

Registry No.—1, 35113-75-8; 2, 118-96-7; 4, 60789-52-8; fluorotrinitromethane, 1840-42-2.

References and Notes

(1) (a) Deceased. (b) NRC Postdoctoral Fellow.
(2) S. K. Yasuda, *J. Chromatog.*, **13**, 78 (1964). An immobile impurity (TLC analysis) present in 2,4,6-trinitrotoluene is assumed to be **1**.
(3) A. N. Parnes, S. M. Shein, M. I. Kalinkin, L. I. Sidelnikova, and D. N. Kursanov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **10**, 2350 (1971). Chloranil oxidized I (X = CH_2NO_2) in 20 h at room temperature to give **1** in 12% yield. *Chemical Abstracts* [**76**, 59172e (1972)] indicates that **1** can be formed in 50% yield



I

from I (X = CH_2NO_2) and tropylium tetrafluoroborate. However, the original Russian article claims this reaction only for X = CH_2COCH_3. Analytical data and physical properties of **1** are not given.
(4) K. G. Shipp, L. A. Kaplan, and M. E. Sitzmann, *J. Org. Chem.*, **37**, 1966 (1972).
(5) L. V. Okhlobystina, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **10**, 2339 (1969), states that reaction of fluorotrinitromethane with reducing and nucleophilic reagents (KI, HI, $NaBH_4$, $FeCl_2$, SO_2, H_2O_2–$NaNO_2$) proceeds by a route involving radical intermediates. If radical intermediates are involved in the reaction of **2** with fluorotrinitromethane, one might expect formation of 2,2′,4,4′,6,6′-hexanitrobibenzyl from 2,4,6-trinitrobenzyl radical. However, no bibenzyl is produced in the reaction. In fact, no product other than **1** is detected by thin layer chromatography.
(6) M. J. Kamlet and H. G. Adolph, *J. Org. Chem.*, **33**, 3073 (1968). However, the formation of fluorodinitromethane in the reaction of fluorotrinitromethane with hydroperoxide ion can be explained either by attack of hydroperoxide ion on carbon with displacement of a nitro group or by attack of hydroperoxide ion on oxygen or nitrogen of one of the nitro groups with displacement of fluorodinitromethide ion.
(7) NMR spectra were determined on a Varian HA-100 spectrometer and the chemical shifts are relative to tetramethylsilane. The melting points are uncorrected.
(8) Reference 6, p 3079.

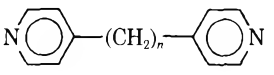
Synthesis of Bis(4-pyridyl)methane[1]

P. L. Gaus, Albert Haim,* and Francis Johnson

Departments of Chemistry and Pharmacology, State University of New York, Stony Brook, New York 11794

Received August 10, 1976

In connection with our studies of intramolecular electron transfer mediated by aromatic nitrogen heterocycles,[2,3] it became important to examine the role of the bridging ligands represented by **1**.



1

Bis(4-pyridyl)methane (compound **1**, where $n = 1$) is not available commercially, but its synthesis via the reaction of chloropyridine with 4-methylpyridine and potassium amide in liquid ammonia has been reported.[4] Unfortunately, repeated (18) attempts (under rigorous exclusion of water and oxygen) to synthesize this compound using the reported method yielded intractable oils, with properties unlike those described by Jampolsky et al.,[4] or those established in the present work for an authentic sample of the desired compound. Therefore, we designed an alternate synthesis of bis(4-pyridyl)methane, and report r results herein.

Bis(4-pyridyl) ketone was prepared using the method of Wibaut and Heeringa.[5] Conversion to the corresponding hydrocarbon was accomplished using the Huang-Minlon[6] modification of the Wolff–Kishner reduction, except that 1-butanol was used as the solvent.

The purified product is a white, crystalline, extremely hygroscopic solid,[7] and, therefore, must be handled by drybox techniques. Proof of the composition and structure of the compound is based on analytical and spectroscopic data reported in detail in the Experimental Section.

Experimental Section

4-Cyanopyridine (Aldrich) was recrystallized from ethanol. Diethyl ether was dried using calcium hydride, and was stored under dry nitrogen. 4-Bromopyridine hydrochloride (Pfaltz and Bauer) and *n*-butyllithium (2.9 M in hexane, Ventron) were used as received.

Visible and ultraviolet spectra were obtained using a Cary 118 spectrophotometer. Infrared spectra were obtained using a 567 Perkin-Elmer spectrophotometer using matched cells (Beckman-RIIC, Ltd). ^1H NMR spectra were obtained on a Varian CFT-20 instrument.[8] The mass spectrum (acetone solution) was obtained using a Hewlett-Packard 5980A mass spectrometer, preceded by a Hewlett-Packard 5710A gas chromatograph. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratories, Inc., Woodside, N.Y.

Bis(4-pyridyl) ketone was synthesized (nitrogen atmosphere) using the literature[5] method, with some modifications. 4-Bromopyridine hydrochloride was neutralized in aqueous solution at 0 °C, and the free base was extracted into ether. The ether solution was dried over magnesium sulfate for 12 h at 5 °C, and then the concentration of 4-bromopyridine was determined gravimetrically.[9] The reaction was allowed to proceed as described[5] and the reported quenching procedure was utilized. The product was isolated as described,[5] except that following the treatment with active carbon, neutralization of the final aqueous phase gave a precipitate of (mostly) potassium sulfate, which was removed by filtration. The faintly yellow filtrate was extracted with ether. Evaporation of the ether gave a white solid which was recrystallized three or four times from ethanol, mp 136–137 °C. The 45% yield of recrystallized product is somewhat higher than that reported.[5]

Bis(4-pyridyl)methane. Bis(4-pyridyl) ketone (4.0 g, 0.022 mol) was added to a solution of 4.0 g of potassium hydroxide in 40 ml of 1-butanol at 60 °C. After stirring for 15 min, 3.7 ml of 85% hydrazine hydrate was added. The solution was refluxed for 1.3 h. Then some solvent was removed by distillation until the temperature of the vapors immediately above the reactant solution had reached 110 °C. Heating was continued under reflux conditions for 8 h. The resulting clear yellow solution was allowed to cool at 60 °C, and then treated with 60 ml of water. The aqueous phase was acidified to pH ~2 by dropwise addition of 6 M hydrochloric acid. The aqueous phase was extracted four times with 50-ml portions of ether, basified to pH 10, and then extracted repeatedly with benzene. The benzene extracts were evaporated at 40 °C to ca. 20 ml in a flash evaporator. The resulting solution was placed on an alumina column (5 × 0.5 in., neutral, activity 1.0, 80–200 mesh), and the column was eluted with 300 ml of benzene. The benzene was removed by evaporation at 40 °C in a flash evaporator to yield a clear, colorless oil. The last traces of benzene were removed at room temperature on a vacuum line, resulting in the crystallization of small, white needles. Since the substance is quite volatile, as a further purification, it was subjected to a short path vacuum distillation at 40 °C onto a cold finger at 15 °C, yielding a white, crystalline solid. The apparatus was filled with dry nitrogen, and then transferred to a dry bag over phosphorus pentoxide. All subsequent manipulations were performed in a glove bag. Yield 3.3 g, 89%; mp 36–37 °C;[10] IR (C_6H_6) 2990 m, 2969 w, 2930 w, 1600 vs, 1565 m, 1420 vs, 1208 w, 1060 w, 982 m, 910 vw, 828 w, 785 m, 770 m, 610 s, 540 m, 475 cm^{-1} w; NMR (C_6D_6/Me_4Si) δ 3.19 (s, 2 H, $-CH_2-$), 6.46 (m, 4 H, aromatic H), 8.40 (m, 4 H, aromatic H); MS *m/e* 170 (P, base), 171 (11.6%) 169 (65%), 168 (11%), 143 (6%), 142 (11%), 141 (4%), 117 (5%), 115 (8%), 92 (3%), 89 (5%), 84 (3%), 65 (5%), 63 (4%), 51 (7%); UV λ_{max} (water) 256 nm.

Anal. Calcd for $C_{11}H_{10}N_2$: C, 77.61; H, 5.93; N, 16.46. Found: C, 77.69; H, 6.10; N, 16.14.

Registry No.—Bis(4-pyridyl) ketone, 6918-15-6; 4-bromopyridine HCl, 19524-06-2; 4-bromopyridine, 1120-87-2; bis(4-pyridyl)methane, 60776-05-8.

References and Notes

(1) This work was supported by Grants GP-37057X and CHE 7610449 from the National Science Foundation.
(2) D. Gaswick and A. Haim, *J. Am. Chem. Soc.*, **96**, 7845 (1974).
(3) J. J. Jwo and A. Haim, *J. Am. Chem. Soc.*, **98**, 1172 (1976).
(4) L. M. Jampolsky, M. Baum, S. Kaiser, L. H. Sternbach, and M. W. Goldberg, *J. Am. Chem. Soc.*, **74**, 5222 (1952).
(5) J. P. Wibaut and L. G. Heeringa, *Recl. Trav. Chim. Pays-Bas*, **74**, 1003 (1955).

(6) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).
(7) Crystals exposed to an atmosphere of 50–60% humidity absorb water and produce a solution within 15–20 s.
(8) The authors are grateful to Dr. L. Altman for carrying out the measurements.
(9) A. Murray, III, and W. H. Langham, *J. Am. Chem. Soc.*, **74**, 6289 (1952).
(10) Compare with the value 138–140 °C reported in ref 4.

Functionalization of 1*H*-Perfluoroalkyl Chains

Claude Wakselman* and Thoai Nguyen

C.N.R.S.-C.E.R.C.O.A. 2, rue Henri Dunant, 94320 Thiais, France

Received April 23, 1976

The terminal hydrogen of 1*H*-perfluoroalkyl chains is known to be extremely inert.[1] These compounds can only be halogenated[2] or oxidized[3] by a radical mechanism at a very high temperature. They are not affected by concentrated potassium hydroxide at 100 °C; however, a slow hydrogen–deuterium exchange has been demonstrated in methanol.[4]

We describe here the mild ionic reaction of lithium dialkylamide on compound **1** yielding the amide **6**. The most probable reaction pathway is as follows:

$$R_F{-}CF_2{-}CF_2H \xrightarrow{R_2NLi} R_F{-}CF_2{-}CF_2^- Li^+$$
1 **2**

$$\xrightarrow{-LiF} R_F{-}CF{=}CF_2 \xrightarrow{R_2NLi} R_F{-}\bar{C}F{-}CF_2{-}NR_2\ Li^+$$
3 **4**

$$\xrightarrow{-LiF} R_F{-}CF{=}CF{-}NR_2 \xrightarrow{H_3O^+} R_F{-}CHF{-}CONR_2$$
5 **6**

The lithium dialkylamide initially reacts as a strong base, abstracting a proton from the CHF_2 group, then as a nucleophile which adds readily on the fluorinated alkene **3**. This attack occurs on the difluoromethylene group and yields the most stable anion **4**. Carbanions **2** and **4** produce respectively the perfluoroalkene **3** and the fluorinated enamine **5**, both by loss of F^-. This enamine **5** may be isolated in aprotic media. For instance, $C_6H_5CH_2OCH_2CF_2CF_2CF{=}CFN(CH_2CH_3)_2$ (**5d**) was enough stable to be recovered unchanged after 1 month at 0 °C; its ^{19}F NMR spectrum shows a cis configuration (J_{FF} = 7 Hz). Using the lithium reagent (1–2 molar equiv) we have found that the reaction needs 2 molar equiv to go to completion and not any olefin **3** could be detected during the reaction by ^{19}F NMR on the crude reaction medium.

Amide **6** can be obtained from 1*H*-perfluoroalkyl chains containing a variety of functional groups such as ether, ketal, amide, etc. This type of compounds is readily available by a radical addition on tetrafluoroethylene.[5] The compounds with $R_F = -(CF_2)_nCH_2OH$ can be obtained commercially.[6] The results obtained with various substrates, using 2 equiv of lithium diethylamide in diethyl ether, are listed in Table I.

Bifunctional fluorinated compounds are relatively rare synthetic intermediates.[7] They are generally symmetrical. The functionalization of 1*H*-perfluoroalkyl chains by lithium dialkylamide constitutes a smooth access to symmetrical or unsymmetrical bifunctional fluorinated intermediates.

Experimental Section

^1H NMR spectra were recorded on a Perkin-Elmer R24 spectrometer with Me_4Si as internal standard. ^{19}F NMR spectra were recorded on a JEOL C-60HL spectrometer with $CFCl_3$ as external standard. Chemical shifts are given in parts per million. A downfield displacement is positive for proton, negative for fluorine. Coupling constants are in hertz. The s, d, t, q, m, usual abbreviations are used with the composite form dd, dt, dm, tt, ddd which are doublet of doublets, doublet of triplets, doublet of multiplets, triplet of triplets, and doublet of doublets of doublets. IR spectra were obtained on a Perkin-Elmer 167 spectrometer. Mass spectra data were obtained on a AEI MS 30 spectrometer.

We thank Mr. Foulletier (PCUK)[11] for a sample of 1*H*-perfluorohexane **1a**. 1*H*,6*H*-Perfluorohexane **1b** was prepared according to the method of Brace.[8] Compounds **1c** and **1d** were prepared starting from commercial (PCR)[11] 1*H*,1*H*,7*H*-dodecafluoroheptanol and 1*H*,1*H*,5*H*-octafluoropentanol. The first alcohol was oxidized following Joyce procedure[9] and the acid was transformed as usual in acid chloride, then in amide **1c**. The second alcohol was transformed in ether **1d** with benzyl bromide. Compound **1e** was obtained by transketalization[10] of 7*H*-dodecafluoroheptanal prepared according to the method of Brace.[7] We thank Mr M. Rubinstein for technical assistance and the D.G.R.S.T.[11] for financial support.

Preparation of *N,N*-Diethyl-2*H*-decafluorohexanoic Acid Amide (6a). Into a 250-ml three-neck flask equipped with a mechanical stirrer, a condenser–drying tube system, and addition funnel fitted to provide an argon atmosphere was placed 5 g (15 mmol) of 1*H*-perfluorohexane in 30 ml of anhydrous diethyl ether. The flask was cooled at −10 °C with a CCl_4–dry ice bath. With stirring, a white suspension of lithium diethylamide [prepared by addition of 3.5 g (48 mmol) of diethylamine in 100 ml of ether on 31 mmol of a butyllithium solution in pentane at 0 °C] was added dropwise. After stirring the mixture for 1 h, it was acidified with 30 ml of 20% HCl solution. The mixture was extracted with diethyl ether. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was evaporated under reduced pressure. The residue was distilled under vacuum to give 3.5 g of **6a:** bp 95–96 °C (12 mm); IR (neat) 1660 cm^{-1} (amide); ^1H NMR ($CDCl_3$) 3.45 (q, 4 H, J = 7 Hz), 1.2 (t, 6 H), 5.5 (ddd, 1 H, J = 46, 16, 7 Hz); ^{19}F NMR ($CDCl_3$) 79 (3 t, 3 F, J = 11, 2 Hz), 124 (m, 2 F), 121 (m, 2 F), 117 (dm, 1 F, J = 280 Hz), 121 (dm, 1 F), 194 (ddd, 1 F); mass spectrum *m/e* (rel intensity) 351 ($M^{\cdot+}$, 67), 336 (M − CH_3, 96), 332 (M − F, 100), 322 (M − C_2H_5, 48).

Anal. Calcd for $C_{10}H_{11}F_{10}NO$: C, 34.15; H, 3.12; F, 54.10. Found: C, 34.06; H, 3.10; F, 54.23.

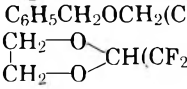
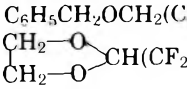
The same general procedure was used to prepare the other amides **6**.

***N,N,N′,N′*-Tetraethyl-2*H*,5*H*-hexafluorohexanedioic Acid Amide (6b):** bp 160–161 °C (0.1 mm); IR (neat) 1670 cm^{-1} (amide); ^1H NMR ($CDCl_3$) 3.4 (q, 8 H, J = 7 Hz), 1.2 (t, 12 H), 5.65 (ddd, 1 H, J = 45, 8, 14 Hz); ^{19}F NMR ($CDCl_3$) 122–123 (m, 4 F), 197 (dm, 2 F); mass spectrum *m/e* (rel intensity) 365 (M + $1^{\cdot+}$, 12), 345 (M − F, 15), 292 (M − NEt_2, 63), 264 (M − $CONEt_2$, 100).

***N,N,N′,N′*-Tetraethyl-2*H*-nonafluoroheptanedioic Acid Amide (6c):** bp 169–170 °C (0.1 mm); IR (neat) 1670 cm^{-1} (amide); ^1H NMR ($CDCl_3$) 1.2 (2 t, 12 H, J = 7 Hz), 3.42 (q, 8 H), 5.65 (ddd, 1 H, J = 46, 12, 9 Hz); ^{19}F NMR ($CDCl_3$) 119–121 (3 m, 6 F), 117 (dm, 1 F, J = 310 Hz), 122 (dm, 1 F), 197 (ddd, 1 F, J = 46, 25, 12 Hz); mass spectrum *m/e* (rel intensity) 432 ($M^{\cdot+}$, 10), 404 (M − C_2H_4, 10), 344 (M − C_2H_4 − HF, 100).

***N,N*-Diethyl-2*H*,5*H*,5*H*-5-benzyloxypentafluoropentanoic**

Table I

	Substrate		Amide	Yield, %
1a	$CF_3(CF_2)_3CF_2CF_2H$	**6a**	$CF_3(CF_2)_3CHFCONEt_2$	60
1b	$HCF_2CF_2(CF_2)_2CF_2CF_2H$	**6b**	$Et_2NCOCHF(CF_2)_2CHFCONEt_2$	60
1c	$Et_2NCO(CF_2)_4CF_2CF_2H$	**6c**	$Et_2NCO(CF_2)_4CHFCONEt_2$	40
1d	$C_6H_5CH_2OCH_2(CF_2)_2CF_2CF_2H$	**6d**	$C_6H_5CH_2OCH_2(CF_2)_2CHFCONEt_2$	60
1e		**6e**		60

Acid Amide (6d): bp 140–141 °C (0.1 mm); IR (neat) 1660 (amide), 1600, 1580, 1500 cm^{-1} (aromatic); ^1H NMR ($CDCl_3$) 7.3 (s, 5 H), 4.6 (s, 2 H), 3.95 (t, 2 H, J = 14 Hz), 5.55 (ddd, 1 H, J = 47, 15, 7 Hz), 3.35 (q, 4 H, J = 7 Hz), 1.1 (t, 6 H); ^{19}F NMR ($CDCl_3$) 121 (dt, 2 F, J = 10, 14 Hz), 122 (ddd, 1 F, J = 294, 15, 16 Hz), 127 (ddd, 1 F, J = 13, 7 Hz), 200 (m, 1 F); mass spectrum m/e (rel intensity) 353 ($M^{\cdot+}$, 43), 334 (M − F, 12), 297 (M − $2C_2H_4$, 10), 262 (M − C_7H_7, 42), 247 (M − C_7H_7 − CH_3, 100).

Anal. Calcd for $C_{16}H_{20}F_5NO_2$: C, 54.38; H, 5.70; N, 3.96. Found: C, 54.65; H, 5.55; N, 3.77.

The enamine **5d** (1-diethylamino-5*H*,5*H*-5-benzyloxyhexafluoropentene-1) was isolated from the crude reaction mixture by evaporation of the solvent before hydrolysis: ^{19}F NMR 117 (tt, 2 F), 122 (m, 2 F), 120 (dt, 1 F, J = 12, 7 Hz), 115 (dt, 1 F, J = 12 Hz).

***N,N*-Diethyl-2*H*,7*H*-7-ethylenedioxynonafluoroheptanoic Acid Amide (6e):** bp 139–140 °C (0.1 mm); IR (neat) 1660 cm^{-1} (amide); ^1H NMR ($CDCl_3$) 3.5 (q, 4 H, J = 7 Hz), 1.25 (t, 6 H), 3.95 (m, 4 H), 4.9 (ddd, 1 H, J = 34, 13, 6 Hz), 5.1 (m, 1 H); ^{19}F NMR 119–121–124 (m, 8 F), 197 (dm, 1 F); mass spectrum m/e (rel intensity) 405 ($M^{\cdot+}$, 10), 361 (M − OC_2H_4, 18), 346 (M − OC_2H_3, 100), 332 (M − $C_3H_5O_2$, 36).

Anal. Calcd for $C_{13}H_{16}F_9NO_3$: C, 38.53; H, 3.98; N, 3.46. Found: C, 38.68; H, 3.84; N, 3.46.

Registry No.—**1a**, 355-37-3; **1b**, 336-07-2; **1c**, 60895-94-5; **1d**, 60895-95-6; **1e**, 60895-96-7; **5d**, 60895-97-8; **6a**, 60895-98-9; **6b**, 60895-99-0; **6c**, 60934-65-8; **6d**, 60896-00-6; **6e**, 60896-01-7.

References and Notes

(1) W. A. Sheppard and C. M. Sharts, "Organic Fluorine Chemistry", W. A. Benjamin, New York, N.Y., 1969, p 417; L. H. Slaugh and E. Bergman, *J. Org. Chem.*, **26**, 3158 (1961).
(2) T. J. Brice, W. H. Pearlson, and J. H. Simmons, *J. Am. Chem. Soc.*, **68**, 968 (1946).
(3) W. A. Severson and T. J. Brice, *J. Am. Chem. Soc.*, **80**, 2313 (1958); V. C. R. McLoughlin, *Tetrahedron Lett.*, 4761 (1968).
(4) S. Andreades, *J. Am. Chem. Soc.*, **86**, 2003 (1964).
(5) J. D. Lazerte and R. J. Koshar, *J. Am. Chem. Soc.*, **77**, 910 (1955).
(6) Peninsular Chemical Research, Gainesville, Fla.
(7) S. Nagase, H. Baba, K. Tanake, and T. Abe, *Kogyo Kagaku Zasshi*, **67**, 2062 (1964); C. Fuller and J. C. Tatlow, *J. Chem. Soc.*, 3198 (1961); P. Robson, J. Roylance, R. Stephens, J. C. Tatlow, and R. E. Worthington, *ibid.*, 5748 (1964); R. R. Twelves and V. Weinmayr, U.S. Patent 3 076 041 (1963); W. Bloechl, Netherlands Appl. 6 414 504 (1965).
(8) N. O. Brace, *J. Org. Chem.*, **26**, 4005 (1961).
(9) R. M. Joyce, Jr., U.S. Patent 2 559 628 (1951).
(10) H. J. Dauben, Jr., B. Loken, and H. J. Ringold, *J. Am. Chem. Soc.*, **76**, 1359 (1954).
(11) PCUK, Produits Chimiques Ugine Kuhlman; PCR, Peninsular Chem Research, Gainesville Fla.; DGRST, Déléguation Générale à la Recherche Scientifique et Technique.

Synthesis and Activity of 29-Hydroxy-3,11-dimethyl-2-nonacosanone, Component B of the German Cockroach Sex Pheromone

Albert W. Burgstahler,* Leland O. Weigel, Mark E. Sanders, and Craig G. Shaefer

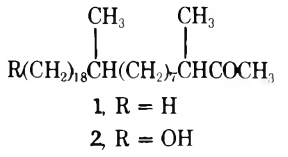
Department of Chemistry, The University of Kansas, Lawrence, Kansas 66045

William J. Bell and Susan B. Vuturo

Department of Entomology, The University of Kansas, Lawrence, Kansas 66045

Received June 2, 1976

In a previous report,[1] we described a synthesis of 3,11-dimethyl-2-nonacosanone (**1**), an active component of the contact mating pheromone present in the cuticle of the female German cockroach (*Blattella germanica*). Recently, Ishii and co-workers, who first isolated and synthesized this substance,[2] have identified a closely related second component, 29-hydroxy-3,11-dimethyl-2-nonacosanone (**2**).[3] In connection with

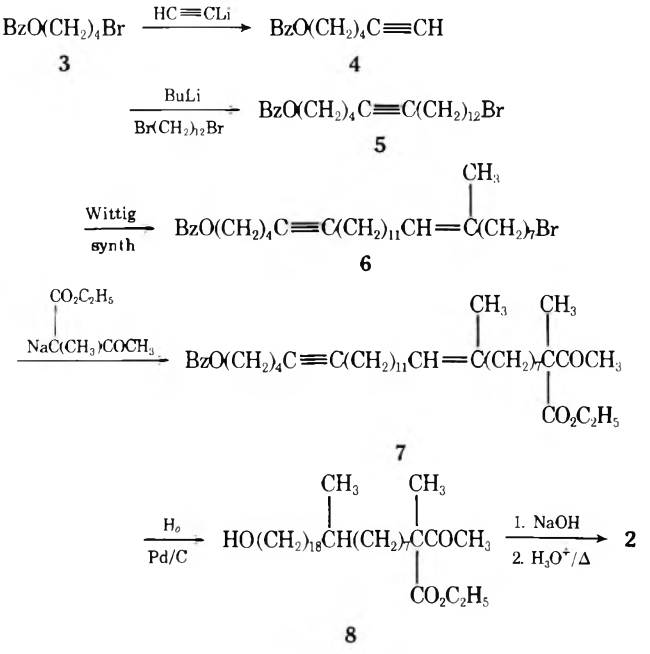


1, R = H
2, R = OH

studies on the behavioral responses of cockroaches to pheromones,[4] we undertook and now describe a synthesis of **2** together with some preliminary bioassays.

As shown in Chart I, the benzyl ether (**3**) of 4-bromo-1-butanol was used to assemble the terminal hydroxy chain.

Chart I



This derivative was selected because of its greater stability and convenience for removal compared to the alternative tetrahydropyranyl ether and because its distinctive spectral features made it especially useful for monitoring subsequent steps. The preparation of **3** was achieved in 88% yield by the phase-transfer catalyzed reaction[5] of 1,4-dibromobutane (5 equiv) with sodium benzyloxide. By alkylation with lithium acetylide (as the ethylenediamine complex), **3** was converted almost quantitatively into the acetylenic ether **4**. Monoalkylation of 1,12-dibromododecane (3 equiv) with the lithium salt of **4** then provided the acetylenic bromo ether **5** in 84% yield.

In the next step, a Wittig reaction of 9-bromo-2-nonanone[2] with the triphenylphosphorane derivative of **5** gave the olefinic bromo ether **6** as a mixture of *Z* and *E* isomers in 56% yield. Alkylation of **6** with ethyl 2-methylacetoacetate then furnished the required benzyloxy keto ester **7** in 91% yield. Finally, hydrogenation–hydrogenolysis of **7** gave the saturated hydroxy keto ester **8** (97% yield), mp 30–32 °C, which, when hydrolyzed and decarboxylated, afforded, in 71% yield from **8**, the desired hydroxy ketone **2** as a mixture of diastereoisomers, mp 41.5–43 °C.

Bioassay by antennation[1,2] showed that synthetic **2** readily evoked the characteristic precopulatory wing raising and 180°-turning response in isolated adult male German cockroaches. Male roaches isolated from their parent colonies were housed and tested in groups of five. In the tests their antennae were stroked intermittently (~10 s/min) with freshly ablated American cockroach (*Periplaneta americana*) antennae that had been dipped for 1–2 s into a carbon tetrachloride solution of the test substance and then allowed to dry.[6] All tests were performed at 24–25 °C during a period of 2.5–4.0 h into the dark phase of a 12/12-h photocycle.

In 3-min tests on males isolated for 2–4 days, synthetic **2** at a concentration of 250 μg/ml exhibited about half the activity of synthetic **1** (23% vs. 48% response; $n = 60$ in each group). With longer periods of isolation and extended testing times considerable increase in response sensitivity was observed. Thus after isolation for 24 days, 40% of 25 males responded to **1** at 100 μg/ml when intermittently antennated for up to 8 min each. Similarly, a low molecular weight analogue, 3-methyl-2-heneicosanone, found previously to be devoid of activity at 500 μg/ml toward males isolated for 2–4 days,[1] produced ~10% response in 8-min tests at 100 μg/ml and ~70% response at 1000 μg/ml in 24-day isolates.

With an isolation period of only 2–4 days and testing for up to 3 min, the response to **1** dropped to ~5% at 70 μg/ml,[1,7] whereas the activity of **2** did not decrease to this level until diluted to ~5 μg/ml. Moreover, under these conditions 3:1 and 1:1 mixtures of **1** and **2** at a total concentration of 250 μg/ml evoked 63 and 60% response, respectively, while a 1:3 mixture showed only 48% response ($n = 60$ in each group). Neither the solvent alone nor the synthetic intermediates **7** or **8** produced any sexual display.

These findings, therefore, not only confirm the pheromonal activity of **2**, but they also suggest a synergistic effect between **1** and **2**. Further study of these compounds is continuing.

Experimental Section

Melting and boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 137B Infracord spectrophotometer. Proton magnetic resonance (^{1}H NMR) spectra were taken on a Varian A-60A instrument in carbon tetrachloride with tetramethylsilane as internal reference. Electron impact mass spectra (MS) were obtained at 70 eV with a Varian CH-5 spectrometer by Mr. Robert Drake, University of Kansas Department of Chemistry. All reactions were conducted under dry argon or nitrogen; organic extracts were dried over anhydrous magnesium sulfate. Homogeneity assays were made by TLC (silica gel 60F-254, 0.25 mm layer), GLC (Varian A90-P3 instrument, 6 ft × 0.25 in. stainless steel column packed with 10% OV-17 on 100–120 mesh Gas-Chrom Q), or HPLC (Waters 6000A unit, 25-cm column of 10 μ Partisil 10 ODS). Preparative layer chromatography (PLC) was conducted on precoated F-254 silica gel plates (20 × 20 × 0.2 cm). Elemental analyses were performed on an HP-185C CHN analyzer by Mr. Tho Nguyen, University of Kansas Department of Medicinal Chemistry microanalyst.

4-Benzyloxy-1-bromobutane (3). To a magnetically stirred solution of 10 g of sodium hydroxide in 20 g of water cooled to 10 °C were added 5.4 g (50 mmol) of benzyl alcohol, 54 g (250 mmol) of 1,4-dibromobutane, and 0.85 g (2.5 mmol) of tetrabutylammonium hydrogen sulfate[5] (Aldrich). After stirring (~300 rpm) for 10 h at 25 °C, the mixture was poured into 300 ml of water and extracted with pentane, and the dried extracts were evaporated. Slow distillation of the product at 0.3 mm through a 25-cm Vigreux column furnished 40 g of recovered 1,4-dibromobutane and benzyl alcohol (bp 30–40 °C) and 10.7 g (88%) of **3** (>99% by GLC): bp 103–105 °C (0.3 mm); IR (film) 3040, 1215, 1110, 740, and 700 cm^{-1}; ^{1}H NMR δ 7.23 (s, 5 H), 4.43 (s, 2 H), 3.42 and 3.36 (overlapping triplets, $J = 7$ Hz, 4 H), 1.83 (m, 4 H); MS *m/e* (rel intensity) 244 (0.2, M$^+$ + 2), 242 (0.2, M$^+$), 92 (42), 91 (100). Anal. Calcd for $C_{11}H_{15}OBr$: C, 54.33; H, 6.22. Found: C, 54.53; H, 6.39.

6-Benzyloxy-1-hexyne (4). To a solution of 2.69 g (28.0 mmol) of lithium acetylide ethylenediamine complex (Alpha, 96%) in 56 ml of dimethyl sulfoxide[8] was added 6.82 g (28.0 mmol) of **3** with stirring at 5–10 °C. After stirring for 12 h at 25 °C the mixture was poured into water and the product recovered by extraction with pentane. Short-path distillation gave 5.12 g (97%) of **4** (>99.5% by GLC): bp 85 °C (0.01 mm); IR (film) 3300, 2120, 1110, 740, and 700 cm^{-1}; ^{1}H NMR δ 7.20 (s, 5 H), 4.42 (s, 2 H), 3.42 (t, $J = 7$ Hz, 2 H), 2.15 (t split 2.5 Hz, $J = 7$ Hz, 2 H), 1.79 (t, $J = 2.5$ Hz, 1 H), 1.68 (m, 4 H); MS *m/e* (rel intensity) 188 (1.4, M$^+$), 91 (100). Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.87; H, 8.59.

1-Benzyloxy-18-bromo-5-octadecyne (5). The monolithium salt of **4** (5.65 mmol in 6 ml of tetrahydrofuran, generated by the method of Schwarz[9]) was added dropwise at 20 °C to a stirred solution of 5.72 g (17.4 mmol) of 1,12-dibromododecane (Aldrich) in 25 ml of hexamethylphosphoramide and 15 ml of tetrahydrofuran. After stirring for 24 h at 25 °C the mixture was diluted with water and extracted with pentane, and the dried pentane extracts were evaporated. Rapid distillation of the residue yielded ca. 4.0 g of recovered dibromide, bp 130 °C (0.005 mm), and then 2.06 g (84%) of **5** (~97% by GLC): bp 238–240 °C (0.005 mm); IR (film) 3340, 1215, 1110, 740, and 700 cm^{-1}; ^{1}H NMR δ 7.21 (s, 5 H), 4.43 (s, 2 H), 3.42 and 3.35 (overlapping triplets, $J = 7$ Hz, 4 H), 2.35–1.87 (broad m, 4 H), 1.87–1.48 (m, 4 H), 1.27 (broad s, 20 H); MS *m/e* (rel intensity) 436 (2.1, M$^+$ + 2), 435 (2.6), 434 (2.3, M$^+$), 433 (2.2), 91 (100). Anal. Calcd for $C_{25}H_{39}OBr$: C, 68.95; H, 9.03. Found: C, 69.31; H, 9.03.

(*Z*)- and (*E*)-26-Benzyloxy-1-bromo-8-methylhexacos-8-en-21-yne (6). A solution of 178 mg (0.409 mmol) of **5** and 108 mg (0.412 mmol) of triphenylphosphine in 1.2 ml of xylene was heated at 140 °C for 20 h. The xylene was removed in vacuo at 20 ° C and the residue washed with three 1-ml portions of dry ether at −78 °C. The vacuum-dried, viscous phosphonium salt (247 mg, 0.354 mmol, 86%) was dissolved in 2 ml of tetrahydrofuran–ether (1:1) and 0.63 ml of 0.57 M methyllithium (in ether) was added slowly at −23 °C, followed by 150 mg (0.678 mmol) of 9-bromo-2-nonanone.[2b,11] After stirring for 0.5 h at −23 °C and then for 6 h at 30 °C the mixture was diluted with water and extracted with pentane. After drying and evaporation of the pentane, PLC (ether–pentane, 1:10) of the residue gave 108 mg (56% from the phosphonium salt) of **6** as a colorless, oily mixture of *Z* and *E* isomers: R_f 0.61; IR (film) 3040, 1215, 1110, 740, and 700 cm^{-1}; ^{1}H NMR δ 7.20 (s, 5 H), 5.05 (t, $J = \sim 6$ Hz, 1 H), 4.42 (s, 2 H), 3.41 and 3.32 (overlapping triplets, $J = 7$ Hz, 4 H), 2.2–1.7 (broad m, 8 H), 1.7–1.5 (m, 7 H), 1.27 (broad s, 28 H); MS *m/e* (rel intensity) 560 (1.2, M$^+$ + 2), 558 (1.2, M$^+$), 91 (100). Anal. Calcd for $C_{34}H_{55}OBr$: C, 72.96; H, 9.91. Found: 72.87; H, 9.92.

Ethyl (*Z*)- and (*E*)-2-Acetyl-28-benzyloxy-2,10-dimethyloctacos-10-en-23-ynoate (7). By means of a syringe, 480 mg (0.858 mmol) of **6** was added at 25 °C to 1.27 mmol of the sodium hydride generated enolate of ethyl 2-methylacetoacetate (Aldrich, fractionally distilled, 98% by GLC) in 3 ml of benzene–dimethylformamide (2:1). This mixture was stirred at 60 °C for 27 h, poured into 100 ml of water, and extracted with pentane. The washed extracts were dried and evaporated at 20 mm, and the yellow residue (550 mg) was purified by PLC (chloroform, two-developments) to give 489 mg (91%) of **7** as a colorless oil: R_{f2} 0.47; IR (film) 3040, 1740, 1720, 1110, 740, and 700 cm^{-1}; ^{1}H NMR δ 7.20 (s, 5 H), 5.03 (t, $J = \sim 6$ Hz, 1 H), 4.42 (s, 2 H), 4.13 (q, $J = 7$ Hz, 2 H), 3.42 (t, $J = 7$ Hz, 2 H), 2.2–1.7 (broad m, 8 H), 2.03 (s, 3 H), 1.65–1.55 (m, 10 H), 1.26 (broad s, 30 H), 1.23 (t, $J = 7$ Hz, 3 H); MS *m/e* (rel intensity) 622 (0.97, M$^+$), 91 (100). Anal. Calcd for $C_{41}H_{66}O_4$: C, 79.05; H, 10.68. Found: C, 79.16; H, 10.68.

Ethyl 2-Acetyl-28-hydroxy-2,10-dimethyloctacosanoate (8). A solution of 147 mg (0.236 mmol) of **7** in 15 ml of absolute ethanol was stirred under 1 atm of hydrogen with 50 mg of 30% palladium–carbon until 4 equiv of hydrogen was absorbed (ca. 12 h). Filtration and evaporation (0.1 mm) gave 127 mg (97%) of **8** as a colorless, waxy solid: mp 31–32 °C; IR (melt) 3360, 1740, and 1720 cm^{-1}; ^{1}H NMR δ 4.13 (q, $J = 7$ Hz, 2 H), 3.52 (t, $J = 6.5$ Hz, 2 H), 2.25 (broad s, 1 H), 2.05 (s, 3 H), 1.55 (m, 1 H), 1.27 (t, $J = 7$ Hz, 3 H), 1.25 (m, 51 H), 0.83 (d, $J = 6$ Hz, 3 H); MS *m/e* (rel intensity) 538 (0.99, M$^+$), 112 (100). Anal. (after PLC, ether–chloroform, 1:2; R_f 0.43) Calcd for $C_{34}H_{66}O_4$: C, 75.78; H, 12.34. Found: C, 75.99; H, 12.45.

29-Hydroxy-3,11-dimethyl-2-nonacosanone (2). A solution of 108 mg (0.200 mmol) of **8** in 0.6 ml of 0.8 M ethanolic sodium hydroxide was stirred at 40 °C for 6 h. After acidification with 1% hydrochloric acid and warming to 60 °C, the mixture was diluted with water and extracted with pentane. Evaporation of the pentane followed by PLC (ether–chloroform, 1:2, two developments) afforded 66 mg (71%) of nearly pure **2**, mp 38–40 °C, R_{f2} 0.50. Recrystallization from pentane at −40 °C furnished an analytical sample: mp 41.5–43 °C; IR (melt) 3340, 1710, 1045, and 710 cm^{-1}; ^{1}H NMR δ 3.52 (t, $J = 6$ Hz, 2 H), 2.34 (m, $J = 6.8$ Hz, 1 H), 2.3 (broad s, 1 H), 2.01 (s, 3 H), 1.53 (m, 1 H), 1.23 (broad s, 48 H), 1.04 (d, $J = 6.8$ Hz, 3 H), 0.84 (d, $J = 6$ Hz, 3 H); MS *m/e* (rel intensity) 466 (2.9, M$^+$), 72 (100). Anal. Calcd for $C_{31}H_{62}O_2$: C, 79.76; H, 13.39. Found: C, 79.64; H, 13.58.

Acknowledgments. Fellowship aid from the Phillips Petroleum Co. to L.O.W. and financial support from the National Science Foundation (BNS75-21019 and SMI76-03094), the National Institute of Mental Health (R03-MH-27545), and the Velsicol Corp. to W.J.B. are gratefully appreciated. We also thank Professor S. Ishii for information concerning results of his investigations in advance of publication.

Registry No.—**2**, 60789-53-9; **3**, 60789-54-0; **4**, 60789-55-1; 4 Li salt, 60789-56-2; **5**, 60789-57-3; *Z*-**6**, 60789-58-4; *E*-**6**, 60789-59-5; *Z*-**7**, 60789-60-8; *E*-**7**, 60789-61-9; **8**, 60815-96-5; benzyl alcohol, 100-51-6;

1,4-dibromobutane, 110-52-1; 1,12-dibromododecane, 3344-70-5; 9-bromo-2-nonanone, 52330-02-6; ethyl 2-methylacetoacetyl enolate, 29537-38-0.

References and Notes

(1) A. W. Burgstahler, L. O. Weigel, W. J. Bell, and M. K. Rust, *J. Org. Chem.*, **40**, 3456 (1975).
(2) (a) R. Nishida, H. Fukami, and S. Ishii, *Appl. Entomol. Zool.*, **10**, 10 (1975); (b) T. Sato, R. Nishida, Y. Kuwahara, H. Fukami, and S. Ishii, *Agric. Biol. Chem.*, **40**, 391 (1976). For other syntheses of **1**, see M. Schwarz, J. E. Oliver, and P. E. Sonnet, *J. Org. Chem.*, **40**, 2410 (1975); also L. D. Rosenblum, R. J. Anderson, and C. A. Henrick, *Tetrahedron Lett.*, 419 (1976).
(3) (a) Reported at the meeting of the Japanese Society of Agricultural Chemistry, Kyoto, Japan, April 1976. (b) **Note Added in Proof.** A synthesis of **2** (diastereoisomeric mixture, mp 40–41 °C) has now also been reported by Professor Ishii's group along with data showing biological activity equivalent to that of the natural pheromone but greater than that of **1**: R. Nishida, T. Sato, Y. Kuwahara, H. Fukami, and S. Ishii, *Agric. Biol. Chem.*, **40**, 1407 (1976).
(4) M. K. Rust, T. Burk, and W. J. Bell, *Anim. Behav.*, **24**, 52 (1976); M. K. Rust and W. J. Bell, *Proc. Natl. Acad. Sci. U.S.A.*, **73**, 2524 (1976).
(5) Cf. H. H. Freedman and R. A. Dubois, *Tetrahedron Lett.*, 3251 (1975); J. Dockx, *Synthesis*, 447 (1973).
(6) In our experience, bioassays conducted with either American cockroach antennae[1] or male German cockroach antennae[2] give comparable results.
(7) Although our test results on synthetic **1** are in accord with those in ref 2a, which noted "distinct activity [for both natural **1** and synthetic **1**] at a concentration of 50 μg/ml" in CCl_4 toward "sexually mature males which had been segregated from females for 1 to 2 weeks after their adult emergence", apparently higher activities are recorded in ref 2b. In the latter report, 50% response to synthetic **1** at 1.7 μg/ml ("3.7×10^{-9} mol/ml") and to 3-methyl-2-heneicosanone at 22.4 μg/ml ("6.9×10^{-8} mol/ml") was indicated for males "segregated from females for 12–13 days after their adult emergence".
(8) F. L. M. Pattison and R. E. A. Dear, *Can. J. Chem.*, **41**, 2600 (1963).
(9) M. Schwarz and R. M. Waters, *Synthesis*, 567 (1972).
(10) H. Normant, *Angew. Chem., Int. Ed. Engl.*, **6**, 1046 (1967).
(11) Prepared in 68% overall yield by alkylation of 1,6-dibromohexane (3 equiv) with the NaH-generated enolate (1 equiv) of ethyl acetoacetate in benzene–dimethylformamide (5:1) at 55–60 °C, followed by hydrolysis–decarboxylation at 25–30 °C in 48% HBr–acetic acid (1:1) for 40 h; bp 83–85 °C (0.01 mm).

Selective Reduction of Sulfoxides[1]

Ralph G. Nuzzo, Henry J. Simon, and Joseph San Filippo, Jr.*

Wright and Rieman Chemistry Laboratories, Rutgers, The State University of New Jersey, New Brunswick, New Jersey 08903

Received July 30, 1976

Sulfoxides are important intermediates in a variety of synthetic transformations. The successful application of these procedures generally requires the removal of the residual sulfoxide moiety and a number of processes have been devised for achieving such transformations. Ostensibly, one of the simplest of these involves the reduction of the sulfoxide to a sulfide which is then further reduced by treatment with Raney nickel or a reducing metal system such as lithium in liquid ammonia or amine.

The mildest and therefore the most desirable procedures for effecting the reduction of sulfoxides to sulfides involve either their prolonged treatment with triphenylphosphine in refluxing carbon tetrachloride,[2] reaction with titanium(III),[3] or their conversion to an alkoxysulfonium salt, which in turn is reduced by reaction with borohydride[4a] or (more selectively) cyanohydride borate.[4b] Each of these procedures possess disadvantages: the former two have limited selectivity, the latter are inconvenient at best.

We wish to report that the reaction of sulfoxides with various complex ions of molybdenum(II), -(III), and tungsten(III) provides a procedure for the reduction of a sulfoxide to the corresponding sulfide that is facile, efficient, and highly selective. This procedure seems applicable to the reduction of a broad spectrum of sulfoxides under mild conditions. Although water is generally a good solvent, the use of methanol as a solvent or cosolvent resulted in improved yields in those instances where (1) the sulfoxide has only a very limited solubility in water or (2) the complex ion is relatively unstable in neutral water as, for example, are salts of octachlorodimolybdenum(II) ion, $Mo_2Cl_8^{4-}$.

Numerous reagents are capable of effecting deoxygenations of various organic substrates. Most of these are not specific. Thus, for example, phosphites and phosphines, two of the most commonly employed deoxygenating agents, will reduce a variety of functional groups including nitrile oxides to nitriles,[6] epoxides to olefins,[7] and certain alkyl halides to the corresponding hydrocarbon. In addition, these reagents also react in less well-defined ways with *N*-oxides, nitro, nitroso, and related functional groups.[8] In contrast, the reduction of sulfoxides to sulfides by the reagents reported here appears to be highly specific. Thus, organic halides (*n*-octyl iodide and benzotrichloride), sulfones, phosphine oxides, epoxides (cyclohexene oxide), ketones, (including α,β-unsaturated ketones), esters, nitriles, and nitro compounds (nitrobenzene) can all be recovered unchanged under the reduction conditions outlined in Table I. It is clear from the results presented that these reagents afford a mild, efficient, and highly selective procedure for the reduction of sulfoxides.

Sharpless and co-workers[9] have studied the deoxygenation of epoxides, aldehydes, and ketones using lower valent tungsten complexes of an undefined nature. The mechanism(s) of these conversions as well as the reduction of sulfoxides by $Mo_2Cl_8^{4-}$, $Mo_2Cl_8H^{3-}$, $MoCl_6^{3-}$, and $W_2Cl_9^{3-}$ is still unclear. However, it is reasonable to assume that the successful utilization of the lower valent complexes of titanium, molybdenum, and tungsten in effecting the deoxygenation of certain organic molecules is in substantial part a consequence of the unusually high thermodynamic stability of titanium–, molybdenum–, and tungsten–oxo bonds.[10,11]

Experimental Section[14]

Tripotassium ennachloroditungstate(III),[5] $K_3W_2Cl_9$, pentaammonium nonachlorodimolybdenum(II) monohydrate,[12] $(NH_4)_4Mo_2Cl_8 \cdot NH_4Cl \cdot H_2O$, and tricesium 1,1,1,2,2,2-hexachloro-μ-(hydrido)bis-μ-(chloro)dimolybdenum(III),[13] $Cs_3Mo_2Cl_8H$, were prepared according to literature procedures. Tripotassium hexachloromolybdenum(III), K_3MoCl_6, was obtained from Climax Molybdenum.

Procedures for Reduction. Similar procedures were used to carry out the reductions for all the sulfoxides examined. Representative procedures for each sulfoxide follow.

Reduction of Diphenyl Sulfoxide Using $K_3W_2Cl_9$. Tripotassium ennachloroditungstate(III) (1.40 g, 1.74 mmol) was placed in a 50-ml flask equipped with a condenser and containing a Teflon-coated stirrer bar, 10 ml of water, and 1 ml of methanol. Diphenyl sulfoxide (0.250 g, 1.26 mmol) and a known amount of hexadecane (GLC internal standard) were added and the flask heated at 60 °C with stirring for 3 h under a static head of nitrogen. Additional water (15 ml) was added and the resulting mixture extracted with three 10-ml portions of chloroform. The combined organic extracts were dried ($MgSO_4$), gravity filtered, and analyzed by GLC.

Reduction of Di-*n*-butyl Sulfoxide with $(NH_4)_4Mo_2Cl_8 \cdot NH_4Cl \cdot H_2O$. In a typical experiment, 1.12 g (1.80 mmol) of pentaammonium ennachlorodimolybdenum(II) monohydrate was placed in a 50-ml flask containing a Teflon-coated stirrer bar. Methanol (10 ml) was added along with 0.260 g (1.61 mmol) of di-*n*-butyl sulfoxide. The flask was equipped with a condenser stoppered with a rubber septum and flushed with nitrogen. The resulting mixture was stirred under a static head of nitrogen for 2 h at 50 °C. Upon cooling to room temperature, 0.180 g of tridecane (GLC internal standard) was added. Water (25 ml) was added and the resulting mixture extracted with three 5-ml portions of chloroform. The combined extracts were dried ($MgSO_4$) and analyzed by GLC.

Reduction of Benzyl Methyl Sulfoxide Using $Cs_3Mo_2Cl_8H$. Into a 50-ml flask equipped with condenser capped with a rubber septum and containing a Teflon-coated stirrer bar was placed benzyl methyl sulfoxide (0.250 g, 1.61 mmol) and $Cs_3Mo_2Cl_8H$ (1.58 g, 1.80 mmol). The contents of the flask were flushed with nitrogen before adding

Table I. Reaction of Sulfoxides and Related Substrates with $W_2Cl_9^{3-}$, $Mo_2Cl_8^{4-}$, $Mo_2Cl_8H^{3-}$, and $MoCl_6^{3-}$

Registry no.	Substrate	Sulfide, %[a] $K_3W_2Cl_9$[b]	$(NH_4)_4Mo_2Cl_8 \cdot NH_4Cl \cdot H_2O$[c]	$Cs_3Mo_2Cl_8H$[d]	K_3MoCl_6[e]
68-68-5	Dimethyl sulfoxide	100_3[f]	75_2[f]	74_2[f]	47_2[f]
2168-93-6	Di-*n*-butyl sulfoxide	95_3	90_{18}	91_{18}	76_{18}
1193-82-4	Phenyl methyl sulfoxide	92_3	94_2	95_2	90_{72}
824-86-2	Benzyl methyl sulfoxide	92_3	72_2	92_{18}	70_{72}
19093-37-9	Allyl phenyl sulfoxide	88_3	59_{18} (63_{72})	54_{18} (60_{72})	54_{18}
4170-69-8	Isopropyl phenyl sulfoxide	97_3	94_{18}	91_{18}	72_{18}
945-51-7	Diphenyl sulfoxide	99_3	97_{22}	99_{72}	79_{72}
33840-74-3	α-Phenylsulfoxyl acetone	95_3	62_{48}	65_{48} (65_{72})	66_{72}
4381-25-3	Phenyl methyl sulfoximine	14_3	56_2	7_2	2_{72}
67-71-0	Dimethyl sulfone	$<1_6$	$<1_{72}$	$<1_{72}$	$<1_{72}$

[a] Subscript denotes reaction time (h). Unless otherwise indicated yields were determined by quantitative vapor phase chromatography and are based on sulfoxide. [b] See ref 5; reaction solvent H_2O–CH_3OH (11:1). [c] See ref 11; reaction solvent CH_3OH. [d] See ref 12; reaction solvent H_2O–CH_3OH (5:1). [e] Obtained from Climax Molybdenum; reaction solvent H_2O–CH_3OH (5:1). [f] Dimethyl sulfide was determined gravimetrically as its mercuric chloride complex: W. F. Faragher, J. C. Morell, and S. Comay, *J. Am. Chem. Soc.*, **51**, 2728 (1929).

10 ml of methanol. The resulting mixture was heated at 50 °C for 18 h, then allowed to cool before adding a known amount of tridecane (GLC internal standard). Water (25 ml) was added, the resulting mixture extracted with three 5-ml portions of chloroform, and the combined extracts dried ($MgSO_4$) and analyzed by GLC.

Reduction of Dimethyl Sulfoxide with K_3MoCl_6. Into a three-necked, 100-ml flask was placed a Teflon-coated magnetic stirrer bar, 1.29 g (3.22 mmol) of tripotassium hexamolybdate, and 30 ml of a 5:1 water–methanol mixture. A condenser was attached. The condenser and the remaining side arms were stoppered with rubber septums and the system purged briefly with nitrogen before injecting dimethyl sulfoxide (0.155 g, 2.00 mmol) by syringe. With vigorous stirring the resulting mixture was heated at 60 °C. Throughout the course of the reaction a slow stream of nitrogen was passed over the reaction mixture and allowed to ebullate through a 0.125-in. Teflon tube that terminated in 75 ml of saturated aqueous solution of mercuric chloride. When no further precipitation was observed (~2 h), the resulting solid was collected by suction filtration and dried in vacuo over P_2O_5 to a constant weight. The yield of dimethyl sulfide was determined gravimetrically as $[(CH_3)_2S]_2(HgCl_2)_3$ (see Table I, footnote *f*).

Registry No.—$W_2Cl_9^{3-}$, 23403-17-0; $(NH_4)_4Mo_2Cl_8 \cdot NH_4Cl$, 40902-25-8; $Cs_3Mo_2Cl_8H$, 24436-25-7; K_3MoCl_6, 13600-82-3.

References and Notes

(1) Supported by the National Institutes of Health (AM-18713-01) and the donors of the Petroleum Research Fund, administered by the American Chemical Society.
(2) J. P. A. Castrillón and H. H. Szmant, *J. Org. Chem.*, **30**, 1338 (1965).
(3) C. R. Johnson and W. G. Phillips, *J. Org. Chem.*, **32**, 1926, 3233 (1967).
(4) (a) H. D. Durst, J. W. Zubrick, and G. R. Kieczykowski, *Tetrahedron Lett.*, 1777 (1974); (b) T.-L. Ho and C. M. Wong, *Synth. Commun.*, **3**, 37 (1973).
(5) R. Sailliant, J. L. Hayden, and R. A. D. Wentworth, *Inorg. Chem.*, **6**, 1497 (1967).
(6) C. Grundmann and H.-D. Frommeld, *J. Org. Chem.*, **30**, 2077 (1965).
(7) M. J. Boskin and D. B. Denney, *Chem. Ind. (London)*, 330 (1959).
(8) I. M. Downie and J. B. Lee, *Tetrahedron Lett.*, 4951 (1960); H. Hoffmann and H. J. Diehr, *Angew. Chem., Int. Ed. Engl.*, **3**, 145 (1964).
(9) K. B. Sharpless, M. A. Umbreit, M. T. Nieh, and T. C. Flood, *J. Am. Chem. Soc.*, **94**, 6538 (1972).
(10) W. E. Dasent, "Nonexistent Compounds", Marcel Dekker, New York, N.Y., 1965, p 135.
(11) oxygen-abstraction reactions are well known in the chemistry of the higher valent early transition metals: R. A. Walton, *Prog. Inorg. Chem.*, **16**, 1 (1972).
(12) J. V. Brencic and F. A. Cotton, *Inorg. Chem.*, **8**, 7, 2698 (1969); **9**, 346 (1970).
(13) M. J. Bennett, J. V. Brencic, and F. A. Cotton, *Inorg. Chem.*, **8**, 1060 (1969). This compound, previously formulated as a salt of the complex ion $Mo_2X_8^{3-}$, has been reformulated as a salt of the complex dinuclear ion 1,1,1,2,2,2-hexahalo-μ-(hydrido)di-μ-(halo)dimolybdenum(III), $Mo_2X_8H^{3-}$: F. A. Cotton and B. J. Kalbacher, *Inorg. Chem.*, **15**, 522 (1976).
(14) Infrared spectra were determined within sodium chloride cells on a Perkin-Elmer Model 137 spectrophotometer. NMR spectra were determined with a Varian T-60 NMR spectrometer. Mass spectra were determined on a Hitachi Perkin-Elmer RMU-7E mass spectrometer. Analytical GLC analyses were performed on a Hewlett-Packard Model 5750 flame ionization instrument. Absolute product yields were calculated from peak areas using internal standard techniques with response factors obtained from authentic samples. All solvents were deoxygenated by purging with nitrogen for 20 min prior to use. GLC analyses were determined on a 2 ft × 0.25 in. column of 7.5% SE-30 on Chromosorb G. Unless otherwise indicated starting sulfoxides and authentic product samples were obtained from commercial sources.

Atomic Oxygen. 7. Reactions of Alkynes with Oxygen (^3P) Atoms[1]

James J. Havel* and Kam H. Chan

Department of Chemistry, Rice University, Houston, Texas 77001

Received August 6, 1976

The reactions of oxygen atoms with alkynes can produce a wide variety of intermediates, including oxirenes, 1,3-biradicals, ketocarbenes, and excited ketenes. The existence of these intermediates is not experimentally reflected in previous studies[2] of the reactions of acetylene and propyne, which are dominated by the fragmentation of initially formed excited reaction products. On the other hand, the reaction of 2-butyne with $O(^3P)$ produces significant amounts of an unfragmented product, 3-buten-2-one, in a pressure dependent process.[3] This pattern has its parallel in the reactions of olefins, in which ethylene and propene show large amounts of fragmentation, while the butenes yield mainly C_4H_8O products.[1,4]

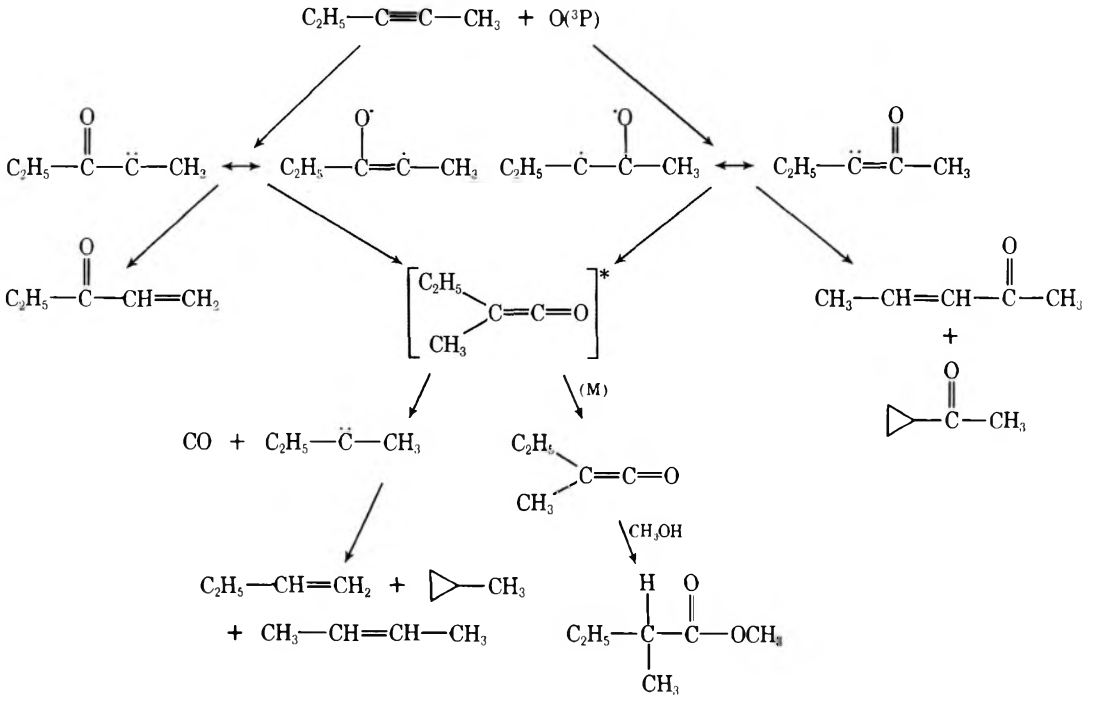
To shed further light on the reactions of $O(^3P)$ with alkynes, we have studied the gas-phase reactions of some C_4, C_5, and C_6 acetylenes. The products of these reactions are summarized in Table I. The relatively low material balance of these reactions and the quenched reactions described below is partially due to the competing reaction of atomic oxygen with mercury.

A major portion of the isolated reaction product consisted of unfragmented carbonyl compounds. The composition of these products is reminiscent of the products obtained from the reactions of peracids with alkynes[5] and also from the decomposition of diazo ketones.[3,6,7] The fragmented products, carbon monoxide and olefins and cyclopropanes, are probably formed by the decomposition of excited ketenes to carbenes. A scheme which summarizes these transformations is shown for the 2-pentyne reaction.

Table I. Product Yields from Reactions of O(^{3}P) with Alkynes[a]

Registry no.	Reactant	Products	Yield, %[b]
5003-17-3	2-Butyne	3-Buten-2-one	18
		Carbon monoxide	27
		Propene	18
627-19-0	1-Pentyne	*trans*-2-Pentenal	19
		trans-2-Methylcyclopropanecarboxaldehyde	2.8
		cis-2-Methylcyclopropanecarboxaldehyde	1.8
		Carbon monoxide	22
		1-Butene	15
		Methylcyclopropane	0.9
627-21-4	2-Pentyne	1-Penten-3-one	17
		trans-3-Penten-2-one	9.6
		Cyclopropyl methyl ketone	1.4
		Carbon monoxide	18
		1-Butene	4.0
		trans-2-Butene	6.0
		cis-2-Butene	3.3
		Methylcyclopropane	≤0.4
917-92-0	3,3-Dimethyl-1-butyne	2,3-Dimethyl-2-butenal	18
		2,2-Dimethylcyclopropanecarboxaldehyde	3.7
		2,2-Dimethylcyclobutanone	1.9
		Carbon monoxide	15
		1,1-Dimethylcyclopropane	7.4
		2-Methyl-2-butene	5.1
928-49-4	3-Hexyne	4-Hexen-3-one	29
		Cyclopropyl ethyl ketone	5.9
		Carbon monoxide	16
		trans-2-Pentene	7.2
		cis-2-Pentene	4.8
		Ethylcyclopropane	≤0.4

[a] Reaction conditions: temperature 25 ± 3 °C; pressure 0.8–0.9 atm; consumption of alkyne <20%; reproducibility among reactions ±13% of the stated yield. [b] Product yields are based on the measured amounts of nitrogen produced by the mercury photosensitized decomposition of nitrous oxide.



The existence of fragmentation products attributable to excited ketenes brought up the possibility of trapping these ketenes as their methanol adducts, methyl esters.[8] The reaction of O(^{3}P) with 50:50 mixtures of methanol and alkyne did indeed produce significant quantities of the methyl esters derived from the corresponding ketenes. The yields of methyl esters from the various alkynes follow: 2-butyne, 10%; 1-pentyne, 15%; 2-pentyne, 16%; 3,3-dimethyl-1-butyne, 22%; and 3-hexyne, 20%. Interestingly, the formation of these methyl esters was not accompanied by decreases in the yields of either the fragmentation products or the carbonyl products. Furthermore, when methanol was added to the alkyne–atomic oxygen product mixture (after photolysis but before workup and distillation), the isolated yield of methyl ester decreased by no more than 8% of its original value. This observation means that the fragmentation products are predominantly

formed by decomposition of an excited adduct in the $O(^3P)$ reaction pathway, rather than by the formation and subsequent photolysis of an isolable ketene. While spin conservation dictates that the initial adduct be a triplet, intersystem crossing to the singlet ketocarbene may precede product formation.

The reaction of atomic oxygen with a 50:50 mixture of 2-pentyne and methanol produced no detectable amounts of methyl 2-ethylbutyrate or methyl 2-methylpropionate and only traces of C_3 and C_5 hydrocarbons. This result indicates that the ketene-forming rearrangement of the $O(^3P)$–alkyne adduct is intramolecular, in that it proceeds without the migrating group becoming detached from the adduct. This pattern is in contrast to that of $O(^3P)$ plus olefin reactions, in which migrating alkyl radicals become detached from the molecule during rearrangement.[4] The Wolff rearrangement of α-diazo ketones is also intramolecular.[10]

Experimental Section

Reaction Technique. Procedures for the reaction of atomic oxygen, generated in situ by the mercury photosensitized decomposition of nitrous oxide, have been described previously.[11] The alkynes were obtained commercially and distilled before use. Relative rate constants of the alkynes vs. cyclopentene were determined by the method of Cvetanovic and converted to the usual standard, 2-methylpropene, using the figure $k_{cyclopentene}/k_{2\text{-methylpropene}} = 1.19$.[4]

Product Analysis. The VPC substrates most often used were noncondensable gases, 5A molecular sieves; hydrocarbon products, DC710; and carbonyl and ester products, dinonyl phthalate. Authentic samples of 3-buten-2-one, 1-penten-3-one, *trans*-3-penten-2-one, cyclopropyl methyl ketone, methyl 2-methylpropionate, and the hydrocarbon products were obtained commercially for comparison of spectra and VPC retention times. Cyclopropyl ethyl ketone and 4-hexen-3-one were prepared by reaction of diethylcadmium with the appropriate acid chloride.[12] Spectra of the other carbonyl and ester products were routinely predictable or available from the literature.[13]

trans-2-Methylcyclopropanecarboxaldehyde was prepared by reaction of 2-butenal with diiodomethane and zinc–silver couple.[14] The published NMR spectrum of this compound contains uncorrected errata. We found the spectrum (in CCl_4) to be δ 0.9–1.4 (m, 6 H), 1.9 (m, 1 H), and 9.08 (d, 1 H).

Acknowledgment. We gratefully acknowledge the support of this research by The Robert A. Welch Foundation.

Registry No.—Atomic oxygen, 17778-80-2; *trans*-2-methylcyclopropanecarboxaldehyde, 50991-21-4.

References and Notes

(1) Part 6: J. J. Havel and C. J. Hunt, *J. Phys. Chem.*, **80**, 779 (1976).
(2) C. A. Arrington, W. Brennen, G. P. Glass, and J. V. Michael, *J. Chem. Phys.*, **43**, 525 (1965); J. M. Brown and B. A. Thrush, *Trans. Faraday Soc.*, **63**, 630 (1967); J. R. Kanofsky, D. Lucas, F. Pruss, and D. Gutman, *J. Phys. Chem.*, **78**, 311 (1974); P. Herbrechtsmeier and H. G. Wagner, *Z. Phys. Chem. Neue Folge*, **93**, 143 (1974).
(3) J. Fenwick, G. Frater, K. Ogi, and O. P. Strausz, *J. Am. Chem. Soc.*, **95**, 124 (1973).
(4) R. J. Cvetanovic, *Adv. Photochem.*, **1**, 115 (1963).
(5) J. Ciabattoni, R. A. Campbell, C. A. Renner, and P. W. Concannon, *J. Am. Chem. Soc.*, **92**, 3826 (1970); V. Franzen, *Chem. Ber.*, **87**, 1219, 1478 (1954); R. N. McDonald and P. A. Schwab, *J. Am. Chem. Soc.*, **86**, 4866 (1964).
(6) V. Franzen, *Justus Liebigs Ann. Chem.*, **602**, 202 (1957).
(7) Oxirenes have been proposed to be intermediates in these reactions. The present study presents no evidence for or against the intermediacy of oxirenes.
(8) The reaction rates of the acetylenes at 25 ± 2 °C (relative to 2-methylpropene as 1.00) were 2-butyne, 0.55; 1-pentyne, 0.74; 2-pentyne, 0.71; and 3,3-dimethyl-1-butyne, 0.99. Atomic oxygen would react with these alkynes at least 100 times faster than with methanol ($k_{ethanol}/k_{2\text{-methylpropene}} = 0.0072$).[9]
(9) A. Kato and R. J. Cvetanovic, *Can. J. Chem.*, **45**, 1845 (1967).
(10) W. Kirmse, Ed., "Carbene Chemistry", 2d ed, Academic Press, New York, N.Y., 1971, p 475.
(11) J. J. Havel, *J. Am. Chem. Soc.*, **96**, 530 (1974).
(12) P. W. Hickmott, B. J. Hopkins, and C. T. Yoxall, *J. Chem. Soc. B*, 205 (1971).
(13) J. M. Conia and J. Salaun, *Bull. Soc. Chim. Fr.*, 1957 (1964); T. Strzalko and J. Seyden-Penne, *C. R. Acad. Sci., Ser. C*, **269**, 604 (1969).
(14) J. M. Denis, C. Girard, and J. M. Conia, *Synthesis*, 549 (1972).

Oxidation of *p*-Toluenesulfonylhydrazide to 1,2-Di(*p*-toluenesulfonyl)hydrazine

Richard L. Jacobs

Research Laboratories, Rezolin Division, Hexcel Corporation, Chatsworth, California 91311

Received July 7, 1976

p-Toluenesulfonylhydrazide (**1**) and catalytic amounts of cobalt salts in solution react with aqueous hydrogen peroxide to give 1,2-di(*p*-toluenesulfonyl)hydrazine (**4**) (or its tautomer **5**) as the major product. The same reactants in the presence of stoichiometric amounts of cobalt salts produce the more complete oxidation products of cobalt sulfonate and cobalt sulfinate salts. A reaction (Scheme I) patterned after

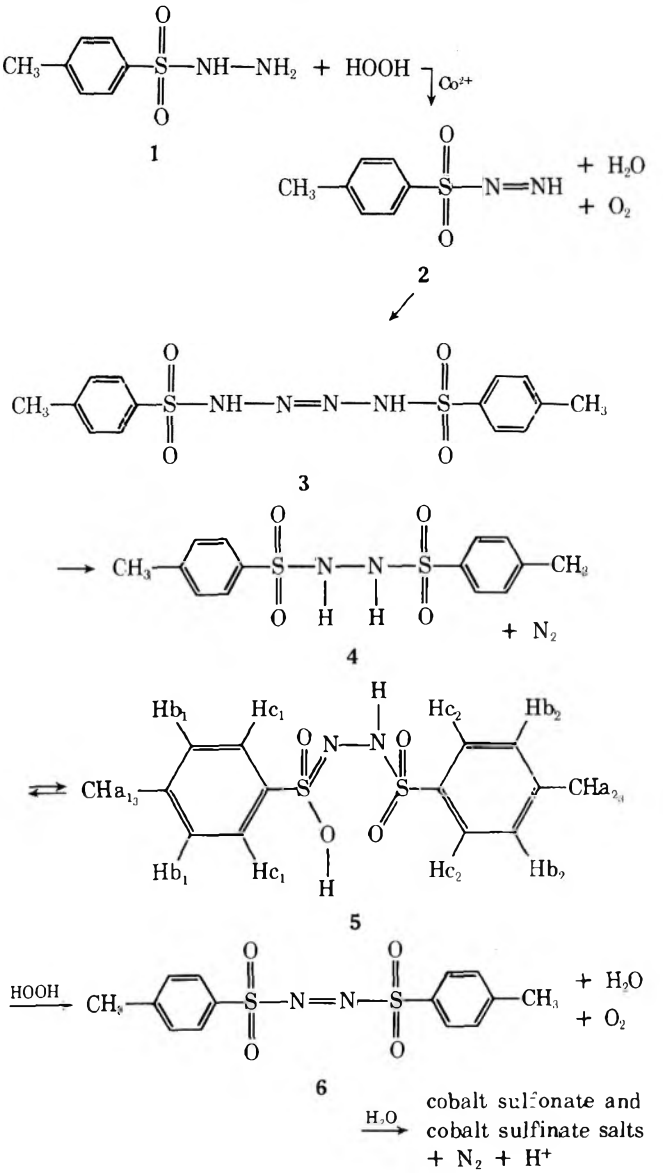
Scheme I

$$HOOH + Co^{2+} \longrightarrow HO\cdot + \bar{O}H + Co^{3+}$$
$$HOOH + Co^{3+} \longrightarrow HOO\cdot + H^+ + Co^{2+}$$

the Haber–Weiss decomposition scheme is expected to produce the free radicals which subsequently oxidize the sulfonhydrazide.[2-4]

The isolation of **4** or **5** as the major product strongly suggests that *p*-toluenesulfonylhydrazide (**1**) undergoes reactions (Scheme II) similar to those of primary alkyl and aryl hydra-

Scheme II



zines. It is expected that *p*-toluenesulfonylhydrazide (**1**) decomposes by oxidation to the corresponding sulfondiazene[1] **2** which dimerizes to form the corresponding sulfontetrazene[1] **3**. The formation of the sulfondiazene is consistent with the findings of McBride and Kruse, who showed that 1,1-dialkylhydrazines are oxidized by halogens to form the corresponding diazenes.[5] McBride and Bens showed that tetrazenes are formed by the dimerization of the dialkyldiazene and its conjugate acid in aqueous media.[6] There is reason to expect the sulfontetrazene to disproportionate in the same manner as the corresponding alkyl and aryl tetrazenes, which explains the formation of **4** or **5** along with the liberation of nitrogen. Horner and Fernekess found that semicarbazide reacts similarly in aqueous media to give the corresponding 2-tetrazene which subsequently produces the disubstituted hydrazine along with nitrogen.[7] Overberger and Marks found analogous oxidation products of disubstituted primary hydrazines from $KMnO_4$ oxidation in acetone.[8] Similar reactions were reported by Schlenk and Bergemann.[9]

The disproportionation of the sulfontetrazene **3** is expected to form sulfonamidyl biradical species in producing **4** or **5**. The formation of biradical species from the corresponding tetraphenyltetrazene in concentrated sulfuric acid was suggested by Hammond et al.[10] Tolles et al. produced cation radicals upon reacting tetramethyl-2-tetrazene with tetranitromethane, and Cowley and Waters obtained dimethylamino radicals by pyrolysis of the same species.[11,12] Michejda and Campbell suggested that tetramethyl-2-tetrazene coordinates with zinc chloride in anhydrous tetrahydrofuran to give the same biradical species.[13] The presence of cobalt ions in the reaction media suggests similar participation in the formation of biradical species, and the formation of a charge transfer complex is not ruled out.

The oxidation of *p*-toluenesulfonylhydrazide (**1**) continues beyond intermediate **4** or **5** under more energetic conditions. Oxidation to the corresponding azo compound **6** and subsequent hydrolysis can explain the apparent formation of a mixture of sulfonate and sulfinate salts in equimolar amounts.

Structure **4** or **5** (mol wt 340) closely explains the value obtained for the equivalent weight (341) based on the titration of one active proton per molecule. Either structure **4** or **5** explains the strong acidity.

The NMR spectrum of **4** or **5** in acetone-d_6 shows only benzylic methyl and aromatic protons similar to the spectra of *p*-toluenesulfonamide and acetone-*p*-toluenesulfonhydrazone. No N–H absorption is found at 6.4 ppm and is probably lost in the background. However, an infrared spectrum of this sample clearly shows N–H absorption at 1360 cm^{-1}. Normal sulfonamide S=O stretching absorption is observed at 1170 and 1360 cm^{-1}. Together, the data support **4**. However, broad infrared absorption at 2600–3100 cm^{-1} suggests possible hydrogen bonding or proton exchange with one of the sulfonyl groups such as in the tautomeric form **5**. The NMR spectrum of the aromatic protons shows splitting of the downfield doublet. A possible assignment consistent with **5** is given in which b_1 and b_2 protons of **5** are nearly coincident while c_1 and c_2 protons are slightly nonequivalent owing to the different sulfur atom bonding. This suggests that **5** is the predominant species.

The strong 2.4-ppm benzylic methyl peak is just slightly downfield relative to *p*-toluenesulfonamide (approximately 2.44 vs. 2.42 ppm). The addition of D_2O to **4** or **5** in acetone-d_6 produces two benzylic peaks, one overlapping *p*-toluenesulfonamide. Therefore, the addition of D_2O appears to be hydrolyzing **5** to a new species.

The cobalt sulfonate–cobalt sulfinate product mixture is nearly insoluble in acetone-d_6. The NMR spectrum is not too informative; however, the infrared spectrum of the solid does show that the sample is a mixture of the sulfonate and sulfinate salts, and water of crystallization is contained. The 1000–1300-cm^{-1} region is very typical of alkylbenzenesulfonates. The absorption at 900–1000 cm^{-1} is very typical of sulfinate salts. Water peaks are at 1640 and 3000–3600 cm^{-1}, and the Karl Fischer test indicates that 1 mol of water of crystallization is contained per mole of cobalt salt. The elemental analysis closely fits the calculated analysis for an equimolar product mixture of cobalt sulfonate and cobalt sulfinate salts.

Experimental Section

p-Toluenesulfonylhydrazide (**1**) was obtained from Eastman Organic and twice recrystallized (mp 110 °C) from 95% ethanol. Nuodex cobalt octoate (in solution) was obtained from Tenneco Chemical Corp., analyzed for Co (12.0%), and used directly. Baker Analyzed Reagent 30% hydrogen peroxide (aqueous) was analyzed for active hydrogen peroxide (33.57%) using an iodometric method[14] and used directly. All other solutions were of reagent quality. Elemental analyses were made by Truesdail Labs, Los Angeles, Calif., and the NMR and IR spectra were obtained by Chevron Research Corp., Richmond, Calif.

Oxidation of *p*-Toluenesulfonylhydrazide to 1,2-Di(*p*-toluenesulfonyl)hydrazine. A solution of 22.5 g (0.12 mol) of *p*-toluenesulfonylhydrazide and 1.2 g (0.0024 mol) of cobalt octoate (solution) in 250 ml of absolute methanol was adjusted to 30 °C with stirring. Hydrogen peroxide (30%) (12.2 g, 0.12 mol) was added slowly with continuous stirring. The mixture exothermed to 40 °C with bubbling, and a rose-colored solution was formed which remained clear. A gas slowly evolved until after 4 h when a white precipitate formed. Mixing was continued for 16 h. The solution was chilled to −10° and the precipitate collected by suction filtration through fine sintered glass. This yielded 9.5 g (93% based upon the limited availability of hydrogen peroxide). The precipitate was twice recrystallized in 100 ml of a mixture of 1 part concentrated HCl to 15 parts 95% ethanol and finally washed in 30 ml of cold 95% ethanol and dried at 110 °C. This yielded 5.0 g (53%) of fine, white needles: mp 182–183 °C; equiv wt 341.3 ± 3.2 (determined by titration with aqueous 0.01 N NaOH in acetone to the phenolphthalein end point); H_2O 0.01% (by Karl Fischer); IR (neat) 1170, 1360, 2600–3100 (broad), 3260 cm^{-1}; NMR (acetone-d_6) δ 2.44 (s, 3), 7.35 (d, 2, J = 8 Hz), 7.72 (d, 2, J = 8 Hz).

Anal. Calcd for $C_{14}H_{18}N_2S_2O_5$ (same as $C_{14}H_{16}N_2S_2O_4 \cdot H_2O$): C, 46.92; H, 5.05; N, 7.82; S, 17.89; O, 22.32. Found: C, 46.96; H, 5.20; N, 7.88; S, 18.82; O, 21.14; Co, <50 ppm. Water of crystallization was present in the sample prepared for elemental analysis.

Oxidation of *p*-Toluenesulfonylhydrazide to a Product Mixture of Cobalt Sulfonate and Cobalt Sulfinate Salts. A solution of 22.5 g (0.12 mol) of *p*-toluenesulfonylhydrazide (**1**) and 14.7 g (003 mol) of cobalt octoate (solution) in 250 ml of butyl acetate was adjusted to 40 °C with stirring. Hydrogen peroxide (30%) (12.2 g, 0.12 mol) was added slowly with stirring. The reaction exothermed to 64 °C with vigorous bubbling, and a pink, colloidal suspension was immediately formed. Mixing was continued for 1 h. The solids were collected by centrifugation, washed three times in 30-ml portions of cold butyl acetate, and dried at 110 °C. This yielded 5.5 g (66% based on available cobalt) of a pink powder: mp 220 °C; IR (neat) 810, 930, 950, 1010, 1040, 1180, 1640, 3000–3600 cm^{-1} (broad).

Anal. Calcd for $CoC_{14}H_{16}S_2O_6$ (same as $Co(C_7H_7SO_3)_2 \cdot Co(C_7H_7SO_2)_2 \cdot 2H_2O$): Co, 14.61; C, 41.70; H, 4.00; S, 15.89; O, 23.80. Found: Co (by ignition test), 14.20; C, 42.08; H, 3.94; N, 0.44; S, 15.93; O, 23.41.

Acknowledgment. I am grateful to Stepan Chemical Co. for providing funds and to Messrs. Donald A. Backley and Walter Beck for their support of this research. I wish to thank Mr. R. M. Bly, Chevron Research, for aid in interpretation of the spectra.

Registry No.—**1**, 1576-35-8; **3**, 60803-17-0; **4**, 14062-05-6; **5**, 60803-18-1; cobalt *p*-toluenesulfonate, 20664-98-6; cobalt *p*-toluenesulfinate, 34045-51-7; cobalt octoate, 1588-79-0.

References and Notes

(1) The nomenclature "sulfondiazene" is tentatively proposed for $ArSO_2N{=}NH$ compounds based on the formal relationship of the sulfonyl group to the unsaturated hydro nitrogens [W. R. McBride and E. M. Bens, *J. Am. Chem.*

Soc., **81**, 5546 (1959)]. The nomenclature "sulfontetrazene" appears to be consistent with the formal relationship of sulfonyl groups to tetrazenes.
(2) F. Haber and P. Weiss, *Proc. R. Soc. London, Ser. A*, **147**, 223 (1939).
(3) N. Uri, *Chem. Rev.*, **50**, 375 (1952).
(4) A. V. Tobolsky and R. B. Mesrobian, "Organic Peroxides", Interscience, New York, N.Y., 1954, p 103.
(5) W. R. McBride and H. W. Kruse, *J. Am. Chem. Soc.*, **79**, 572 (1957).
(6) W. R. McBride and E. M. Bens, *J. Am. Chem. Soc.*, **81**, 5546 (1959).
(7) L. Horner and H. Fernekess, *Chem. Ber.*, **94**, 712 (1961).
(8) C. G. Overberger and B. S. Marks, *J. Am. Chem. Soc.*, **77**, 4097 (1955).
(9) W. Schlenk and E. Bergemann, *Justus Liebigs Ann. Chem.*, **463**, 281 (1927).
(10) G. S. Hammond, B. Seidel, and R. E. Pincock, *J. Org. Chem.*, **28**, 3275 (1963).
(11) W. M. Tolles, D. W. Moore, and W. E. Thun, *J. Am. Chem. Soc.*, **88**, 3476 (1966).
(12) B. R. Cowley and W. A. Waters, *J. Chem. Soc.*, 1228 (1961).
(13) C. J. Michejda and D. H. Campbell, *J. Am. Chem. Soc.*, **96**, 929–930 (1974).
(14) C. D. Wagner, R. H. Smith, and E. D. Peters, *Ind. Eng. Chem., Anal. Ed.*, **19**, 976 (1947).

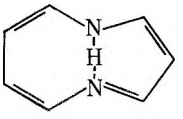
A 10-π-Electron Heterocycle: 2,3,4-Tricarbomethoxy-6,7,8,9-dibenzo-1,5-diazonine

Donald G. Farnum* and Khalid Rasheed

Department of Chemistry, Michigan State University, East Lansing, Michigan 48824

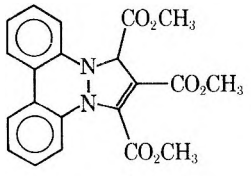
Received July 27, 1976

Several years ago we reported[1] the synthesis of some novel heterocycles as potential precursors to derivatives of the 10-π-electron 1,5-diazonine system, **1**, in which the intraannular hydrogen repulsions inhibiting coplanarity in some other potentially aromatic 10-π-electron systems might be relieved by transannular hydrogen bridging as shown.[2]

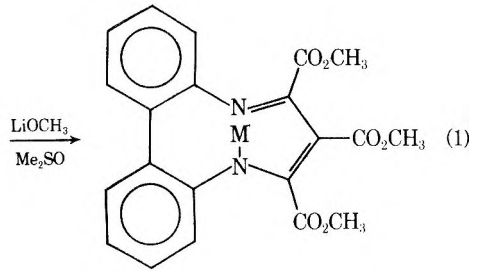


1

Although we did prepare a number of novel heterocycles, including 1,2,3-tricarbomethoxy-1*H*-benzo[*c*]pyrazolo[1,2-*a*]cinnoline (**2**), we were not able to effect the conversion of any of them to 1,5-diazonine derivatives, as in eq 1, by any conditions then tried. Others have reported both theoretical[4] and experimental[5] studies of some of the heterocycles we discussed, but 1,5-diazonine and its derivatives have not yet appeared in the literature. We now wish to report the successful conversion of **2** to 2,3,4-tricarbomethoxy-6,7,8,9-dibenzo-1,5-diazonine (**3**, M = H) and some of its derivatives.



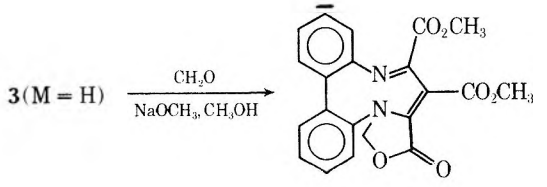
2



3

When a yellow solution of **2** in dimethyl sulfoxide (Me_2SO) is added to a suspension of 2 equiv of lithium methoxide in Me_2SO, the initially formed intense blue-green color slowly fades to an orange yellow. The bright yellow salt (73%, mp 227–230 °C) obtained on workup could not be purified satisfactorily by recrystallization, but analyzed moderately well for the lithium salt of **3** (**3**, M = Li)[6] containing 0.7 equiv of lithium hydroxide. The use of only 1 equiv of lithium methoxide in the reaction gave less than 50% of the product. Sodium methoxide (2 equiv) worked as well, but potassium methoxide was less effective. Acidification of an aqueous solution of the salt with acetic acid gave the more tractable pale yellow **3**, M = H (80%, mp 110–140 °C). Again, only moderately satisfactory combustion analyses could be obtained on chromatographically purified material; but the 1:1 crystalline solvate with Me_2SO (mp 145–147 °C) gave excellent analytical results. The substance also formed well-defined crystalline solvates with carbon tetrachloride and with acetone.

The structure of **3**, M = H, was established by its spectroscopic properties and some chemical transformations. Thus, the methyl ester functions revealed themselves in the IR (1740, 1710 cm^{-1}) and NMR [δ 3.61 (6 H, s), 3.53 (3 H, s)], as did the proton on nitrogen (3380 cm^{-1}, δ 6.76, washed out with D_2O). Rapid proton exchange at 30 °C between the nitrogens in **3**, M = H, resulting in NMR equivalence of the flanking ester methyls, was suggested by the separation of the lower field, six-hydrogen singlet (δ 3.61) into a broad doublet at −10 °C, whose higher field signal merged with the higher field singlet (δ 3.53) at −30 °C to give two peaks of reversed intensity at δ 3.63 (3 H, s) and 3.55 (6 H, broad singlet). The prototropic change was more clearly revealed in the ^{13}C NMR, which transformed from three peaks for the ester methyl carbons (δ 51.7, 52.7, 53.1) at 25 °C to only two peaks (51.5, 52.6) at 50 °C with an accompanying, though less easily interpretable, simplification of the olefinic–aromatic carbons (δ ~120–170). The higher temperature required for equivalence of the methyl signals in the ^{13}C NMR than in the ^1H NMR presumably reflects the larger chemical shift difference. The substance could be converted with methyl iodide and potassium carbonate to the nicely crystalline, yellow *N*-methyl (NMR δ 2.80) derivative **3**, M = CH_3 (68%, mp 203–205 °C), in which all three ester methyls were now differentiated in the NMR (δ 3.61, 3.66, 3.81). Reaction of **3**, M = H, with formaldehyde and sodium methoxide in methanol gave orange-yellow, crystalline lactone **4** (36%, mp 184–186 °C). The lactone



4

carbonyl was revealed by the IR absorption (1812 cm^{-1}), while the NMR of the two different methylene protons betrayed the conformational rigidity of the system (δ 4.68, 1 H, d, J = 6 Hz, 5.28, 1 H, d, J = 6 Hz[7]). Other spectroscopic data were consistent with structure **4**. Hydrolysis of **3**, M = H, with hot aqueous potassium hydroxide afforded an 85% yield of *o,o'*-diaminobiphenyl, thereby confirming that the N–N bond of **2** had been cleaved, and that more deep-seated transformations of the aromatic nuclei had not taken place. Samples of **3**, M = H, stored for several years in the solid state, showed no evidence of reconversion to any **2**.

The heavy substitution by fused benzene rings and carbo-

methoxy groups in **3** precludes speculation about the presence of bridging or aromaticity in its derivatives. However, the ring opening reaction is novel and may be applicable to less highly substituted derivatives.

Experimental Section

Melting points (uncorrected) were measured on a Thomas-Hoover capillary melting point apparatus. Infrared spectra were taken on a Perkin-Elmer 137 IR spectrophotometer. NMR spectra were recorded on a Varian T-60 (^{1}H NMR) or CFT-20 (^{13}C NMR) and are reported as δ values downfield from Me_4Si (δ 0.0) internal standard. Mass spectra were measured on a Hitachi Perkin-Elmer RMU-6 instrument. Combustion analyses were performed by Spang Microanalytical Laboratories.

2,3,4-Tricarbomethoxy-6,7,8,9-dibenzo-1,5-diazonine Lithium Salt (3, M = Li). To a stirred suspension of 285 mg (7.5 mmol) of CH_3OLi in 20 ml of dry Me_2SO in an atmosphere of N_2 was added a solution of 1.477 g)3.75 mmol) of the orange-yellow triester **2** [λ_{max}, (CH_3OH) 260 nm, ϵ ~6300; 295, ~1700; 382, ~2400) in ~10 ml of Me_2SO. A blue-green coloration instantly formed (λ_{max} 588 nm) which on further stirring at room temperature (~90 min) discharged to give an orange-yellow solution (λ_{max} 300 nm, sh 410 nm). The solvent was removed in vacuo (oil bath temperature 80–90 °C), and the viscous brown residue was triturated with chloroform and allowed to stand for 1–2 h. The bright yellow salt was filtered and washed with $CHCl_3$ until the filtrate was colorless. The vacuum dried salt weighed 1.1 g (73%) and had mp 227–230 °C dec. (Use of only 1 equiv of CH_3OLi yields only 50% Li salt.) Attempts to crystallize the product were not successful. NMR (Me_2SO-d_6) δ 6.35–7.30 (8 H, m), 3.47 (6 H, s), 3.22 (3 H, s), no other absorption observed from −4 to 15; IR (Nujol) 1754, 1740, 1660 cm^{-1}; UV (Me_2SO) λ_{max} 310 nm (ϵ ~12 800), 410 (~2800). An analytical sample was washed well with $CHCl_3$ and dried at 60 °C in vacuo.

Anal. Calcd for $C_{21}H_{17}N_2O_6Li$: C, 63.00; H, 4.28; N, 6.99; Li, 1.73. Calcd for $C_{21}H_{18}N_2O_7Li_2$: C, 59.46; H, 4.28; N, 6.60; Li, 3.27. Calcd for $C_{21}H_{17}N_2O_6Li$ (0.7 LiOH): C, 60.47; H, 4.28; N, 6.72; Li, 2.83. Found: C, 60.56; H, 4.25; N, 6.98; Li, 2.83.

2,3,4-Tricarbomethoxy-6,7,8,9-dibenzo-1,5-diazonine (3, M = H). Li salt **3** (M = Li) (1.0 g) was dissolved in 30 ml of H_2O and filtered. The clear yellow filtrate was acidified with 50% acetic acid to pH 7. The pale-yellow solid which separated was filtered, washed with H_2O, and dried in vacuo over $CaCl_2$ to give 0.76 g (~80%): mp 110–140 °C; NMR ($CDCl_3$) (33 °C) δ 6.5–7.5 (9 H, m), 3.61 (6 H, s), 3.53 (3 H, s); (10 °C) 3.58, 3.62 (br, 6 H), 3.54 (3 H, s); (−30 °C) 3.62 (3 H, s), 3.55 (6 H, br, s); ^{13}C NMR ($CDCl_3$) (50 °C) 51.5, 52.6, 127–166 (six broad peaks); (25 °C) 51.7, 52.7, 53.1, 124–166 (16 peaks). Addition of a few drops of D_2O to an acetone complex of the amino ester in $CDCl_3$ washed out a resonance at 6.75. NMR (Me_2SO-d_6) δ 9.2 (broad, s), 6.5–7.5 (m), 3.6 (s) 3.48 (s). Addition of D_2O washed out the absorption at 9.2. IR (Nujol) 3320 (broad), 1740, 1695, 1640 cm^{-1}. IR ($CHCl_3$) 3380 (sharp), 1740, 1710, 1650 cm^{-1}.

An analytical sample was prepared by chromatographing 600 mg of the product over 100 g of Merck Al_2O_3, eluting with $CHCl_3$–C_6H_6 (1:3), and collecting the yellow band. TLC of this material gave a single spot. The product was freed from solvent by heating to 150 °C in vacuo for 3 h to give material of mp 110–140 °C. TLC of the dried sample showed only one component.

Anal. Calcd for $C_{21}H_{18}N_2O_6$: C, 63.95; H, 4.60; N, 7.10. Found: C, 64.74, H, 4.91; N, 6.80.

Samples stored for several years showed unchanged NMR spectra.

Formation of Solvates. The amino ester forms solvates with almost all solvents tried (CCl_4, acetone, dimethyl sulfoxide). Recrystallization from CCl_4 gives a product which begins to froth at 100 °C. A weighed amount of this sample when heated to 130–140 °C in vacuo showed a loss in weight of 1418%. The IR spectrum remained unchanged.

A concentrated solution of the material in acetone gradually deposits a nicely crystalline product, mp 120 °C (frothing). An NMR ($CDCl_3$) of this sample shows the acetone singlet (δ 2.0).

Particularly stable is the Me_2SO complex. The amino ester (450 mg) was shaken well with 3.5 ml of dry Me_2SO and filtered from a small amount of insoluble material, and the clear filtrate was treated dropwise with H_2O until a cloudiness persisted. After 2 h at room temperature, the crystalline material was filtered, washed with water, and dried over $CaCl_2$ in vacuo to give 348 mg (~75% recovery), mp 145–147 °C. A sample for analysis was dried at 90–95 °C in vacuo for 2 h: NMR ($CDCl_3$) δ 6.5–7.5 (m), 3.62 (6 H, s), 3.56 (3 H, s), 2.5 (6 H, s); IR (Nujol) 3180 (w), 3270 (w), 1745, 1730, 1710, 1650 cm^{-1}. Heating a sample at 150–155 °C in vacuo for 20 min resulted in removal of only ~30% Me_2SO as indicated by NMR.

Anal. Calcd for $C_{21}H_{18}N_2O_6$·C_2H_6SO: C, 58.46; H, 5.12; N, 5.93. Found: C, 58.54; H, 5.12; N, 5.84.

***N*-Methyl-2,3,4-tricarbomethoxy-6,7,8,9-dibenzo-1,5-diazonine (3, M = CH_3).** Ester **3**, M = H (197 mg, 0.5 mmol), CH_3I (0.9 mmol), and K_2CO_3 (0.6 mmol) were stirred in 10 ml of methanol at room temperature overnight. CH_3OH was removed in vacuo, and the residue was dissolved in benzene and filtered. Pentane was added dropwise to a concentrated benzene solution until crystals begin to separate. After a few hours, the crystalline material was filtered and dried in vacuo to give 140 mg of yellow crystals (68%): mp 203–205 °C; NMR ($CDCl_3$) δ 6.75–7.60 (8 H, m), 3.81 (3 H, s), 3.66 (3 H, s), 3.61 (3 H, s), 2.8 (3 H, s); mass spectrum parent peak *m/e* 408.

Anal. Calcd for $C_{22}H_{20}N_2O_6$: C, 64.71; H, 4.94; N, 6.86. Found: C, 64.91; H, 4.87; N, 6.74.

Hydrolysis of Amino Ester 3, M = H. Amino ester **3**, M = H (245 mg, 0.62 mmol) was dissolved in 20 ml of hot 4 N KOH and refluxed in an oil bath. After 5 h the mixture was allowed to cool, whereby the oily droplets which had formed solidified. These were filtered and washed with water. The filtrate was heated to 100 °C for another 5 h, then allowed to stand at room temperature overnight. The insoluble material was again filtered. Heating the filtrate for another 8 h and allowing to cool yielded another 10 mg of product. The total yield of o,o′-diaminobiphenyl was 94 mg (85%). Recrystallization from cyclohexane gave shiny plates: mp 78–80 °C (lit. mp 80 °C); NMR ($CDCl_3$) δ 6.5–7.2 (8 H, m), 3.6 (4 H, broad m); IR ($CHCl_3$) 3497, 3401, 3030 cm^{-1}; mass spectrum parent peak *m/e* 184.

Reaction of 3, M = H, with Formaldehyde. Formation of Lactone 4. Amino ester **3**, M = H (556 mg, 1.41 mmol), CH_3ONa (15 mg, 0.3 mmol), and a solution of formaldehyde in dry methanol (6 ml, 0.1 g/ml) were stirred at room temperature overnight. The solvent was removed in vacuo and the residue extracted with 40 ml of hot benzene–cyclohexane (60:40 my volume). The filtrate was allowed to stand for 3 h, the insoluble material filtered, and the filtrate concentrated to 25 ml. The insoluble material which separated was again filtered. The filtrate was finally concentrated to 10 ml and allowed to crystallize overnight. The orange-yellow crystals were filtered to give 150 mg, mp 178–180 °C. Further concentration of filtrate yielded another 50 mg of product, mp 180–182 °C, to give a total yield of 200 mg (36%). An analytical sample, mp 184–186 °C, was obtained by recrystallization from a 60:40 mixture of benzene–cyclohexane: mass spectrum parent peak *m/e* 392; IR (Nujol) 1812, 1761, 1709, 1653 cm^{-1}; NMR ($CDCl_3$) δ 6.7–7.6 (8 H, m), 5.28 (1 H, d, J = 6 Hz), 4.68 (1 H, d, J = 6 Hz), 3.75 (3 H, s), 3.73 (3 H, s).

Anal. Calcd for $C_{21}H_{16}N_2O_6$: C, 64.28; H, 4.11; N, 7.14. Found: C, 64.42; H, 4.15; N, 7.14.

Acknowledgment. This work was supported by Grant GM 12383 from the National Institutes of Health, Division of General Medical Sciences. We thank Thomas Clausen and Bruce McGlone for assistance in determining some of the NMR spectra.

Registry No.—**2**, 7593-55-7; **3** (M = Li), 60734-18-1; **3** (M = H), 60734-19-2; **3** (M = CH_3), 60734-20-5; **4**, 60734-21-6; o,o′-diaminobiphenyl, 1454-80-4; formaldehyde, 50-00-0.

References and Notes

(1) D. G. Farnum, R. J. Alaimc, and J. M. Dunston, *J. Org. Chem.*, **32**, 1130 (1967).

(2) A completely planar **1** would require either an abnormally short N–H· · ·N distance (ca. 1.6 Å) or an abnormally open C–N=C bond angle (ca. 180°). However, distortion from coplanarity with the resulting bent N–H· · ·N bond could relieve these strains considerably without complete loss of delocalization as illustrated by the anion **i**.[3]

i

(3) W. Grimme, M. Kaufold, U. Dettmeier, and E. Vogel, *Angew. Chem.*, **78**, 643 (1966); P. Radlick and W. Rosen, *J. Am. Chem. Soc.*, **88**, 3461 (1966).

(4) V. Galasso and G. DeAlti, *Tetrahedron*, **25**, 2259 (1969).

(5) E. Carp, M. Dorneanu, and I. Zugravescu, *Rev. Roum. Chim.*, **19**, 1507 (1974).

(6) Structures of derivatives of **3** are drawn with the trans C=N as though bridged only from convenience and prejudice. We have little information on the configurations or conformations of these compounds, although it is clear that **3**, M = H, does not exist in a symmetrically hydrogen-bonded form (vide infra).

(7) The small geminal coupling constant probably reflects increased s character from the electronegative substituents and strained ring.

Thermal Decomposition of 1,2,3-Benzothiadiazole

Luisa Benati,* Pier Carlo Montevecchi, and Giuseppi Zanardi

Istituto di Chimica Organica dell'Università, 40136 Bologna, Italy

Received July 27, 1976

Several papers have described the decomposition of thiadiazoles, and several structures have been claimed for the reaction intermediate. It was proposed that the thermal decomposition[1] or photolysis[2] of 1,2,3-benzothiadiazole (**1**) gives thianthrene (**2**) by dimerization of the intermediate (**3**) obtained by cleavage of the heteroaromatic nucleus and nitrogen loss. Two structures were suggested for **3**:[2] a 1,3-dipolar form (**3a**) in resonance with a thioketocarbene (**3b**) or a 1,3-diradical structure (**3c**). Recently[3] Seybold and Heibl found that the flash thermolysis of 1,2,3-thiadiazoles may be used as a convenient method for the synthesis of thioketenes, even though thioketene **4** generated from **1** already begins to polymerize at −120 °C, and could therefore only be detected indirectly. Analogous thioketenes, derived by Wolff rearrangement of the parent thioketocarbenes, were reported by Kirmse and Horner[4] in the photolysis of 1,2,3-thiadiazoles (Scheme I).

3 displays surprisingly sluggish reactivity; it does not add to carbon–carbon double bond or to carbon–nitrogen triple bond, but only to carbon–sulfur double bond. By decomposition of **1** in carbon disulfide, 1,3-benzodithiol-2-thione and spirobis-1,3-benzodithiol were obtained.[5] Our interest in the reactivity[6,7] of 1,2,3-benzothiadiazole (**1**) has led us to study the thermal decomposition of **1** in various solvents, such as ethyl acetate, ethyl acetate/phenylacetylene, ethyl acetate/tolane, toluene, and methyl benzoate, in order to gain further information on the structure and reactivity of **3**. By decomposition of **1** in ethyl acetate at 220 °C, thianthrene (**2**), dibenzo[c,e]-o-dithiin (**5**), dibenzothiophene (**6**), and thiophenol (**7**) were obtained (Scheme II).

Decomposition carried out in toluene or methyl benzoate gave, besides products described above, a mixture of 1-, 2-, 3-, and 4-methyl- and 1-, 2-, 3-, and 4-methoxycarbonyldibenzothiophene (**8**). The relative isomer ratios are listed in Table I.

Table I. Relative Ratios of 1-, 2-, 3-, and 4-X-Dibenzothiophene (8) and Ratios of Ortho, Meta, and Para Attack of the Intermediate Species 3c (or 3a) on PhX

	% of 1-, 2-, 3-, and 4-X-dibenzothiophene (8)				% of ortho, meta, and para attack on PhX		
X	1-	2-	3-	4-	Ortho	Meta	Para
CH_3	42[a]	14[b]	20[c]	24[d]	42	38	20
$COOCH_3$	57[e]	6[f]	19[g]	18[h]	57	24	19

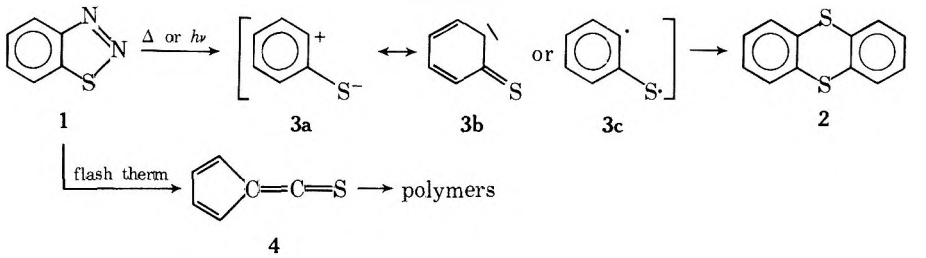
Registry numbers: [a] 31317-07-4; [b] 20928-02-3; [c] 16587-52-3; [d] 7372-88-5; [e] 40488-61-7; [f] 22099-28-1; [g] 60718-96-9; [h] 60718-97-0.

8 could arise from attack on the monosubstituted benzene ring either by the carbonium ion of **3a** and following trapping of ionic σ complex **9a** or by the carbon radical of **3c** and trapping of radical σ complex **9b** (Scheme III).

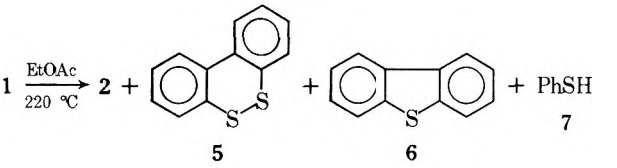
However, as show in Table I, the ortho, meta, para isomer ratios of σ complex **9** better agree with a radical mehanism rather than an ionic one, thus indicating that the intermediacy of the dipolar species **3a** is not very likely.

We can also exclude the intervention of a benzothiirene as reaction intermediate, as claimed by Cadogan and co-workers[8] to explain the formation of **2** by thermolysis of o-bromobenzenethiolate. Analogous thiirenes, in equilibrium with the parent thioketocarbenes, were also proposed by Rees[9] in the

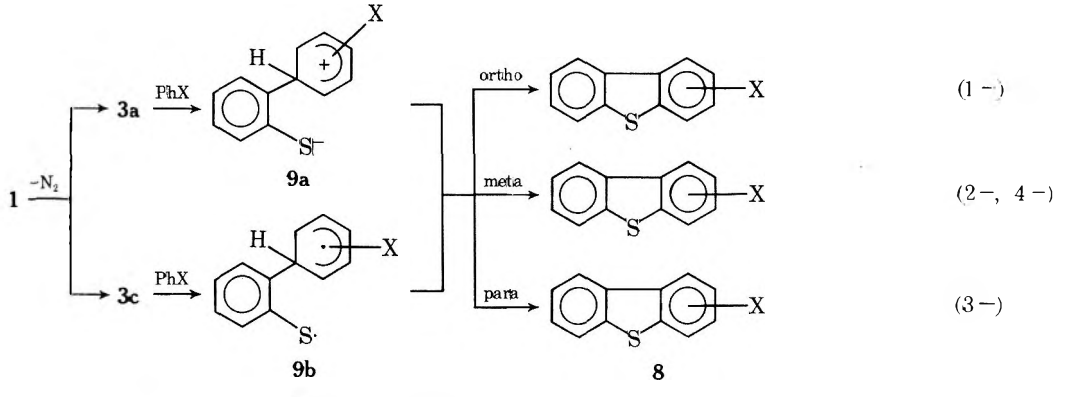
Scheme I



Scheme II



Scheme III



X = CH_3, $COOCH_3$

Scheme IV

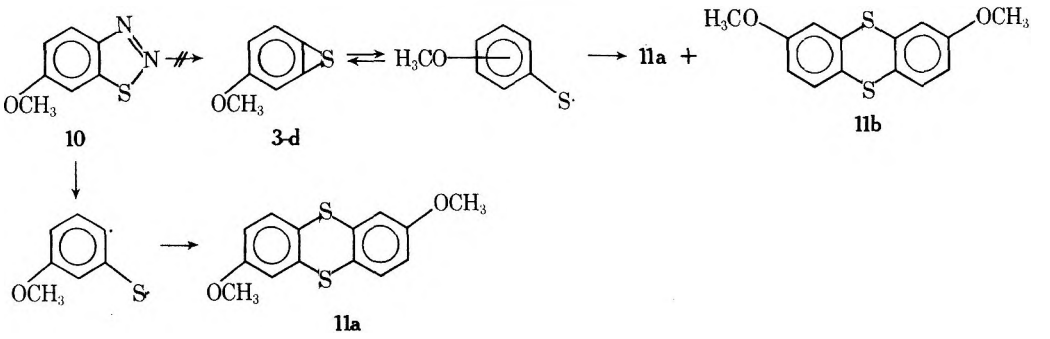


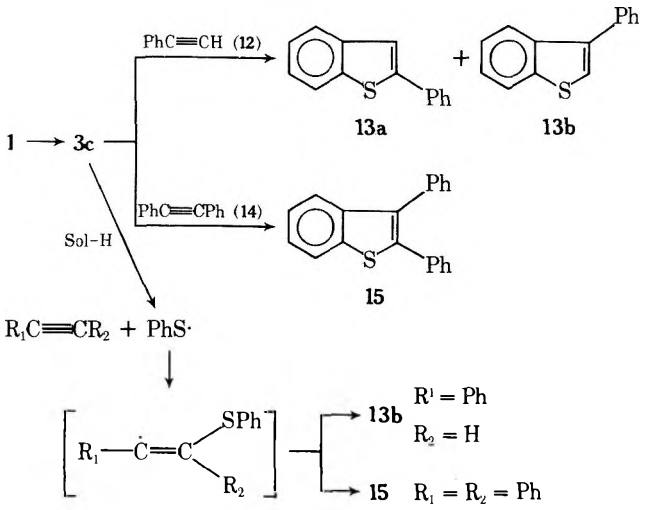
Table II. Relative Yields (%) of the Products Obtained by Decomposition of 1

Solvent	2	5	6	8	13	15
Ethyl acetate	42	46	12			
Monosubstituted benzene	33	37	10	20		
Tolane	27	30	8			17
Phenylacetylene	31	34	9		26	

reaction of 4,5-disubstituted 1,2,3-thiadiazoles with nonacarbonyldiiron. In fact, decomposition of 6-methoxy-1,2,3-benzothiadiazole (**10**) gives only 2,7-dimethoxythianthrene (**11a**) instead of a mixture of **11a** and 2,8-dimethoxythianthrene (**11b**), which would be expected from reaction of the 3-methoxybenzothiirene (**3d**) (Scheme IV).

When the decomposition of **1** was carried out in the presence of phenylacetylene (**12**), 2- and 3-phenylbenzo[*b*]thiophene (**13a** and **13b**) were obtained together with **2** and **5**; moreover, decomposition of **1** in tolane (**14**) gave 2,3-diphenylbenzo[*b*]thiophene (**15**) and a mixture of *cis*- and *trans*-1-phenylthiostilbene, which formed from addition of **7** on the triple bond.[10] **13** and **15** can be explained as cycloaddition products of **3** with **12** and **14**, though addition of phenylthio radicals, followed by intramolecular cyclization of the intermediate carbon radical, cannot be completely ruled out in the formation of **13b** and **15** (Scheme V).

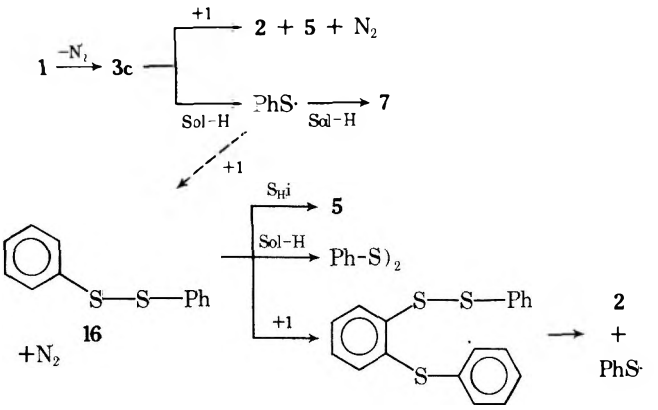
Scheme V



The relative yields of the products obtained from decomposition of **1** in the different solvents are listed in Table II.

The rather low yields of **8**, **13**, and **15** could be attributed to the high reactivity of **1**, which has been shown to have high reactivity with aryl[6] and thiyl[7] radicals toward diradicalic **3c**, rather than the low reactivity of **3c** toward monosubstituted benzenes or triple bonds. On these bases, **2** and **5** could arise from induced decomposition on **1** by the carbon and sulfur radical end of **3c**, respectively; **6** very probably arises from **5** by interaction with a radical species,[11] while **7** is the hydrogen abstraction reaction product of **3c** via thiyl radical. An alternative route to **2** and **5** could be the thioarylation of **1** by thiyl radicals through the radical intermediate **16**,[7] but we can exclude a large contribution of this reaction because if hydrogen abstraction reaction by carbon radical were faster than induced decomposition on **1**, only small amounts of **2** should be formed (Scheme VI).

Scheme VI



Experimental Section

Gas chromatographic analysis was carried on with a Varian Model 1440/1 instrument (5% FFAP and 5% APL on Varaport 80–100 columns). The reaction products were identified by mixture melting points with prepared authentic specimens or by comparison of their IR (Perkin-Elmer 257) and NMR (JEOL 60 MHz) spectra.

Thianthrene (**2**), dibenzothiophene (**6**), and thiophenol are commercial products. 1,2,3-Benzothiadiazole (**1**),[1] dibenzo[c,e]-*o*-dithiin (**5**),[12] diphenyl disulfide,[13] 1-, 2-, 3-, and 4-methyldibenzothiophene,[14,15] 1-, 2-, 3-, and 4-methoxycarbonyldibenzothiophene,[15,16] 6-methoxybenzothiadiazole (**10**),[17] 2- and 3-phenylbenzothiophene,[18,19] 2,3-diphenylbenzothiophene,[20] and *cis*- and *trans*-phenylthiostilbene[21] were prepared as described in the literature.

2-Nitro-4,5′-dimethoxy-2′-phenylthiodiphenyl Sulfide. The crude 2-mercapto-4-methoxydiphenyl sulfide, obtained from 2-amino-4-methoxydiphenyl sulfide[22] (11.5 g, 0.05 mol) with Leuckart reaction modified by Campaigne,[23] was dissolved in sodium methylate, 1 M (50 ml), and added to a solution of 2-nitro-4-methoxychlorobenzene[24] (9.5 g, 0.05 mol). The mixture was refluxed for 3 h, then poured into cold water. The yellow solid was filtered, washed with 2% NaOH, and crystallized with EtOH, mp 103–105 °C. Anal. Calcd for $C_{20}H_{17}NO_4S_2$: C, 60.1; H, 4.29; S, 16.05; N, 3.51. Found: C, 60.19; H, 4.28; S, 16.09; N, 3.60.

2-Nitro-5,5′-dimethoxy-2′-phenylthiodiphenyl sulfide was prepared from 2-mercapto-4-methoxydiphenyl sulfide and 2-nitro-5-methoxychlorobenzene[25] as described above, mp 104–105 °C. Anal. Calcd for $C_{20}H_{17}NO_4S_2$: C, 60.1; H, 4.29; S, 16.05; N, 3.51. Found: C, 59.62; H, 4.47; S, 16.18; N, 3.55.

2-Amino-4,5′-dimethoxy-2′-phenylthiodiphenyl sulfide was obtained by reduction with H_2 over 10% palladium on charcoal of the parent nitro derivative, mp 101–102 °C. Anal. Calcd for $C_{20}H_{19}NO_2S_2$:

C, 65.0; H, 5.18; S, 17.35; N, 3.79. Found: C, 65.0; H, 5.16; S, 17.34; N, 3.84.

2-Amino-5,5′-dimethoxy-2′-phenylthiodiphenyl sulfide was obtained from the parent nitro derivative by reduction as described above, mp 105–107 °C. Anal. Calcd for $C_{20}H_{19}NO_2S_2$: C, 65.0; H, 5.18; S, 17.35; N, 3.79. Found: C, 65.0; H, 5.31; S, 17.23; N, 3.90.

2,7-Dimethoxythianthrene (11a) was synthesized as described in the literature.[26] *n*-Pentyl nitrite (0.015 mol) was added to a solution of 2-amino-4,5′-dimethoxy-2′-phenylthiodiphenyl sulfide (0.01 mol) in ethyl acetate (50 ml). The mixture was kept at 50 °C for 5 h and then the solvent was evaporated. The residue was chromatographed on a silica gel column, and the thianthrene (**11a**) obtained in 45% yield: mp 134–135 °C (lit. 131,[27] 133 °C[28]); IR ν (CS_2) 1290 (s), 1260 (s), 1230 (s), 1220 (s), 1180 (m), 1105 (m), 1050 (s), 1040 (s), 1020 (m), 870 (m), 860 (m), 840 (s), 810 (s), 800 cm^{-1} (s).

2,8-Dimethoxythianthrene (11b) was obtained from 2-amino-5,5′-dimethoxy-2′-phenylthiodiphenyl sulfide in 45% yield as described above: mp 104–105 °C; IR ν (CS_2) 1295 (s), 1290 (s), 1280 (m), 1260 (s, doublet), 1230 (s, doublet), 1225 (s), 1220 (s), 1180 (m), 1105 (m), 1050 (s), 1045 (s), 1040 (s), 1030 (m), 870 (m), 860 (m), 840 (s), 810 (s), 800 cm^{-1} (s).

Thermal Decomposition of 1,2,3-Benzothiadiazole (1). A. In Ethyl Acetate. A solution of **1** (2.70 g, 0.02 mol) in ethyl acetate (50 ml) was kept in a "bomb" at 220 °C for 18 h. The crude was washed with 5% aqueous NaOH. From alkaline solution, after acidification and extraction with Et_2O, thiophenol was separated (0.1 g, 5%). The organic layer was chromatographed on a silica gel column; dibenzothiophene (**6**, 0.11 g, 6%), thianthrene **2**, 0.43 g, 20%), and dibenzo[*c,e*]-o-dithiin (**5**, 0.48 g, 22%) with small amounts of diphenyl disulfide (0.04 g, 2%) were separated. Independent experiments were carried out to prove the thermal stability of the products in reaction conditions. Thianthrene (**2**), dibenzothiophene (**6**), and thiophenol (**7**) were recovered unchanged, while dibenzodithiin (**5**) gave dibenzothiophene (3%).

B. In Toluene. A solution of **1** (3.3 g, 0.024 mol) in toluene (33 ml) was kept in a "bomb" at 220 °C for 18 h. By column chromatography on silica gel of the crude was separated, with **2, 5,** and **6,** a mixture of 1-, 2-, 3-, and 4-methyldibenzothiophene (~12%). The relative yields, determined by ratio of peak areas of methyl groups in the NMR spectrum, are 42, 14, 20, and 24%, respectively. The assignment of peaks was determined by comparison with NMR spectra of authentic specimens.

C. In Methyl Benzoate. A solution of **1** (2.6 g, 0.019 mol) in methyl benzoate (30 ml) was treated as described above. The relative yield of 1-, 2-, 3-, and 4-methoxycarbonyldibenzothiophene (~12%) separated by chromatography on a silica gel column, determined by GLC analysis, are 57, 6, 19, and 18%, respectively.

D. In Diphenylacetylene. A solution of **1** (1.36 g, 0.01 mol) and tolane (**13,** 1.78 g, 0.01 mol) in ethyl acetate (15 ml) was thermolyzed at 220 °C for 18 h. By column chromatography on a silica gel column dibenzothiophene (**6,** 3%), thianthrene (**2,** 11%), dibenzo[*c,e*]-o-dithiin (**5,** 12%), 2,3-diphenylbenzothiophene (**15,** 7%), and a cis–trans mixture of 1-phenylthiostilbene (7%) were separated. The indicated yields were detected by GLC analysis of the reaction mixture.

E. In Phenylacetylene. A solution of **1** (1.36 g, 0.01 mol) and phenylacetylene (1.00 g, 0.01 mol) in ethyl acetate (15 ml) was thermolyzed as above. By column chromatography **6** (5% yield), 2 (17%), **5** (18%), 2-phenylbenzothiophene (**13a,** 10%), and 3-phenylbenzothiophene (**13b,** 4%) were separated.

Thermal Decomposition of 6-Methoxy-1,2,3-benzothiadiazole (10). **10** was heated at 205 °C for 18 h in a "bomb". The crude was chromatographed on a silica gel column and the thianthrene was isolated: mp 134–135 °C; IR spectra of this fraction and **11a** were identical; mixture melting point with **11a** was undepressed.

Acknowledgment. We acknowledge support from the Consiglio Nazionale delle Ricerche, Rome.

Registry No.—**1**, 273-77-8; **2**, 92-85-3; **5**, 230-26-2; **6**, 132-65-0; **10**, 1753-90-8; **11a**, 54815-69-9; **11b**, 60718-98-1; **13a**, 1207-95-0; **13b**, 14315-12-9; **15**, 22751-52-6; 2-nitro-4,5′-dimethoxy-2′-phenylthiodiphenyl sulfide, 60718-99-2; 2-mercapto-4-methoxydiphenyl sulfide, 60718-00-8; 2-nitro-4-methoxychlorobenzene, 10298-80-3; 2-nitro-5,5′-dimethoxy-2′-phenylthiodiphenyl sulfide, 60719-01-9; 2-nitro-5-methoxychlorobenzene, 28987-59-9; 2-amino-4,5′-dimethoxy-2′-phenylthiodiphenyl sulfide, 60719-02-0; 2-amino-5,5′-dimethoxy-2′-phenylthiodiphenyl sulfide, 60719-03-1; diphenyl disulfide, 882-33-7; *cis*-1-phenylthiostilbene, 41796-39-8; *trans*-phenylthiostilbene, 24466-59-9; phenylacetylene, 501-65-5.

References and Notes

(1) P. Jacobson and H. Janssen, *Justus Liebigs Ann. Chem.*, **277**, 209 (1893).
(2) K. P. Zeller, H. Meier, and E. Müller, *Tetrahedron Lett.*, 537 (1971).
(3) G. Seybold and C. Heibl, *Angew. Chem., int. Ed. Engl.*, **14**, 248 (1975).
(4) W. Kirmse and L. Horner, *Justus Liebigs Ann. Chem.*, **614**, 4 (1958).
(5) R. Huisgen and V. Werberndorfer, *Experientia*, **14**, 566 (1961).
(6) L. Benati, P. C. Montevecchi, A. Tundo, and G. Zanardi, *J. Chem. Soc., Perkin Trans. 1*, 1276 (1974).
(7) L. Benati, P. C. Montevecchi, A. Tundo, and G. Zanardi, *J. Org. Chem.*, in press.
(8) J. I. G. Cadogan, J. T. Sharp, and M. J. Trattles, *J. Chem. Soc., Chem. Commun.*, 900 (1974).
(9) T. L. Gilchrist, P. G. Mento, and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 2165 (1972).
(10) N. Kharasch and C. Y. Meyers in "The Chemistry of Organic Sulfur Compounds", Vol. 2, Pergamon Press, Oxford, 1967, p 246.
(11) L. Benati, P. C. Montevecchi, A. Tundo, and G. Zanardi, *Gazz. Chim. Ital.*, **105**, 841 (1975).
(12) W. L. F. Amarego and E. E. Turner, *J. Chem. Soc.*, 1665 (1965).
(13) H. Lecker, *Ber.*, **58**, 409 (1925).
(14) H. Gilmann and G. R. Wilder, *J. Org. Chem.*, **22**, 523 (1957).
(15) H. Gilmann and A. L. Jacoby, *J. Org. Chem.*, **3**, 108 (1938).
(16) H. Gilmann, A. L. Jacoby, and H. A. Pacevitz, *J. Org. Chem.*, **3**, 120 (1938).
(17) P. Kirby, S. B. Soloway, J. H. Davies, and S. B. Webb, *J. Chem. Soc. C*, 2250 (1970).
(18) J. Russel, *J. Am. Chem. Soc.*, **74**, 4950 (1952).
(19) S. Middleton, *Aust. J. Chem.*, **12**, 218 (1959).
(20) H. Staudinger and J. Siegwart, *Helv. Chim. Acta*, **3**, 840 (1920).
(21) E. E. Campaigne and J. R. Leal, *J. Am. Chem. Soc.*, **76**, 1272 (1954).
(22) J. Schumtz, F. Kuenzle, F. Hunziker, and A. Buerki, *Helv. Chim. Acta*, **48**, 336 (1965).
(23) E. E. Campaigne and S. W. Osborn, *J. Org. Chem.*, **22**, 561 (1957).
(24) H. H. Hodgson and J. H. Crook, *J. Chem. Soc.*, 1812 (1932).
(25) H. H. Hodgson and F. W. Handley, *J. Chem. Soc.*, 543 (1926).
(26) L. Benati, P. C. Montevecchi, A. Tundo, and G. Zanardi, *J. Chem. Soc., Perkin Trans. 1*, 1272 (1974).
(27) K. Fries and E. Engelbertz, *Justus Liebigs Ann. Chem.*, **407**, 194 (1915).
(28) H. Baw, G. M. Bennett, and P. Dearns, *J. Chem. Soc.*, 680 (1934).

An Improved Synthesis of 1-Picryl-2,2-diphenylhydrazyl Radical. Purification and Storage of 1,1-Diphenylhydrazine as the Tosylate Salt[1]

Sally E. O'Connor and Robert I. Walter*

Chemistry Department, University of Illinois at Chicago Circle, P.O. Box 4348, Chicago, Illinois 60680

Received September 28, 1976

The conventional synthesis of 1-picryl-2,2-diphenylhydrazyl (DPPH) free radical requires as an intermediate 1,1-diphenylhydrazine (**3**), which is picrylated and then oxidized to the radical with lead dioxide.[2] The classical (and until recently the only) synthesis of **3** proceeds from diphenylamine by sequence a:[3]

$$\underset{\mathbf{1}}{Ph_2NH} \xrightarrow[\text{or NOCl}]{\text{HONO}} \underset{\mathbf{2}}{Ph_2N\text{–}NO} \xrightarrow[\text{or LiAlH}_4]{\text{Zn, AcOH}} \underset{\mathbf{3}}{Ph_2N\text{–}NH_2} \qquad \text{(a)}$$

Simultaneous reductive cleavage of the N–N bond during conversion of **2** to **3** has been well documented,[4] as have the labor and erratic results in the separation of the "pure" hydrazine. Heroic efforts devoted to purification of **3** give a crystalline solid variously reported[5] to melt through the range 31–44 °C, but the usual product is an oil identified only by its boiling point in a vacuum distillation. Furthermore, in our experience both the hydrazine and its hydrochloride deteriorate upon storage after purification, so it is impossible to maintain a stock of the compound which can be relied upon for further synthetic work.

Anselme and Koga[6] have published an alternate route to **3** from **1** by Curtius rearrangement of 1,1-diphenylcarbamyl azide (**5**) dissolved in a tertiary alcohol, followed by hydrolysis of the *tert*-alkyl 3,3-diphenylcarbazate formed:

$$1 \xrightarrow{COCl_2} \underset{4}{Ph_2N\text{-}COCl} \xrightarrow{NaN_3} \underset{5}{Ph_2N\text{-}CON_3} \xrightarrow[H_2O,\ TsOH,\ reflux]{t\text{-}AmOH,\ reflux} 3 \quad (b)$$

When we repeated their sequence, we observed formation of a small amount of solid in the hydrolysis mixture. This was identified as the salt of **3** with *p*-toluenesulfonic acid (TsOH), **6**. It proved to be readily purified and quite stable. It can be precipitated directly by adding excess TsOH in *tert*-amyl alcohol to an ether solution of **3**, and the latter can be regenerated immediately before use by addition of a base to a solution of the salt, **6**.

Our comparison of these routes to **3** was motivated by a need to synthesize isotopically labelled derivatives of **3** and of DPPH. Clearly it is necessary for this purpose to use procedures which are reliable even on a small scale, and give maximum yields. By these criteria, we have had significantly better success with both sequences when **3** was isolated as its salt **6** with TsOH. Overall yields have averaged 70–80% from **1** by both routes, even on a 1-g scale.

The advantage of a source of pure **3** becomes clear during its subsequent picrylation in the sequence of reactions for the preparation of DPPH: yields of the hydrazine are close to 99% before recrystallization. In contrast, picrylation yields by our older procedure in normal cases not complicated by the substituents present were in the range 75–95%.[7]

Experimental Section

All melting points were taken on a Thomas calibrated hot stage. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill.

2,2-Diphenylhydrazinium Tosylate (6) from 2. **2** (0.1 mol) in 50 ml of ether was reduced with 50% excess powdered lithium aluminum hydride using the inverse addition procedure of Poirier and Benington.[8] After decomposition of the reduction intermediate,[7] the mixture was stirred for 1 h, and the ether layer separated, combined with an ether wash of the aqueous layer, and dried over sodium sulfate. A solution of 0.12 mol of TsOH in 20 ml of *tert*-amyl alcohol was added, and the colorless, crystalline precipitate filtered, washed well with ether, and dried. The average yield is 76%, mp 189.0–189.5 °C dec. NMR in Me_2SO-d_6 shows peaks at 10.1 ($-NH_3^+$, broad, variable position) and 2.28 ppm ($-CH_3$) with equal areas, and multiple lines from 7.1 to 7.6 ppm for the 14 aromatic protons. Anal. Calcd for $C_{19}H_{20}N_2O_3S$: C, 64.04; H, 5.62; N, 7.86; S, 8.99. Found: C, 64.26; H, 5.74; N, 7.99; S, 8.79.

2,2-Diphenylhydrazinium Tosylate (6) from 5. Anselme and Koga's procedure[6] for conversion of **5** to **3** was followed, except that the amount of TsOH added was increased to 20 g. After the 5-h reflux period, the precipitated product was filtered off and thoroughly washed with ether. Yield was 80%, with properties identical with those already described above.

***N*-Aminocarbazole Hydrogen Tosylate (7).** *N*-Aminocarbazole was converted by the first procedure above to **7**. Product was obtained as colorless crystals in 65% yield, with mp 199.0–199.5 °C. The NMR in Me_2SO-d_6 shows peaks at 10.8 ($-NH_3^+$, variable position) and 2.28 ppm ($-CH_3$) with equal areas, and multiple lines from 7.1 to 8.25 ppm for the aromatic protons. Anal. Calcd for $C_{19}H_{18}N_2O_3S$: C, 64.41; H, 5.08; N, 7.91; S, 9.04. Found: C, 64.40; H, 5.15; N, 8.01; S, 8.88.

Recovery of 3 as the Tosylate Salt. A known amount of pure **3** was generated from a solution of 1.0 g of **6** in 20 ml of methanol by adding a solution of 0.3 g of sodium carbonate in 10 ml of water. Most of the solvents were removed on a rotary evaporator, and the residue taken up in 1:1 ether–water. The ether layer was combined with two ether washes of the aqueous layer and dried. A solution of 0.6 g of TsOH in *tert*-amyl alcohol was added, and the colorless needles filtered and dried. Recovery was 95%.

1-Picryl-2,2-diphenylhydrazine. Salt **6** and picryl chloride (0.1 mol each) were dissolved in 50 ml of methanol, 0.5 g of sodium carbonate in 20 ml of H_2O added, and the mixture stirred for 2 h. The brick-red product was filtered, washed with fresh solvent mixture, and dried. The yield was 99%, with mp 174–175 °C before recrystallization; the product is pure enough to use directly for preparation of DPPH, by the conventional lead dioxide oxidation.[2,7]

Registry No.—**2**, 86-30-6; **3**, 530-50-7; **5**, 17223-83-5; **6**, 61064-13-9; **7**, 61064-14-0; TsOH, 104-15-4; *N*-aminocarbazole, 17223-85-7; 1-picryl-2,2-diphenylhydrazine, 1707-75-1; picryl chloride, 88-88-0; 1-picryl-2,2-diphenylhydrazyl radical, 1898-66-4.

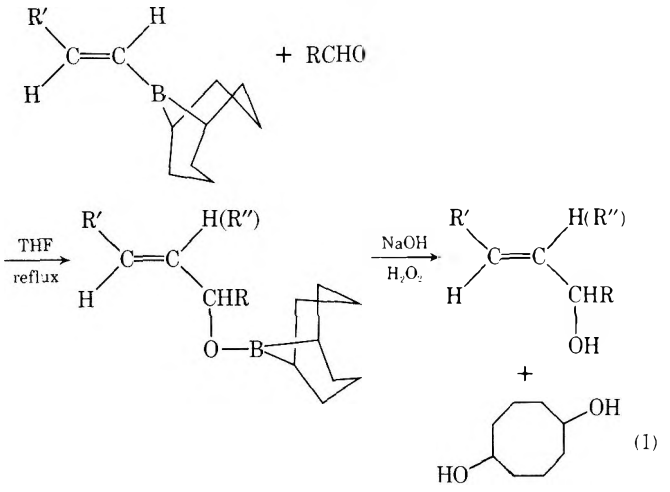
References and Notes

(1) We are pleased to acknowledge support in part by the National Science Foundation through Grant GP33518, and in part by the UICC Research Board through a research assistantship to S. E. O'Connor.
(2) S. Goldschmidt and K. Renn, *Chem. Ber.*, **55B**, 628–643 (1922).
(3) E. Fischer, *Justus Liebigs Ann. Chem.*, **190**, 174–176 (1878).
(4) N. Koga and J.-P. Anselme, *J. Org. Chem.*, **33**, 3963–3964 (1968).
(5) The highest melting point, 44 °C, is reported by F. M. Jaeger, *Z. Kristallogr. Mineral.*, **42**, 160 (1907). He acknowledges his sample as a gift, with no mention of the method of preparation.
(6) J.-P. Anselme and N. Koga, *Org. Prep. Proced.*, **2**, 125–128 (1970).
(7) M. M. Chen, A. F. D'Adamo, and R. I. Walter, *J. Org. Chem.*, **26**, 2721–2727 (1961).
(8) R. H. Poirier and F. Benington, *J. Am. Chem. Soc.*, **74**, 3192 (1952).

A Grignard-Like Addition of *B*-Alkenyl-9-borabicyclo[3.3.1]nonanes to Aldehydes, A Novel Synthesis of Allylic Alcohols with Defined Stereochemistry

Summary: *B*-Alkenyl-9-BBN derivatives add across the carbonyl group of representative aldehydes to give the corresponding allylic alcohols with the corresponding stereochemistry.

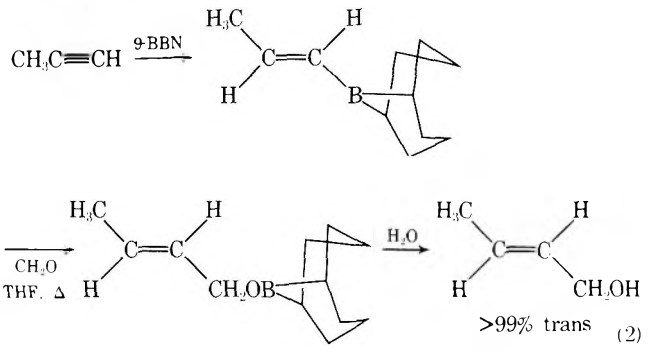
Sir: *B*-Alkenyl-9-borabicyclo[3.3.1]nonanes (*B*-alkenyl-9-BBN), in contrast to their saturated counterparts,[1] add across the carbonyl group of simple aldehydes. The products are the corresponding allylic alcohols (eq 1) with retained stereochemistry. Since the *B*-alkenyl-9-BBN derivatives are readily prepared by the hydroboration of acetylenes with 9-BBN,[2,3] this reaction sequence provides a remarkably simple synthesis of such allylic alcohols.



(1)

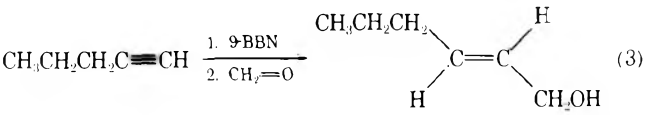
The reaction evidently proceeds with complete retention of the vinylborane stereochemistry. Thus, GC examination of the products reveals only a single peak. The ^{1}H NMR spectra are also consistent with the presence of only a single isomer. The IR spectra of the products derived from terminal acetylenes displayed a strong absorption at ~970 cm^{-1}, indicating the presence of a trans disubstituted olefinic linkage.[4] Consequently, it is highly probable that all of the reactions proceed with retention of configuration.

In one case, this conclusion was tested by comparing the product with authentic cis and trans isomers. Thus, propyne was treated with 9-BBN to form 1-propenyl-9-BBN,[5] which in turn was treated with formaldehyde. The product was crotyl alcohol, >99% trans by GC analysis (eq 2).

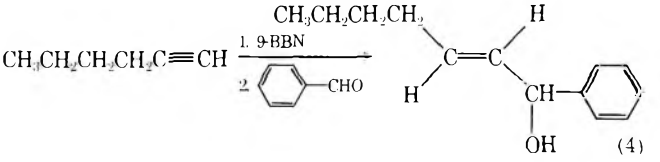


(2)

The addition of *B*-alkenyl-9-BBN to aldehydes appears to be a reaction of considerable generality (Table I). (The reaction of other alkenyldialkylboranes is less satisfactory.) A variety of simple aldehydes undergo the reaction. Furthermore, various substituents on the vinylborane moiety can be accommodated (eq 3–6).



(3)

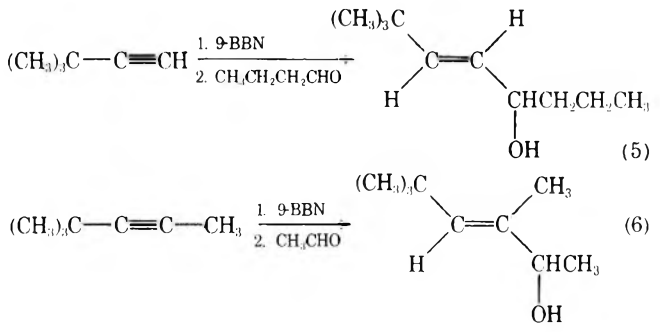


(4)

Table I. Coversion of Alkynes into Allylic Alcohols by the Reaction of the Corresponding *B*-Alkenyl-9-BBN Derivatives with Aldehydes[a]

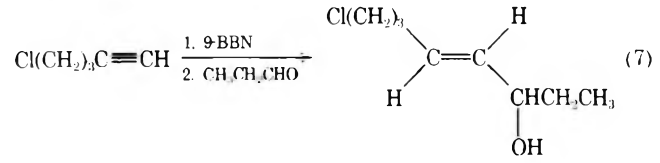
Alkyne	Aldehyde	Product[b]	Yield,[c,d] %	n^{20}D
Propyne[e]	Formaldehyde[i]	*trans*-Crotyl alcohol	48	
1-Pentyne[f]	Formaldehyde[i]	*trans*-2-Hexen-1-ol	(36)	
1-Hexyne[g]	Benzaldehyde	1-Phenyl-*trans*-2-hepten-1-ol	86	1.5184
3,3-Dimethyl-1-butyne[h]	Butyraldehyde	7,7-Dimethyl-*trans*-5-octen-4-ol	(55)	1.4438
4,4-Dimethyl-2-pentyne[h]	Acetaldehyde	3,5,5-Trimethyl-*trans*-3-hexen-2-ol	69 (56)	1.4472
5-Chloro-1-pentyne[f]	Propionaldehyde	8-Chloro-*trans*-4-octen-3-ol	47	1.4718

[a] All reactions were carried out for 16 h in refluxing THF unless otherwise noted. [b] Satisfactory IR, ^{1}H NMR, and high resolution mass spectral data was obtained for all new compounds. [c] By GLC analysis. [d] Numbers in parentheses are isolated yields. [e] A 4-fold excess of propyne was used. [f] 100% excess alkyne was used. With straight-chain terminal alkynes, an excess is required to minimize dihydroboration. [g] Reaction was carried out for 2 h in refluxing toluene with distilled organoborane. [h] A 10% excess of the alkyne was used. [i] Monomeric formaldehyde was generated externally by the pyrolysis of paraformaldehyde.



The following procedure is representative. An oven-dried 100-ml flask fitted with a reflux condenser and magnetic stirring bar was flushed with nitrogen and charged with 50 ml of 0.50 M 9-BBN[3] (25 mmol) in THF. To the solution was added 2.7 g (28 mmol) of 4,4-dimethyl-2-pentyne, and the solution was stirred overnight to ensure complete hydroboration. Acetaldehyde (2.2 g, 50 mmol[6]) was added, and the solution was heated under reflux for 16 h. After cooling to room temperature, the reaction mixture was oxidized by adding 15 ml of 3 N sodium hydroxide followed by the slow addition of 15 ml of 30% hydrogen peroxide (*Caution:* exothermic!). The solution was maintained at 50 °C to ensure complete oxidation. The aqueous layer was saturated with anhydrous potassium carbonate, separated, and extracted with hexane. The combined organic layer was dried over anhydrous magnesium sulfate and analyzed by GC, which indicated a 69% yield of 3,5,5-trimethyl-3-hexen-2-ol. Distillation provided 1.97 g (56%) of colorless liquid: bp 80–81 °C (12 mm); n^{20}D 1.4472; IR (neat) 3350 cm^{-1}; ^{1}H NMR (CCl_4, TMS) δ 1.1–1.2 (s + d, 12 H), 1.7 (d, J = 1.5 Hz, 3 H), 4.1 (q, J = 6 Hz, 1 H), 5.4 (q, J = 1.5 Hz, 1 H).

Since the hydroboration reaction is known to be tolerant of a variety of functional groups,[5] we were intrigued with the possibility of achieving a "Grignard-like" synthesis with a reactive substituent present on the organometallic reagent. Thus, 5-chloro-1-pentyne was hydroborated with 9-BBN and then reacted with propionaldehyde to give *trans*-8-chloro-4-octen-3-ol (eq 7). Past experience with the application of



such organoborane intermediates indicate that this reaction should accommodate many functional groups, such as ester and nitrile, providing chemists with a versatile new approach to the synthesis of functionalized allylic alcohols.

It should be emphasized that this communication describes an unexpected development. All previous attempts to achieve a Grignard-like reaction of organoboranes had failed.[1] Evidently, the present development provides a remarkably simple, stereospecific, synthetic route to allylic alcohols. Furthermore, there is the definite implication that such alkenylboranes will undergo other reaction types previously believed to be possible only with far more reactive organometallic compounds. This represents a promising new area.

References and Notes

(1) Heating *B-n*-butyl-9-BBN with benzaldehyde resulted in reduction of the carbonyl group: J. D. Buhler, Ph.D. Thesis, Purdue University, West Lafayette, Ind., 1973. In contrast, *B*-allyl-9-BBN (G. W. Kramer and H. C. Brown, manuscript in preparation) and other allylboranes readily add to the carbonyl groups: B. M. Mikhailov, *Organomet. Chem. Rev. A*, 1 (1972).
(2) H. C. Brown, E. F. Knights, and C. G. Scouten, *J. Am. Chem. Soc.*, **96**, 7765 (1974); C. G. Scouten, Ph.D. Thesis, Purdue University, West Lafayette, Ind., 1974.
(3) Available from Aldrich-Boranes, a subsidiary of the Aldrich Chemical Co.
(4) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds", Wiley, New York, N.Y., 1975.
(5) The hydroboration of acetylenes involves a clean cis addition of the B–H bond: H. C. Brown, "Boranes in Organic Chemistry", Cornell University Press, Ithaca, N.Y., 1972; H. C. Brown, G. W. Kramer, A. B. Levy, and M. M. Midland, "Organic Syntheses via Boranes", Wiley-Interscience, New York, N.Y., 1975.
(6) Because of the high volatility of acetaldehyde (bp 21 °C), we employed a large excess. In most cases, the use of excess aldehyde is unnecessary.

(7) Graduate research assistant on grants provided by the National Science Foundation (GP-41169X) and by the G. D. Searle and Co. Chicago, Ill.

Peyton Jacob, III,[7] Herbert C. Brown*

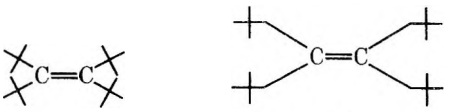
Richard B. Wetherill Laboratory
Purdue University, West Lafayette, Indiana 47907

Received October 25, 1976

Tetraneopentylethylene

Summary: The highly hindered tetraneopentylethylene has been synthesized and was shown to exhibit a temperature dependent ^{1}H NMR spectrum demonstrating the nonequivalence of methylene protons, with the barrier of rotation across the sp^2–sp^3 bond being $\Delta G^{\ddagger}$ = 21.7 ± 5 kcal/mol at 145 °C.

Sir: In continuation of our studies on highly hindered olefins and their electrophilic reactions,[1,2] such as adamantylideneadamantane and homoadamantylidenehomoadamantane, the extremely hindered tetra-*tert*-butylethylene **1** would



1 **2**

be of great interest, but it remains elusive despite efforts in different laboratories.[3] Recent methods developed by McMurry and Flemming[4] and their modifications[4d] for the reductive coupling of carbonyl compounds with low-valent titanium reagent has greatly facilitated attempts to prepare hindered olefins.[5-7] We wish now to report the synthesis of tetraneopentylethylene (**2**), one of the most crowded symmetrical tetraalkyl-substituted ethylenes.

Tetraneopentylethylene, mp 59 °C, a white crystalline solid was obtained in 38% yield by the reductive coupling of dineopentyl ketone[7b] using titanium(II) reagent[2,4] in tetrahydrofuran solution. In a 500-ml three-necked flask fitted with a reflux condenser under nitrogen is weighed $TiCl_3$ (31.3 g, 0.2 mol); 200 ml of anhydrous THF is added to it under stirring, and the flask is cooled to −40 °C (dry ice/acetone bath). Under stirring $LiAlH_4$ (3.8 g, 0.1 mol) is added in portions; rapid gas evolution is seen. After the addition, the mixture is warmed to room temperature and refluxed for 1 h, dineopentyl ketone (16.8 g, 0.1 mol) in 50 ml of THF is added dropwise, and the mixture is refluxed for 8 h more. Then the mixture is cooled, poured over 10% ice-cold NH_4Cl solution, and worked up with ether in the usual manner. The product is purified by chromatography on alumina (petroleum ether eluent): ^{13}C NMR (25.1 MHz, $CDCl_3$, from capillary TMS, 37 °C) δ 136.56 (vinylic carbon), 47.36 (CH_2, J_{CH} = 121.0 Hz), 35.23)quaternary carbon), 32.47 (CH_3, J_{CH} = 128.1 Hz); mass spectrum (70 eV) (relative abundance) *m/e* 308 (78.1, M$^+$), 252 (40.6), 251 (50.2), 196 (30.2), 195 (63.8), 167 (11.2), 154 (7.7), 140 (18.7), 139 (58.3), 125 (20.6), 111 (15.8), 99 (10.5), 85 (11.4), 83 (19.6), 71 (13.0), 57 (100), 41 (24.3), 29 (15.7). Elemental Anal.[8a] Calcd for $C_{22}H_{44}$: C, 85.71; H, 14.29. Found: C, 85.76; H, 14.39.

Of particular interest is the marked temperature dependence of the ^{1}H NMR spectrum[8b] of **2**. The methylene protons show an AB pattern, centered at δ 2.18 (J_{AB} = 13.0 Hz) up to 104 °C; coalescence occurs at 145 °C. The methyl groups resonate at δ 0.97 as a singlet without any change with temperature. The appearance of two different methylene protons is

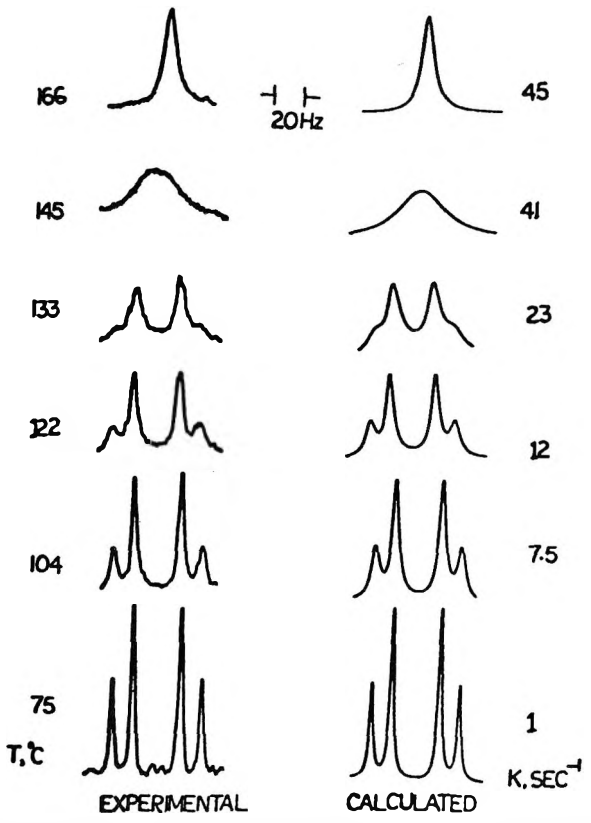


Figure 1. Experimental and calculated 60-MHz NMR absorptions of methylene protons of **2** at various temperatures, T, °C; K, rate constant.

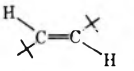
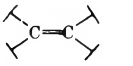
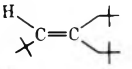
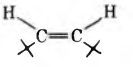
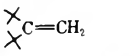
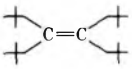
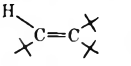
as expected. This type of hindered rotation across sp^2–sp^3 carbon–carbon bonds has been observed in many neopentyl-substituted benzenes.[9] The coalescence temperature at which collapse of the nonequivalent proton absorptions occurs is rather high.[10] A complete NMR line-shape analysis (Figure 1) using the "QUABEX" computer program[11] shows the activation energy barrier at coalescence to be $\Delta G^{\ddagger} = 21.7 \pm 0.5$ kcal/mol. This is one of the highest energy barriers yet reported for this kind of hindered rotation in comparison with other neopentyl-substituted systems.[10] The olefinic carbons are more shielded (by 8.34 ppm) compared to the olefinic carbons of tetraisopropylethylene **3**.[5b] This effect is, however, in great part due to the neighboring-group effects, as a similar ipso carbon shift difference[11c] (9.1 ppm) is observed between cumene and neopentylbenzene. The methylene carbons did not show any change in coupling with the nonequivalent hydrogens at different temperatures.

The laser Raman spectrum of **2** (488.0 nm, crystalline sample) shows bands at 1607 cm^{-1} (C=C stretch), 1450 (sh), 1445, 1430 (sh), 1394, 1364, 1357, 1316, 1226, 1199, 1175, 1157, 934, 907, 900, 890, 862, 778, 641, 500, 467, 386, 257, 240, and 215. The C=C stretching frequency is rather low compared to that of other crowded olefins[3a,5b] (Table I).

The continuous decrease in C=C stretching frequency with the increase in steric crowding of the double bond is apparent, though such a correlation cannot be generalized.[11d] Such shift in stretching frequency is considered to arise from change in bond angles and hence change in hydridization.[12-14] It has also been argued[12b,13] that the primary contributor for the shift in frequencies is the coupling of the double-bond stretching with the adjacent single bonds, such that the compression and elongation of the single bond occurs during double-bond vibration which is also angle dependent.

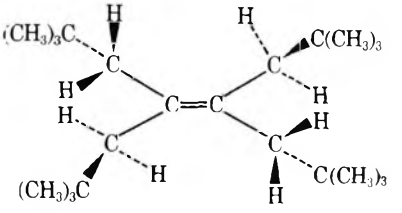
Tetraneopentylethylene (**2**) does not react with bromine in CCl_4 solution and the system stays unchanged for days. The

Table I. Raman C=C Bond Stretching Frequencies of Alkyl-Substituted Olefins

Compd	$\nu_{C=C}$, cm^{-1}
	1656
	1638
	1636
	1629
	1615.5
	1607
	1583

^{13}C NMR spectrum of **2** in $Br_2/CDCl_3$ shows no shift changes indicating absence of any detectable π-complex formation. **2** also shows no evidence of protonation and is unchanged in FSO_3H/SO_2ClF solution. However, the much stronger FSO_3H/SbF_5 system cleaves the neopentyl groups giving *tert*-butyl cation and polymeric products. The lack of reactivity of **2** to electrophilic additions further demonstrates the steric constraints imposed by the four neopentyl groups.

Conformation **2a** is consistent with the nonequivalence of the methylene protons in the ^1H NMR spectrum and mini-



2a

mizes steric interactions between the four neopentyl groups. It also explains the lack of reactivity of the double bond in **2**. since both sides of the molecule are shielded by two *tert*-butyl groups.

In the mass spectrum of **2** the base peak at m/e 57 corresponds to C_4H_9, i.e., *tert*-butyl group. The molecular ion peak at m/e 308 is also intense. The fragmentation peaks can be accounted for by the progressive loss of *tert*-butyl, isobutylene, ethylene, or methyl moities. The peak at m/e 154 should come from the cission of the C=C bond as observed in the case of tetraisopropylethylene.[5b]

Di-*tert*-butyl ketone, *tert*-butyl isopropyl ketone, and neopentyl *tert*-butyl ketone failed to undergo coupling reaction. We are continuing our studies on **2** and other related highly crowded olefins[3c] and their behavior under electrophilic conditions.

Acknowledgment. Support of our work by the National Institutes of Health and the National Science Foundation is gratefully acknowledged.

References and Notes

(1) G. A. Olah, P. Schilling, P. W. Westermann, and H. C. Lin, *J. Am. Chem. Soc.*, **96**, 3581 (1974).
(2) G. A. Olah, G. K. Surya Prakash, and G. Liang, *Synthesis*, 318, (1976).

(3) (a) G. J. Abruscato and T. T. Tidwell, *J. Am. Chem. Soc.*, **92**, 4125 (1970); (b) D. H. R. Barton, F. S. Guziec, Jr., and I. Shahak, *J. Chem. Soc., Perkin Trans 1*, 1793 (1974); (c) unpublished results in our laboratory.
(4) (a) J. E. McMurry, *Acc. Chem. Res.*, **7**, 281 (1974); (b) J. E. McMurry and M. P. Flemming, *J. Am. Chem. Soc.*, **96**, 4708 (1974); (c) J. E. McMurry and M. P. Flemming, *J. Org. Chem.*, **41**, 896 (1976); (d) E. J. Corey, R. L. Danheiser, and S. Chandrasekaran, *ibid.*, **41**, 260 (1976).
(5) (a) R. F. Langler and T. T. Tidwell, *Tetrahedron Lett.*, 777 (1975); (b) D. S. Bombse and T. H. Morton, *ibid.*, 781 (1975).
(6) H. Wynberg, K. Lammertsma, and L. A. Hulshoff, *Tetrahedron Lett.*, 3749 (1975).
(7) (a) See also W. H. Richardson and K. W. Gunderson, *J. Org. Chem.*, **41**, 2054 (1976); (b) J. Ciabattoni, E. C. Nathan, A. E. Feiring, and P. J. Kocienski, *Org. Synth.*, **54**, 97 (1975).
(8) (a) Analysis by Galbrath Laboratories, Inc., Knoxville, Tenn. (b) Spectrum was taken in hexachloroacetone, shifts from capillary TMS.
(9) (a) D. T. Dix, G. Frankel, H. A. Karnes, and M. S. Newman, *Tetrahedron Lett.*, 517 (1966); (b) A. J. M. Reuvers, A. Sinnema, T. J. Nieumstad, F. V. Rantwijk, and H. V. Bekkum, *Tetrahedron*, **27**, 3713 (1971).
(10) S. Sternhell in "Dynamic Nuclear Magnetic Resonance Spectroscopy", L. M. Jackmann and F. A. Cotton, Ed., Academic Press, New York, N.Y., 1975, p 170.
(11) (a) G. Binch in "Topics in Stereochemistry", Vol. 3, E. L. Eliel and N. L. Allinger, Ed., Wiley-Interscience, New York, N.Y., 1968, pp 180, 181. (b) Calculations were performed on a Univac 1108 computer equipped with a CALCOMP plotter. $\Delta G^{\ddagger}$ was calculated from the rate constants using the Eyring equation

$$\Delta G^{\ddagger} = 4.576\ TC\ (10.319 + \log TC/K)$$

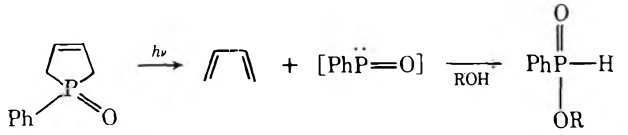
In the equation the transmission coefficient (TC) was assumed to be unity. E_a was found to be 13.07 ± 0.5 kcal/mol from a linear Arrehenious plot. $\Delta H^{\ddagger}$ and $\Delta s^{\ddagger}$ were found to be 11.68 ± 0.5 kcal/mol and −20 ± 2.0 eu, respectively. (c) ^{13}C NMR: cumene, δ_{ipso} 149.40; neopentylbenzene, δ_{ipso} 140.30. (d) O. Ermer and S. Lifson, *Tetrahedron*, **30**, 2425 (1974).
(12) (a) N. Sheppard and D. M. Simpson, *Quart. rev. Chem. Soc.*, **6**, 1 (1962); (b) D. G. Rea, *Anal. Chem.*, **32**, 1638 (1960); (c) F. h. A. Rummens, *Recl. Trav. Chim., Pays-Bas*, **84**, 5 (1965).
(13) L. J. Bellamy, "Advances in Infrared Group Frequencies", Methuen and Co., London, 1968, pp 22–26, 30–32, 132–135.
(14) S. Bank, W. D. Closson, and L. T. Hodgins, *Tetrahedron*, **24**, 381 (1968).

George A. Olah,* G. K. Surya Prakash
Department of Chemistry
Case Western Reserve University
Cleveland, Ohio 44106
Received October 18, 1976

Stereochemistry and Kinetics of Photochemical Fragmentation of 1-Phenyl-3-Phospholene Oxides

Summary: The rate and stereospecificities of the novel photochemical extrusion of phosphinidene oxide from the excited singlet states of 3-phospholene oxides are shown to be sensitive to the configuration of an asymmetric leaving group, indicating that the steric influence on the transition state is substantial.

Sir: During a study of the photochemical reactions of phosphorus heterocycles,[1] we have found, upon UV irradiation, that 1-phenyl-3-phospholene oxides efficiently cleave to dienes and phenylphosphinidene oxide. In contrast to the



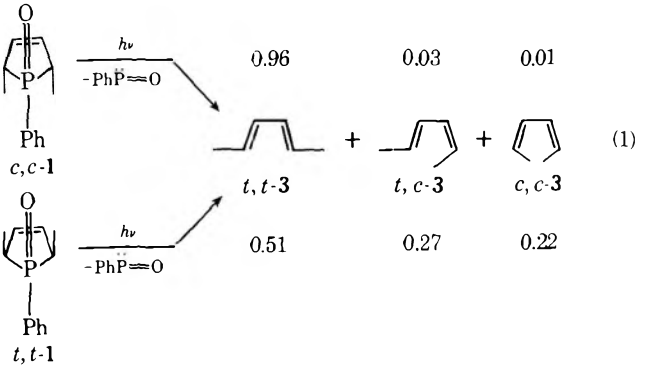
other closely related five-membered cheletropic cycloregressions,[2,3] this formally cheletropic reaction[4] has an asymmetric leaving group and would be expected to reveal how the direction of ring opening and the rate of the reaction depend on the stereochemical disposition of the leaving group.

It was found that the stereochemical disposition of the leaving group exerted a substantial effect on the rate of the fragmentation. This can be explained by considering the steric influence in the transition state during bond reorganization. The all-trans isomers furnished a mixture of dienes, whereas the all-cis isomers gave predominantly the all-trans olefins. This is the first five-membered cheletropic cycloregression observed to proceed through the singlet excited state.

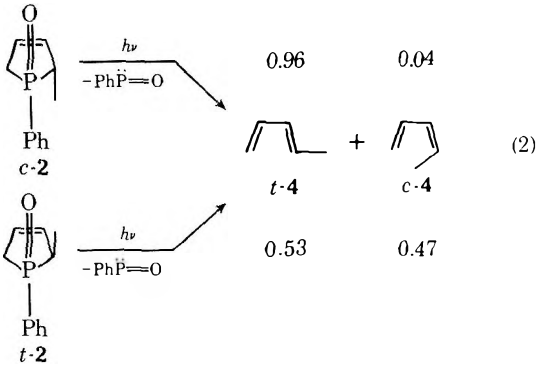
The stereoisomeric pairs of 3-phospholene oxides (**1** and **2**) were prepared according to Quin[5] and the isomers[6] were separated by silica gel chromatography followed by short-path distillation at 10^{-3} mm.

Direct irradiation of **1** and **2** with 254-nm light from a monochromator was performed in methanol containing methylcyclohexane as the internal standard. This resulted in quantitative formation of 1,3-dienes (**3** and **4**) and methyl phenylphosphinate. No photochemical cis–trans isomerization of **1** and **2** was observed even after prolonged irradiation. These phospholene oxides were thermally stable and gave no trace of dienes in refluxing diethyl phthalate (300 °C). Prolonged refluxing caused rearrangement to the 2-phospholene oxide isomer.

Irradiations were interrupted at low conversion (<2%) and yields of 1,3-diene were extrapolated to zero conversion[7] as an appropriate correction for possible sensitized diene isomerization by phospholene oxide (vide infra). The results are shown in eq 1 and 2.[8]



(1)



(2)

Quenching of the reactions 1 and 2 occurred with 1,3-dienes (e.g., 2,5-dimethyl-2,4-hexadiene) to yield linear Stern–Volmer plots. The 1,3-diene photoproduct compositions were the same as those obtained by extrapolation. Triplet sensitization[9] (benzophenone) of **1** and **2**, however, gave no detectable amount of **3** and **4**. Fluorescence quenching of **1** and **2** by 1,3-diene also occurred. The quenching gave good linear Stern–Volmer plots whose slopes are in agreement within experimental errors with those obtained in the quenching of the photochemical reactions (Table I). Unlike other closely related systems,[3] photofragmentation of the phospholene oxides proceeds via the lowest excited singlet state.

Table I. Quantum Yield, Quenching Constant, Fluorescence, and Relative Rate Data for the Photofragmentation of 1-Phenyl-3-phospholene Oxides

Compd	Φ_r[a]	$k_q\tau_r$ ($k_q\tau_f$),[b] M^{-1}	$k_f \times 10^{-6}$,[c] sec^{-1}	$\Phi_{f(rel)}$[d]	$k_{r(rel)}$[e]
3,4-Dimethyl	0.88		1.3	0.11	467
c,c-**1**	0.35	28 (25)	1.8	0.23	123
3-Methyl	0.18		1.4	0.30	37
c-**2**	0.14	23 (26)	1.5	0.26	35
t-**2**	0.031	35 (39)	1.3	0.35	5.0
t,t-**1**	0.020	36 (35)	1.7	0.91	1.7
Parent[f]	0.016		1.4	1.00	1.0

[a] The quantum yields were measured at 254 nm in methanol for the total diene production. [b] Slopes of Stern–Volmer plots for 2,5-dimethyl-2,4-hexadiene quenching of the fragmentation (r) and fluorescence (f), respectively. [c] Rate constants for fluorescence calculated from the absorption spectrum. [d] The relative intensities at the maximum (288 nm) in the fluorescence spectrum. [e] Relative rates of the fragmentation calculated from the equation $k_r/k_{ro} = \Phi_r\Phi_{fo}k_f/\Phi_{ro}\Phi_f k_{fo}$. See ref 10. [f] Unsubstituted 1-phenyl-3-phospholene oxide.

Quantum yields of the fragmentation at 254 nm were determined and are listed in Table I. Since quantum yields are not always an indication of relative rates, the relative rates[10] of the fragmentation were calculated using absorption and fluorescence data (Table I).

The lack of stereospecificity in the present reaction is reminiscent of other closely related photoextrusion reactions,[3] whereas thermal processes have been found to be stereospecific in related systems.[2] The apparent photochemical nonstereospecificity has been interpreted as a consequence of dual linear and nonlinear concerted pathways for photodecarbonylation[3a] of cyclopentenone and concerted loss of SO_2 followed by SO_2-catalyzed isomerization of the resulting dienes in the photolysis[3b] of sulfolene. The present stereochemical and kinetic results, indicating increased stereospecificity and reactivity of the cis isomers relative to the trans isomers, can be attributed to steric forces operative during the concerted bond reorganization necessary for phosphinidene oxide extrusion. As disrotatory[11] bond rotation in c,c-**1** would commence to give c,c-**3**, two methyl groups are effectively brought into close proximity to the phenyl group. The conrotatory counterpart to give *t,c*-**3** also suffers from 1,2-phenyl–hydrogen and nonbonded methyl–hydrogen interactions occurring in the rotation. Such repulsive forces, which are absent when disrotation to *t,t*-**3** is effected, are apparently sufficient to raise the energy of activation associated with rotation to *t,c*- and *c,c*-**3** to extent which permits exclusive formation of *t,t*-**3**. Similar repulsive forces also determined the mode of fragmentation of *c*-**2**, in spite of the fact that such steric demand seems to be less severe. *trans*-1,3-Pentadiene probably is formed via the disrotatory process since the alternative conrotatory pathway suffers from a concomitantly high degree of steric interaction.

The much lower degree of product specificity (*t,t*-**3**/c,c-**3** $\approx$ 2) from *t,t*-**1** might be explained as a steric effect superimposed on the concerted motion. Disrotatory opening to *t,t*-**3** from *t,t*-**1** suffers from substantial repulsive phenyl–hydrogen interaction, while competing disrotation to c,c-**3** has severe nonbonded methyl–methyl repulsion in the transition state. Consequently, conrotatory motion appears to occur as a minor process.[12]

Alternatively, one cannot exclude two-step mechanisms since such considerations can equally be applied to mechanisms involving phosphorus centered biradicals or zwitterions which retain their configuration on the time scale of the reaction.[13] The approximate 100-fold acceleration in decomposition of cis isomer of **1** relative to the trans isomer, along with the slower rate of *t,t*-**1** compared to *t*-**2**, indicates that a steric strain in the transition state for the concerted rotation is substantial. A similar configurational effect of an α-methyl group on the rate of decomposition has been observed in the concerted SO_2 extrusion from sulfolene.[2e] The larger rate enhancement by β-methylation compared to cis α-methylation in the present reaction is rather unusual since alkylation in the β position markedly reduced the rate of the thermal SO_2 extrusion[2e] by stabilizing the starting sulfolene. The rate of α cleavage to give biradicals is enhanced only by α-methylation in the photolysis[14] of cycloalkanone derivatives. It would appear that product (diene) stabilities have some influence on the transition state since emission and absorption data seem to exclude the possible destabilization of reacting excited state by β-methylation.

The present evidence is not yet conclusive as to which mechanisms are operative and further work is required to distinguish between the possibilities.

Acknowledgments. This research is supported in part by a grant from the Japan Ministry of Education. The authors wish to thank Professor L. D. Quin for sending us ^1H NMR spectra of authentic 3-phospholene oxides and Professor J. E. Gano for his helpful discussions.

References and Notes

(1) H. Tomioka and Y. Izawa, *Tetrahedron Lett.*, 5059 (1973); H. Tomioka, Y. Hirano, and Y. Izawa, *ibid.*, 1865 (1974).
(2) For stereochemical studies of thermal five-membered ring cheletropic reactions, see (a) S. D. McGregor and D. M. Lemal, *J. Am. Chem. Soc.*, **88**, 2858 (1966), and references cited therein; (b) W. L. Mock, *ibid.*, **88**, 2857 (1966); (c) D. M. Lemal and S. D. McGregor, *ibid.*, **88**, 1335 (1966); (d) J. E. Baldwin, *Can. J. Chem.*, **44**, 2051 (1966). (e) W. L. Mock, *J. Am. Chem. Soc.*, **97**, 3666, 3673 (1975), and references therein.
(3) For photochemical five-membered-ring cheletropic reactions, see (a) J. Saltiel and L. Metts, *J. Am. Chem. Soc.*, **89**, 2232 (1967); (b) T. R. Darling, J. Pouliquen, and N. J. Turro, *ibid.*, **96**, 1247 (1974).
(4) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Academic Press, New York, N.Y., 1970.
(5) L. D. Quin and T. P. Barket, *J. Am. Chem. Soc.*, **92**, 4303 (1970).
(6) Configurational assignments for the isomeric 3-phospholene oxides are based on the NMR spectra.
(7) Aliquots were removed at 1-min intervals and analyzed by GLC on a 3-m column packed with 10% β,β'-oxydipropionitrile on Diasolid L at 32 °C.
(8) The symbols *c* and *t* in **1** and **2** refer to the cis and trans orientation of phenyl with respect to the methyl(s).
(9) That energy transfer occurred was indicated by the observation of quenching of photoreduction of benzophenone in isopropyl alcohol by **1** and **2**.
(10) S. S. Hixon, *J. Am. Chem. Soc.*, **94**, 2507 (1972).
(11) We could not use the label "linear" or "nonlinear" in this reaction since we do not know the exact nature of the reacting excited state at present.
(12) Other explanation for the difference in the stereochemical results between trans and cis isomers might involve a consideration of conformational ef-

fects. With the all-cis compound, the ground state is already distorted with all carbon substituents in pseudoequatorial position, owing to the Me–Ph nonbonded repulsion along a pathway which could lead to *t,t*-diene. The trans isomer, on the other hand, should exist as two rapidly equilibrating envelope conformers leading to *t,t*- and *c,c*-dienes since there is no such steric demand. We thank referee for drawing our attention on this point.

(13) The fact that even a rather long-lived intermediate can possess sufficient stereochemical integrity has been shown in the SO–diene cycloaddition; see P. Chao and D. M. Lemal, *J. Am. Chem. Soc.*, **95,** 920. 922 (1973).

(14) (a) J. C. Dalton, K. Dawes, N. J. Turro, D. S. Weiss, J. A. Barltrop, and J. D. Coyle, *J. Am. Chem. Soc.*, **93,** 7213 (1971); (b) P. S. Engel, M. A. Schexnayder, H. Ziffer, and J. I. Seeman, *ibid.*, **96,** 924 (1974).

Hideo Tomioka, Yasuji Izawa*

Department of Industrial Chemistry
Faculty of Engineering
Mie University, Tsu, Mie, 514 Japan

Received October 25, 1976

Tape Recordings for Lab Professionals

☐ **TLC—Best for Drug Abuse Screening**
Low-cost alternative to immunoassays

☐ **Microcomputers in Biochemistry Research**
New computers make possible hitherto impossible measurements

☐ **Data Analysis in the Lab**
Today and tomorrow in chem lab data analysis methods

☐ **Use of Enzymes in Immunology**
Detection of bound and free antigen without separation

☐ **Elemental Analysis of Blood: Cancer Patients & Controls**
Detailed comparisons, plus evaluation of analytical methods used

☐ **Polarographic Analysis in Drug Development**
D.P.P. assays of drugs in biological fluids

☐ **Bioanalysis with Membrane Electrode Probes**
Recent advances in electrode development

☐ **In Vivo Electrochemistry for Monitoring Drugs**
Reveals drug's chemical fate in the brain

☐ **Detection of Lipids & Amines in Biological Samples**
Chemical ionization mass spec speeds assay of closely related chemicals

☐ **Pulse Polarography Analysis in Environmental Toxicology**
Solves tough problems in human and animal poisoning

☐ **New Developments in Measurement of Proteins**
Light scattering of immune complexes provides a specific method for proteins in body fluids

☐ **Direct Determination of Drugs in Plasma & Urine**
Non-chromatographic procedure uses chemical ion zation mass spec & stable isotope labeling

☐ **DSC: New Developments in Clinical Analysis**
Differential Scanning Calorimetry—a new analytical tool

☐ **Serum Electrolytes Using Vidicon Flame Spectrometry**
Fast, simultaneous determination of sodium, potassium, and calcium

☐ **Enthalpimetric Analysis of Immunological Reactions**
Thermometric enthalpy titration may revolutionize serological analysis

☐ **Clinical Application of Titration Calorimetry**
Thermochemical methods look very promising for clinical work

☐ **GC Determination of Apomorphine in Urine**
Study of apomorphine metabolism

☐ **Metals in Liver & Kidney Tissue by AA**
AA determination of copper, zinc, magnesium, and calcium

☐ **Bromazepam in Blood by Electron Capture GLC**
A sensitive, specific assay

☐ **Drug Analysis by Direct Multiple-Ion Detection**
Unique computerized system analyses drugs without use of GC

☐ **Thermochemical Analysis in Clinical Chemistry**
Total protein content in biological material can be determined with a precision of better than 0.6%

☐ **Amperometric Measurement of Enzyme Reactions**
Enzyme reactions are monitored by amperometric measurement of substrate depletion, product formation

☐ **Homovanillic Acid by GC-MS**
A simple procedure for HVA in urine

☐ **Kinetic Assay of Enzyme Activity**
Centrifugal fast analyzer provides data at output rate suitable for direct input into small computer

☐ **Automated Photochemical Analysis of Phenothiazines**
Samples were assayed by this system at the rate of 20 per hour

☐ **Automation in Clinical Medicine**
A Bureau of Standards colloquium

☐ **Analysis of Trace Elements**
Sensitive, reliable analytical methods are needed for trace elements

☐ **Electrochemical Approaches to Clinical Instrumentation**
Precise, accurate, highly specific analyses using ultramicro samples

☐ **Standardization of Protein & Enzyme Assays**
Biuret reaction as standard for measuring total serum protein

☐ **Pharmacologic Studies Using GC-MS**
Utility of GC-MS is emphasized in a report of two pharmacologic studies

☐ **Method Evaluation Studies in Clinical Analyses**
Method evaluation studies on precision and accuracy of lab methods

ORDER FROM:
American Chemical Society
1155 16th St., N.W.
Washington, D.C. 20036
ATTN: Dept. AP

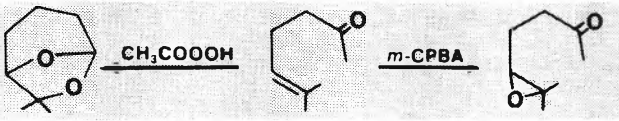
PRICE: $8.95 per title, includes visual materials. **CASSETTES ONLY** **CHECK TITLES DESIRED**
(Allow 4 to 6 weeks for delivery)

Name _____

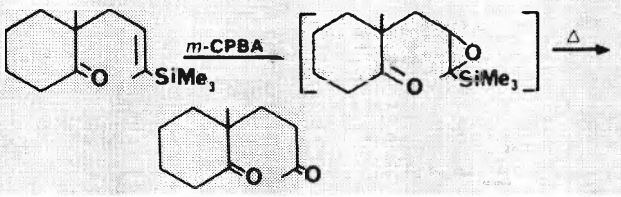
Address _____

m-Chloroperoxybenzoic acid {m-CPBA}

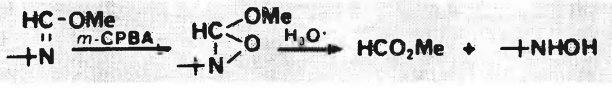
m*-Chloroperoxybenzoic acid** (m*-CPBA**) is a superior reagent for the selective epoxidation of isolated double bonds[1] and acid-sensitive olefins which produce rearranged products with other peracids.[2] Routine use of ***m*-CPBA** for the epoxidation of olefins has been reviewed.[3]



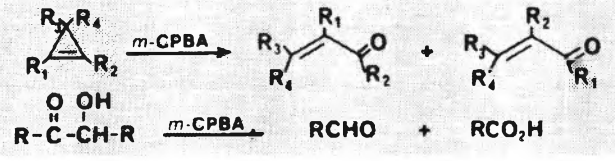
Trimethylsilyl vinyl systems react readily with ***m*-CPBA** to form trimethylsilyl epoxides which act as latent precursors to carbonyl groups.[4]



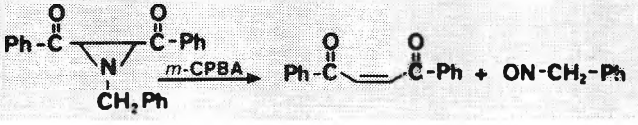
***m*-CPBA** oxidizes disubstituted acetylenes to oxirenes[5,6] and imines to oxazirines;[7] iminoethers can be epoxidized and hydrolyzed to esters and hydroxylamines.[8]



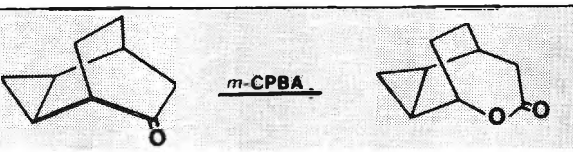
Cyclopropenes are oxidized to α,β-unsaturated ketones or aldehydes;[9] similarly, allenes[10] or α-hydroxy ketones[11] can be converted to aldehydes or acids.



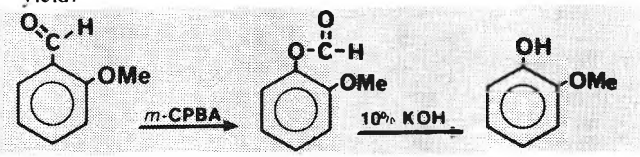
***m*-CPBA** has been used to convert primary amines to nitroalkanes,[12] nucleic acid components to their respective *N*-oxides,[13] and *N*-substituted aziridines to *cis*-olefins.[14]



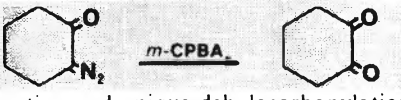
Thioketones are oxidized with ***m*-CPBA** to sulfines,[15] while alkyl mercaptans are converted to alkyl sulfinic acids.[16] ***m*-CPBA** is an excellent reagent for the Baeyer-Villiger oxidation of ketones to esters,[17] acid chlorides to alcohols,[18] and ketals to ortho esters.[19]



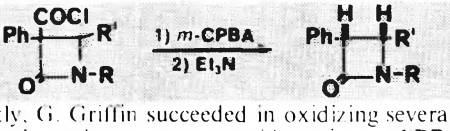
Various mono-, di- and trimethoxybenzaldehydes are oxidized with ***m*-CPBA** to formate esters which can be easily hydrolyzed to the corresponding methoxyphenols in high yield.[20]



α-Diketones are obtained in excellent yield from α-diazoketones by ***m*-CPBA** oxidation. For example, α-diazocyclohexanone is oxidized to 1,2-cyclohexanedione in 99% yield.[21]



An interesting and unique dehalocarbonylation reaction with ***m*-CPBA** provides aryl-β-lactam derivatives from β-lactam acid chlorides.[22]



Recently, G. Griffin succeeded in oxidizing several polynuclear hydrocarbons to arene oxides using ***m*-CPBA**.[23]

References: **(1)** *J. Org. Chem.*, **38**, 3145 (1973); **(2)** *ibid.*, **38**, 2267 (1973); **(3)** *Reagents for Organic Synthesis*, **1**, 1136 (1968); *Org. Syn.*, **49**, 62 (1969); **(4)** *J. Amer. Chem. Soc.*, **96**, 3682 (1974); **(5)** *ibid.*, **86**, 4871 (1964); **(6)** *ibid.*, **92**, 3826 (1970); **(7)** *ibid.*, **87**, 4365 (1965); *ibid.*, **91**, 6078 (1969); *ibid.*, **92**, 4902 (1970); **(8)** *Tetrahedron Lett.*, 1807 (1973); **(9)** *J. Org. Chem.*, **39**, 388 (1974); **(10)** *Acta Chem. Scand.*, **27**, 1421 (1973); **(11)** *ibid.*, **27**, 3365 (1973); **(12)** *J. Org. Chem.*, **31**, 524 (1966); **(13)** *Biochemistry*, **8**, 3059 (1969); *J. Chem. Soc., Perkin Trans. 1*, 333 (1973); **(14)** *Angew. Chem.*, **82**, 395 (1970); **(15)** *J. Chem. Soc., Perkin Trans. 1*, 73, (1973); **(16)** *J. Org. Chem.*, **38**, 4070 (1973); **(17)** *ibid.*, **40**, 2070 (1975); **(18)** *ibid.*, **30**, 3760 (1965); **(19)** *J. Chem. Soc. C*, 2934 (1968); **(20)** *J. Chem. Soc., Perkin Trans. 1*, 1353 (1974); **(21)** *J. Org. Chem.*, **39**, 3295 (1974); **(22)** *Tetrahedron Lett.*, 1811 (1973); **(23)** *ibid.*, in press; *Angew. Chem.*, in press.

C6270-0 ***m*-Chloroperoxybenzoic acid**.....**25g $8.00**
(Write for bulk prices) **100g $23.50; 1kg $180.00**

Aldrich Chemical Company, Inc.

Craftsmen in Chemistry

Corporate Offices:
Aldrich Chemical Co., Inc.
940 W. Saint Paul Ave.
Milwaukee, Wisconsin 53233
U. S. A.

Great Britain:
Aldrich Chemical Co., Ltd.
The Old Brickyard, New Road
Gillingham, Dorset SP8 4JL
England

Belgium/
Continental Europe:
Aldrich-Europe
B-2340 Beerse
Belgium

West Germany/
Continental Europe:
EGA-Chemie KG
7924 Steinheim am Albuch
West Germany