VOLUME 43 AUGUST 4, 1978 NUMBER 16 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; Susan H. Reich, Assistant Editor; Robert J. Palangio and Kenneth E. Phillips, Editorial Assistants; Mark Hackworth, Staff Editor

Magazine and Production Department: Bacil Guiley, Head

Research and Development Department: Seldon W. Terrant, Head

Advertising Office: Centcom, Ltd., 25 Silvan Road South, 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 address below.

Page charges of $70.00 per page may be paid for papers published in this journal. Payment 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.

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

Subscription and Business Information

1978 subscription prices, printed or microfiche, including postage. Microfiche by air mail; printed by surface mail. Printed edition air mail or air freight rates available from Membership & Subscription Services at the address below.

	U.S.	Foreign
Member	$26.00	$36.00
Nonmember	104.00	114.00
Supplementary material (available in microfiche only)	20.00	38.00

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 Membership & Subscription Services. 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 by Membership & Subscription Services.

Microfiche editions of all ACS primary publications, by single volume or entire back issue collection, are available. For additional microfilm (and microfiche) information, contact Microforms Program at the ACS Washington address or call (202) 872-4554.

To order **single issues or back volumes,** printed or microfiche, contact Special Issue Sales at the ACS Washington address, or call (202) 872-4365. Current year single issue $5.00. Prior year single issue $5.00. Back volume $115.00. Foreign postage additional.

Supplementary material mentioned in the journal appears in the microfilm edition. Papers containing supplementary material are noted in the Table of Contents with a ■. See Supplementary Material notice at end of article for number of pages. Orders over 20 pages are available only on 24× microfiche. Orders must state photocopy or microfiche. Full bibliographic citation including names of all authors and prepayment are required. Prices are subject to change.

	U.S.	Foreign
Microfiche	$3.00	$4.00
Photocopy		
1–8	$5.50	$7.00
9–20	6.50	8.00

Single microfiche or paper copies of Supplementary Material may be ordered from Business Operations, Books and Journals Division at the ACS Washington address, or call (202) 872-4559.

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

Editorial Department
American Chemical Society
P.O. Box 3330
Columbus, Ohio 43210
(614) 421-6940, Ext. 3171

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

Notice to Authors last printed in the issue of January 6, 1978

JOCEAH 43(16) 3095–3248 (1978)
ISSN 0022-3263

THE JOURNAL OF Organic Chemistry®

VOLUME 43, NUMBER 16

AUGUST 4, 1978

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.

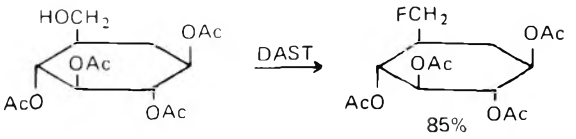
A NEW FLUORINATING REAGENT

DIETHYLAMINOSULFUR TRIFLUORIDE (DAST)

Recently, Middleton[1] and Markovskij and co-workers[2] have shown diethylaminosulfur trifluoride (DAST)[3] to be an excellent reagent for the replacement of the oxygen function in alcohols and carbonyl containing compounds with fluorine.

The use of DAST has several advantages over other fluorinating reagents such as SF_4. The reagent itself is a liquid which can be handled in conventional laboratory glassware. Reactions can be carried out under very mild conditions allowing multi-functional alcohols to be selectively fluorinated. Furthermore, side reactions such as carbonium ion rearrangements and dehydrations are less likely to occur when using DAST.

Primary, secondary and tertiary alcohols can be fluorinated with DAST usually in high yields. Reaction with most substrates is rapid, even at -50°C. DAST is also finding applications in sugar chemistry. It has been utilized in the synthesis of 3-deoxy-3-fluoro-D-glucose[5] and was found to be a mild enough reagent to allow the use of the O-acetyl protecting group in the synthesis of 6-fluoro-6-deoxy-D-glucopyranose[6].



Aldehydes and ketones undergo reaction with DAST, usually at ambient temperature, to give good yields of the *gem*-difluoro derivatives. A particular advantage here is that the reaction can be run under non-acidic conditions rendering it especially useful for acid-sensitive substrates (e.g. pivaldehyde).

$$(CH_3)_3CCHO \xrightarrow[CCl_3F]{DAST} (CH_3)_3CCHF_2 \quad 78\%$$

Carboxylic acids give the acid fluoride[2]. A more recent publication[7] has described the application of DAST to prepare *gem*-difluorosaccharides from sugar aldehydes and ketones in the pyranosyl form.

Tetraalkylthiuran disulfide, triphenylphosphine, triphenylphosphine disulfide and trimethylchlorosilane are also fluorinated with DAST[2].

Available from stock:

11976-8 **Diethylaminosulfur trifluoride** 10g—$25.00; 50g—$88.50

References

1. W. J. Middleton, *J. Org. Chem.*, **40**, 574 (1975).
2. L. N. Markovskij, V. E. Pashinnik and A. V. Kirsanov, *Synthesis*, 787 (1973).
3. S. P. von Halasz and O. Glemser, *Chem. Ber.*, **104**, 1247 (1971).
4. G. A. Olah, M. Nojima and I. Kerekes, *J. Am. Chem. Soc.*, **96**, 925 (1974).
5. T. J. Tewson and M. J. Welch, *J. Org. Chem.*, **43**, 1090 (1978).
6. M. Sharma and W. Korytnyk, *Tet. Lett.*, 573 (1977).
7. R. A. Sharma, I. Kavia, Y. L. Fu and M. Bobek, *Tet. Lett.*, 3433 (1977).

AUTHOR INDEX

THE JOURNAL OF Organic Chemistry®

VOLUME 43, NUMBER 16

AUGUST 4, 1978

Alkyl Effects on Equilibrium Acidities of Carbon Acids in Protic and Dipolar Aprotic Media and in the Gas Phase

F. G. Bordwell,* John E. Bartmess, and Judith A. Hautala[1]

Department of Chemistry, Northwestern University, Evanston, Illinois 60201

Received February 22, 1977

The effects on acidity of substitution of methyl for hydrogen at carbon in 28 weak acids are divided into four types: (a) acid-weakening hyperconjugative and polar methyl effects; (b) acid-strengthening hyperconjugative methyl effects (on ketones, nitroalkanes, and 9-methylfluorene); (c) acid-weakening polar methyl effects (on sulfones and nitriles); and (d) acid-weakening steric methyl effects. Similar methyl effects are observed within groups a–c *in the gas phase, in Me_2SO solution, and in H_2O solution.* σ^*_H is found to be inadequate as a measure of the polar effect of hydrogen. Decreasing acidities of mononitroalkanes, RCH_2NO_2, in the series R = Me, Et, *i*-Pr, *t*-Bu, were observed to be remarkably alike in 50% aqueous MeOH and Me_2SO. These alkyl effects are believed to be the result of a complex blend of hyperconjugative, polar, polarizability, and steric effects. Ph and CH_2=CH groups exhibit substantial conjugative effects which are larger in Me_2SO than in aqueous MeOH. The cyclopropyl group exhibits no observable conjugative effect in the c-$PrCH{=}NO_2^-$ anion. Substitution of R for H in RCH_2NO_2 produces, for the most part, the same relative effects as observed for substitution of R for H in HCH_2NO_2. However, substitution of c-Pr for H in HCH_2NO_2 and $MeCH_2NO_2$ is acid strengthening, whereas substitution of c-Pr for H in c-$PrCH_2NO_2$ is (unexpectedly) acid weakening.

Alkyl groups are omnipresent in organic molecules and often are the determining factor in controlling relative rates or equilibrium positions in organic reactions. Detailed analysis of alkyl effects has proved difficult, however, because they often vary in nature and magnitude depending on the type of atom to which they are attached, the reaction, and the reaction conditions. Investigations of alkyl effects on equilibria involving carbon acids have been limited by the relatively low acidities of such compounds. Nitroalkanes are the only monofunctional carbon acids that are acidic enough to permit equilibrium acidity measurements to be made in aqueous (or other protic) media. As a consequence our knowledge of the effect of alkyl effects on the equilibrium acidities of carbon acids has previously come primarily from measurements made on nitroalkanes. Scientists in the Soviet Union have been particularly active in this area.[2,4,6,8] The data have been correlated over the years with various types of linear free-energy relationships. Data for mononitroalkanes, $R_1R_2CHNO_2$, were originally correlated using Taft σ^* constants to represent the polar effects of alkyl and other substituents, with additional parameters added to take into account hyperconjugative and steric effects.[2] In the past few years this treatment has been modified in that all alkyl groups have been assigned $\sigma^*_R = 0$, following the suggestion of Ritchie,[3] and the data have been correlated with (a) σ^*'s (for alkyl groups containing hetero atoms), (b) two separate steric factors, E'_s (steric hindrance to resonance) and E^0_s (intramolecular steric interactions between remote atoms), and (c) a φ constant, to account for the change from sp^3 to sp^2 hybridization during anion formation.[4] Hyperconjugation was assumed to be absent (or to be included in the φ constant). Another recent analysis, made by selecting data from ten nitroalkanes, RCH_2NO_2 and $R_1R_2CHNO_2$, including points for seven simple alkyl groups, together with points for CH_2CH_2Ph, CH_2CH_2CN, and $CH_2CH_2CH_2NO_2$ groups, employed the original Taft σ^* constants ($\Sigma\sigma^*$) and either a parameter representing the degree of hyperconjugation or one representing the change in hybridization.[5] It was concluded that hyperconjugation rather than changes in C–H and C–C bond energies due to hybridization changes offered the better interpretation of the data.

A correlation of substituent effects on equilibrium acidities in water for 14 alkyl-1,1-dinitroalkanes, $RCH(NO_2)_2$, with Taft σ^* values ($\rho^* = 1.74$) was reported some time ago,[6] but when alkyl groups with heteroatom substituents were added to the list a ρ^* of 3.60 was obtained (28 compounds).[7] The p*K*'s of 70 aliphatic 1,1-dinitroalkanes have been reported recently.[8] For 44 of these, in which the substituent is insulated from the reaction center by a single methylene group, a ρ^* of 3.29 ($r = 0.992$) was obtained.[8] The data for 20 aliphatic 1,1-dinitroalkanes, including examples where the substituent has not been insulated from the acidic site, have also been correlated with the E^0_s, E'_s, φ, and σ^* constants mentioned above.[4]

The variety of parameters used to correlate the acidity data for nitroalkanes and the variety of ways in which these parameters have been combined has led to a complex and confusing picture, to say the least.

Introduction to the Series of Papers

Investigations in our laboratory during the past five years have been concerned not only with alkyl effects on equilibrium acidities of nitroalkanes, but also alkyl effects on equilibrium

0022-3263/78/1943-3095$01.00/0

Table I. Effects of Substitution of Methyl for Hydrogen on Equilibrium Acidities in the Gas Phase and in Solution (Protic and Dipolar "Aprotic" Solvents)

	acid	registry no.	pK	solvent	(pK_H − pK_{Me})[a]	ref
	(a) Acid-Weakening Hyperconjugative and Polar Methyl Effects					
1.	$HCOCH_3$			none	(0.0)	*c*
	$MeCOCH_3$			none	−2.14[b]	*c*
2.	HCO_2H			none	(0.0)	*d*
	$MeCO_2H$			none	−1.6[b]	*d*
3.	HCO_2H		3.75	H_2O	(0.0)	*e*
	$MeCO_2H$		4.75	H_2O	−1.0	*e*
4.	$HCONH_2$		23.5	Me_2SO	(0.0)	*f*
	$MeCONH_2$		25.5	Me_2SO	−2.0	*f*
5.	$H_2C{=}NO_2H$		3.25	H_2O	(0.0)	*e*
	$MeCH{=}NO_2H$		4.41	H_2O	−1.16	*e*
	$Me_2C{=}NO_2H$		5.11	H_2O	−1.86	*e*
6.	$HC(=OH)NH_2^+$		−2.0	H_2O–H_2SO_4	(0.0)	*g*
	$MeC(=OH)NH_2^+$		−0.9	H_2O–H_2SO_4	−1.1	*g*
17.	$H_2C{=}CHCH_2NO_2$	625-46-7	5.22	H_2O	(0.0)	*h*
	$MeCH{=}CHCH_2NO_2$	1809-69-4	5.44	H_2O	−0.22	*h*
	$Me_2C{=}CHCH_2NO_2$	1809-65-0	5.55	H_2O	−0.33	*h*
8.	fluorene		22.6	Me_2SO	(0.0)	*i*
	2-methylfluorene		23.1	Me_2SO	−0.5	*i*
	(b) Acid-Strengthening Hyperconjugative and Polar Methyl Effects					
1.	CH_3NO_2			none	(0.0)	*c*
	$MeCH_2NO_2$			none	0.5[b]	*c*
	Me_2CHNO_2			none	1.2[b]	*c*
2.	CH_3NO_2	75-52-5	17.20	Me_2SO	(0.0)	*h*
	$MeCH_2NO_2$	79-24-3	16.72	Me_2SO	0.68	*h*
	$(CH_3)_2CHNO_2$	79-46-9	16.88	Me_2SO	0.795	*h*
	$(CD_3)_2CHNO_2$	52809-86-6	17.03	Me_2SO	0.645	*h*
3.	CH_3NO_2		10.22	H_2O	(0.0)	*j*
	$MeCH_2NO_2$		8.60	H_2O	1.8	*j*
	Me_2CHNO_2		7.74	H_2O	2.96	*j*
	$(CH_3)_2CHNO_2$		7.475	H_2O		*k*
	$(CD_3)_2CHNO_2$		7.566	H_2O		*k*
4.	CH_3NO_2		11.11	MeOH–H_2O	(0.0)	*h*
	$MeCH_2NO_2$		9.63	MeOH–H_2O	1.7	*h*
	Me_2CHNO_2		8.85	MeOH–H_2O	2.7	*h*
5.	CH_3COCH_3			none	(0.0)	*c*
	CH_3COCH_2Me			none	1.3[b]	*c*
6.	$PhCOCH_3$			none	(0.0)	*c*
	$PhCOCH_2Me$			none	1.2[b]	*c*
7.	$PhCOCH_3$	98-86-2	24.7	Me_2SO	(0.0)	*h*
	$PhCOCH_2Me$	93-55-0	24.4	Me_2SO	0.5	*h*
8.	fluorene		22.6	Me_2SO	(0.0)	*l*
	9-methylfluorene		22.3	Me_2SO	0.60	*l*
	(c) Acid-Weakening Polar Methyl Effects					
1.	$PhSO_2CH_3$			none	(0.0)	*c*
	$PhSO_2CH_2Me$			none	−1.1	*c*
2.	$PhSO_2CH_3$	3112-85-4	29.0	Me_2SO	(0.0)	*h*
	$PhSO_2CH_2Me$	599-70-2	31.0	Me_2SO	−1.8	*h*
3.	$F_3CSO_2CH_3$		18.8	Me_2SO	(0.0)	*m*
	$F_3CSO_2CH_2Me$		20.4	Me_2SO	−1.4	*m*
4.	$CNCH_3$			none	(0.0)	*n*
	$CNCH_2Me$			none	−1.2[b]	*n*
5.	$(CN)_2CH_2$		11.4	H_2O	(0.0)	*o*
	$(CN)_2CHMe$		12.8	H_2O	−1.1	*o*
6.	$(CN)_2CH_2$	109-77-3	11.1	Me_2SO	(0.0)	*h*
	$(CN)_2CHMe$	3696-36-4	12.4	Me_2SO	−1.0	*h*
7.	$CN(Ph)CH_2$		21.9	Me_2SO	(0.0)	*p*
	$CN(Ph)CHMe$		23.0	Me_2SO	−0.8	*p*
8.	$(EtSO_2)_2CH_2$		12.2	H_2O	(0.0)	*q*
	$(EtSO_2)_2CHMe$		14.6	H_2O	−2.1	*q*
9.	$(EtSO_2)_2CH_2$		14.4	Me_2SO	(0.0)	*r*
	$(EtSO_2)_2CHMe$		16.7	Me_2SO	−2.6	*r*
	(d) Acid-Weakening Steric Methyl Effects					
1.	$CH_3CH{=}CHCH_2NO_2$		5.44	H_2O	(0.0)	*h*
	$CH_3CH{=}CHCH(Me)NO_2$	1806-28-6	5.35	H_2O	0.39	*h*
2.	$H_2C{=}C(CH_3)CH_2NO_2$	1606-31-1	7.27	H_2O	(0.0)	*h*
	$H_2C{=}C(CH_3)CH(Me)NO_2$	19031-81-3	7.85	H_2O	−0.28	*h*

Table I (*continued*)

	acid	registry no.	pK	solvent	$(pK_H - pK_{Me})^a$	ref
3.	$H_2C{=}CHCH_2NO_2$		5.22	H_2O	(0.0)	*h*
	$H_2C{=}CMeCH_2NO_2$		7.27	H_2O	−2.1	*h*
4.	$PhCOCH_2CH_3$		24.4	Me_2SO	(0.0)	*h*
	$PhCOCH(Me)CH_3$	611-70-1	26.3	Me_2SO	−1.6	*h*

[a] Corrected statistically for the number of hydrogen atoms at the acidic site. [b] (DH − EA)/1.37. [c] References 27, 51, 58. [d] Reference 52. [e] Reference 53. [f] Reference 9d. [g] Reference 12. [h] Present work. [i] Reference 36b. [j] Reference 54. [k] Reference 5. [l] Reference 50. [m] Reference 17. [n] Reference 51. [o] Reference 55. [p] Reference 56. [q] Reference 57. [r] Reference 59.

acidities of a variety of other weak acids. In this, the first paper in a series, we present equilibrium data for various types of weak acids in protic media and Me_2SO solution, and compare these data with recent data obtained from gas-phase studies. In the second paper in the series the Taft equation is examined in light of data obtained for substituent effects on equilibrium acidities of the nitroalkane system $G(CH_2)_nNO_2$, where G is a heteroatom substituent and n is 1, 2, or 3. Then, in the third paper, the relationship between substituent effects on equilibrium and on kinetic acidities for acyclic saturated nitroalkanes is examined. This examination of Brønsted relationships is continued in the fourth and fifth papers in the series, which are concerned with nitrocycloalkanes and β,γ-unsaturated nitroalkanes, respectively.

Results and Discussion

Effects on Acidity of Methyl vs. Hydrogen. As is apparent from the introduction, the substituent effects of hydrogen and alkyl groups on equilibria (and rates) have been the subject of much discussion and controversy occasioned by their diverse nature and (frequently) small magnitude.[3,9] Traditionally, following Ingold, the major effect of Me (vs. H) has been considered to be electron release to an sp^3 carbon atom by a polar (inductive) and polarizability effect. It is now clear that these effects are enhanced when Me is attached to a (more electronegative) sp^2 carbon atom, and that they are then augmented by hyperconjugation.

Much confusion has arisen from the original assignment by Taft of σ^*_{Me} and σ^*_H "polar" substituent constants of 0.0 and 0.49, respectively, based on ester hydrolysis data of $MeCO_2R$ and HCO_2R.[10] The σ^*_H, σ^*_{Me}, and other σ^*_R constants derived in this way have been used successfully to correlate rate data for many reactions in which R (or H) is attached to a carbon atom that is becoming more electronegative in the transition state by changing hybridization from sp^3 to sp^2 and/or developing a positive charge (e.g., solvolysis reactions).[11] On the other hand, the correlation of rate or equilibrium data for other types of reactions are at least as successful when all σ^*_R constants and σ^*_H are taken as zero.[3,12] (The hydrogen point usually deviates widely in a Taft σ^* plot for such reactions.) Furthermore, derivations of polar constants from RCH_2CO_2H acidities[12] or $RCONH_2$ acidities[9d] lead to small or negligible electron-releasing effects for alkyl, relative to hydrogen. The extent of the confusion with regard to Me and H effects is indicated by the fact that σ^*_{Me} and σ^*_H constants continue to be presented in many recent textbooks on physical organic chemistry without critical comment,[13] despite the fact that there now appears to be general agreement that the difference in polar effects of Me and H are much smaller than is suggested by these constants ($\sigma_I^{Me} = -0.04$; $\sigma_I^H = 0.0$).[14] A recent analysis of alkyl effects on gas-phase acidities appears to have been successful in separating intrinsic inductive effects from polarizability effects.[15] A substantial electron release in the original Taft order, Me < Et < n-Pr < i-Pr < t-Bu, was observed. It now appears that the variable nature of alkyl effects observed in solution[3,9d,12] arise because a variety of other substantial effects are present which can modify and sometimes override the intrinsic inductive effects.

Alkyl effects on acid–base reactions are complicated further by the necessity of considering the alkyl effect on both the undissociated acid and on its conjugate base, and by the frequent presence of steric effects. The position of such equilibria depend on a blend of hyperconjugative, polar, polarizability, steric, and medium effects, which may operate to varying degrees on the undissociated acid and its conjugate base. In Table I we have attempted to group the acids into four classes depending on whether hyperconjugation, polar electron release, or steric effects are *dominant*. In groups a and b hyperconjugative effects of Me are believed to produce dominant acid-weakening and acid-strengthening effects, respectively, augmented or modified by electron-releasing polar effects. In group c an acid-weakening polar effect is believed to be dominant, and in group d acid-weakening steric effects are believed to be dominant. For acids in groups a–c comparable effects are observed in the gas phase, in dipolar aprotic solvents, and in protic solvents, indicating that the effects are independent of medium. (Gas-phase data are not yet available for group d acids.)

Acid-Weakening Hyperconjugative and Polar Methyl Effects. In most of the compounds in group a the Me group is attached to the positive end of the dipole of an sp^2-hybridized carbon atom, i.e., $Me{-}C^+{-}O^- \leftrightarrow Me{-}C{=}O$, or the like. Hyperconjugative and polar stabilization by Me is greater in the undissociated form of the acid than in the anion, causing equilibria such as that shown in eq 1 to be shifted to the left (acid weakening Me effect).

$$MeCO_2H + HCO_2^- \rightleftarrows MeCO_2^- + HCO_2H \quad (1)$$

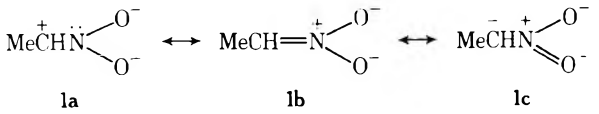
Examination of Table I shows that this effect is independent of medium (gas phase, H_2O, or Me_2SO) and is found in carbon and nitrogen acids, as well as in oxygen acids. Most of the effects are of the order of 1–2 pK units, but the effect is much smaller in $H_2C{=}CHCH_2NO_2$ vs. $MeCH{=}CHCH_2NO_2$ or fluorene vs. 2-methylfluorene, where the charge density of the carbon atom at which Me substitution is made changes but little on removal of the proton.

Acid-Strengthening Hyperconjugative and Polar Methyl Effects. The compounds in group b differ from those in group a in that stabilizing hyperconjugative and polar methyl effects are important in the anion, where Me is attached to an sp^2 carbon atom, but not in the undissociated acid, where Me is attached to an sp^3 carbon atom. As a consequence, the equilibria, such as eq 2, are shifted to the right (acid-strengthening Me effect).

$$MeCH_2NO_2 + H_2C{=}NO_2^- \rightleftarrows MeCH{=}NO_2^- + H_3CNO_2 \quad (2)$$

The postulate of an important hyperconjugative and polar Me stabilizing interaction in the anions for group b compounds is based on the assumption that the negative charge density on the carbon atom to which Me is attached is rela-

tively low. (We will see shortly that an *opposite* Me effect is believed to result when the negative charge density is high.) In valence-bond terminology this requires **1a** to be an important resonance contributor in nitronate anions.[16] (Form **1b** is, of course, the major contributor.)



1a **1b** **1c**

The larger Me effect observed in H_2O than Me_2SO or in the gas phase for the HCH_2NO_2, $MeCH_2NO_2$, Me_2CHNO_2 series may be rationalized by the strong H bonding to oxygen in water, which increases the positive charge density on carbon, and by the high dielectric constant of water, which helps to stabilize charge separation, as in **1a**. It is noteworthy that the acidifying effects of Me are smaller for both nitroalkanes and ketones in Me_2SO than in the gas phase. Perhaps the greater importance of polarizability in the gas phase is the reason.

Acid-Weakening Polar Methyl Effects. The effect of α-Me substitution for nitriles and sulfones (group c in Table I) is the inverse of that for nitroalkanes and ketones (group b in Table I) despite the structural similarities of carbon acids. The acid-weakening α-Me effects are observed in the gas phase and in Me_2SO solution, as well as in water. The effect seems to be independent of the acidity of the parent acid, since it is observed for weak carbon acids ($PhSO_2CH_3$), moderately weak carbon acids ($F_3CSO_2CH_3$ and $PhCH_2CN$), and moderately strong carbon acids ($CNCH_2CN$ and $EtSO_2CH_2SO_2Et$).

The origin of this effect is puzzling. At first we attributed it to steric inhibition of solvation by α-Me in these carbanions where the negative charge is concentrated on carbon to a much greater extent than is true for nitronate or enolate anions. However, the fact that α-Me effects on the gas phase acidities for nitriles and sulfones are also the inverse of those for nitroalkanes and ketones (Table I) rules out this explanation. A steric explanation seems unlikely also because the same α-Me effect is observed for sulfone functions, where the steric effect is high, as for the cyano function where steric demands are negligible. There is evidence that α-sulfonyl carbanions, as well as α-cyano carbanions, are planar,[17] which rules out a difference in hybridization between these carbanions and α-nitro or α-keto carbanions as a cause for the reversal of Me effects. We are left with polar electron release from Me, relative to H, to the sp^2 carbon atom in the anion as the most likely acid-weakening effect. The available evidence points to a small polar effect of this kind in solution when Me is attached to an sp^3 carbon atom[14] and an appreciable effect in the gas phase.[15] These effects would be expected to be enhanced when Me is attached to an sp^2 carbon atom, as in α-Me sulfonyl and α-Me cyano carbanions. This destabilizing effect may be offset to some degree by a stabilizing hyperconjugative effect, since there is evidence for such an effect in MeX^- anions (X = O, S, or NH) in the gas phase.[18] Also, the polarizability effect of R in RO^- appears to stabilize in the gas phase,[19] and lesser, but still important polarizability effects appear to be stabilizing in solution, at least toward cations.[20] Polarizability is a short-range force, falling off as $1/r^4$,[19] and therefore should provide the greatest acid-strengthening Me effect for the most localized carbanions (group c). The observed effect is, however, exactly the opposite to that predicted by anionic hyperconjugation[18] or by polarizability.[19] We conclude that the destabilizing effect observed has its origin in electrostatic repulsion between Me and the anionic site.[15]

Analysis on the Basis of Thermochemical Data. These acidities may also be analyzed in terms of the thermochemistry for the corresponding gas-phase acidities.[19] For the carbon acid GCH_3, its gas-phase enthalpy of heterolytic cleavage, eq 7, can be determined from the C–H bond energy DH°, the electron affinity EA of $GCH_2\cdot$, and the ionization potential of the hydrogen atom, IP, by means of eq 3–7.[19]

$$GCH_2\text{–}H \rightarrow GCH_2\cdot + H\cdot \qquad DH° \qquad (3)$$

$$GCH_2\cdot + e^- \rightarrow GCH_2^- \qquad -EA \qquad (4)$$

$$H\cdot \rightarrow e^- + H^+ \qquad IP \qquad (5)$$

$$GCH_2\text{–}H \rightarrow H^+ + GCH_2^- \qquad (6)$$

$$\Delta H°_{acid} = DH° - EA + IP \qquad (7)$$

Since IP = 313.6 kcal/mol is common to all GCH_3 systems, the factors determining relative acidity are DH° and EA. In general, α-Me substitution results in a decrease in DH° for the C–H bond both for systems giving localized radicals, such as the alkanes,[21] and for radicals delocalized to phenyl[21,22] or carbonyl.[23] The weakening of the bond is 3–6 kcal/mol in both cases. Since approximately the same effect is seen in such widely differing structures, we assume that this decrease is general to all carbon acids discussed here. The mechanism for this lowering of DH° appears to be radical stabilization by delocalization onto the methyl group, as shown by ESR.[24] This is roughly equivalent to the hyperconjugative interaction noted above. They are not strictly equivalent, since the thermochemical argument ignores any hyperconjugative stabilization in the anion.[18]

Methyl substitution decreases EA for aldehydes and ketones by 2–4 kcal/mol.[25] This can be attributed to methyl stabilization of the radical, as just mentioned.[24,26] For the compounds in group b this acid-weakening effect is overshadowed by a decrease in DH°, but for compounds in group c EA is decreased further by the (larger) destabilizing polar effect of Me on the anion, and the acid-weakening effect wins out. For group a acids Me substitution *increases* DH°, judging from data for $MeCOCH_3$ vs. $HCOCH_3$ ($\Delta DH° = 2$ kcal/mol).[27] The EA also increases (by ~1 kcal/mol for $MeCOCH_2\cdot$ vs. $HCOCH_2\cdot$) but, since the DH° increase is numerically larger, the net Me effect is acid weakening.

Acid-Weakening Steric Methyl Effects. Acid-weakening steric effects are no doubt present in some of the anions derived from compounds in groups a–c, but these effects are believed to be minor. For compounds in group d they become an important or dominant factor. In example 1 in group d we see that the strongly acidifying α-Me effect observed for $MeCH_2NO_2$ vs. HCH_2NO_2 is almost negated for $CH_2{=}CHCHMeNO_2$ vs. $CH_2{=}CHCH_2NO_2$ by a steric effect in the anion. In examples 2 and 3 Me substitution introduces progressively larger steric effects in the anions, and the Me effect becomes acid weakening. (These steric effects are discussed in greater detail in the final paper in this series.) In the series CH_3NO_2, $MeCH_2NO_2$, Me_2CHNO_2 (group b) we saw that the α-Me acidifying effect becomes progressively smaller in water, and that in dimethyl sulfoxide Me_2CHNO_2 is only a slightly stronger acid than $MeCH_2NO_2$. We attribute this trend to the increasing importance of an acid-weakening steric effect and/or a diminution of hyperconjugation. In the ketone series, CH_3COPh, $MeCH_2COPh$, $Me_2CHCOPh$, the first methyl substitution is mildly acid strengthening (group b), but the second is strongly acid weakening (group d). In the latter instance the steric effect is apparently overshadowing the hyperconjugative and polar acidifying Me effects.

Alkyl Effects for RCH_2NO_2 in the Series Me, Et, *i*-Pr, *t*-Bu. The order of acidities for mononitroalkanes, RCH_2NO_2, is Me > Pr > Et > *i*-Pr > H > *t*-Bu (Table II). Remarkably similar effects are observed for this series in 50% (v/v) MeOH–H_2O and in Me_2SO, despite differences in absolute

Table II. Equilibrium Acidities of Nitroalkanes, RCH_2NO_2, in 50% (v/v) MeOH–HOH and in Dimethyl Sulfoxide

R	registry no.	pK	solvent	pK_R − pK_{Me}
H		11.11	50% MeOH–H_2O	1.47
Me		9.63	50% MeOH–H_2O	(0.0)
Et	108-03-2	9.99	50% MeOH–H_2O	0.35
Pr	627-05-4	9.77	50% MeOH–H_2O	0.19
i-Pr		10.38	50% MeOH–H_2O	0.74
t-Bu	34715-98-5	11.40	50% MeOH–H_2O	2.08
c-Pr	2625-33-4	9.41	50% MeOH–H_2O	−0.23
Ph	622-42-4	7.85	50% MeOH–H_2O	−1.73
CH_2=CH		6.29	50% MeOH–H_2O	−3.29
H		17.20	Me_2SO	0.48
Me		16.72	Me_2SO	(0.0)
Et		17.01	Me_2SO	0.29
Pr		16.83	Me_2SO	0.11
i-Pr		17.1 ± 0.3	Me_2SO	0.38
t-Bu		18.13	Me_2SO	1.41
c-Pr		16.53	Me_2SO	−0.19
Ph		12.20	Me_2SO	−4.52
CH_2=CH		11.25	Me_2SO	−5.47

acidities in the two media of about seven powers of ten. The nature of the solvent effects in the two media are markedly different (H bonding only in H_2O and stronger dipole interactions in Me_2SO), but the *relative* effects with substituent changes in R near the acidic site are similar. This appears to be a general characteristic for these two solvents, since it holds true also for substituent effects operating across benzene rings.[28] We can analyze these effects in terms of eq 8.

$$RCH{=}NO_2^- + MeCH_2NO_2 \rightleftarrows RCH_2NO_2 + MeCH{=}NO_2^- \quad (8)$$

Assuming that the stabilizing (or destabilizing) effect will be larger in the anion than in the undissociated acid, we see that Me produces a larger stabilizing effect than other alkyl groups, and a much larger effect than does hydrogen. The Me > H effect is consistent with hyperconjugative stabilization by Me. The larger R groups contribute lesser stabilizing hyperconjugative and/or polar effects. Polarizability evidently plays little role, since it would produce an order opposite to that observed. This is not surprising. Note that acidities in the gas phase for alcohols and thiols increase with increasing alkyl size because of stabilizing polarizability effects on RO^- and RS^- ions,[19,29] but in solution polarizability effects on these anions are overshadowed by other effects and the acidities decrease with increasing alkyl size.

Examination of Table II shows that cyclopropyl, phenyl, and vinyl groups cause acidifying effects, relative to Me, of 0.2, 1.7, and 3.3 pK units, repsectively, in water, and 0.2, 4.5, and 5.5 pK units, respectively, in Me_2SO. The small acidifying effect of c-Pr is consistent with its established small electron-withdrawing polar effect,[30] and points to little or no conjugative effect.[31-34] On the other hand, appreciable conjugative effects for phenyl and vinyl groups are indicated by the data. The conjugative effects are greater in Me_2SO than in H_2O by 2.2–2.8 pK units (3.3–3.8 kcal/mol). In water the strong H bonding to the oxygen atoms in the $PhCH{=}NO_2^-$ and $CH_2{=}CHCH{=}NO_2^-$ nitronate ions shifts the negative charge density toward oxygen and away from carbon. As a consequence, the negative charge density on the α-carbon atom in the anion is greater in Me_2SO than in H_2O, and the conjugative interaction with phenyl or vinyl groups is much greater.[35,36]

Enthalpy and Entropy Data. Thermodynamic data for the ionization of some of the nitroalkanes in various media are collected in Table III. In aqueous solution, methyl substitution decreases both enthalpy and entropy of ionization, with the enthalpic term winning out in determining free-energy trends. The decrease in $\Delta S°$ on methyl substitution is similar to that observed for the carboxylic acid series (HCO_2H, $\Delta S° = -17.2$; $MeCO_2H$, $\Delta S° = -22.1$).[37] This can be attributed to steric disruption of the solvation shell about the acids upon methyl substitution. The solvent effect on the neutral acid is more important than that on the anion.[37,38] The stabilization of negative charge in the nitronate on oxygen due to solvent hydrogen bonding reduces the charge on the carbon. This should reduce the polar destabilization of the carbanion by methyl, increasing EA and $\delta\Delta H°$ thereby, as observed. In Me_2SO, the lack of hydrogen-bond donation by solvent should increase charge on carbon, resulting in more balance between polar and hyperconjugative effects, and reduce $\delta\Delta H°$ with α-Me substitution. The non-monotonic trends in $\Delta H°$ and $\Delta S°$ can be ascribed to varying solvation effects on acid and nitronate. The first Me, as in H_2O, decreases $\Delta S°$ by the reason given above; the second Me may reverse the trend by increasing the interaction with solvent to the point where it now affects the less sensitive anion.[37,38] The higher entropy values observed in Me_2SO than in water are consistent with less solvent orientation, but the values are much lower than with most other carbon acids, which have entropies of ionization near zero in Me_2SO.[39]

Table III. Enthalpy and Entropy of Ionization of Some Nitroalkanes[a]

nitroalkane	$\Delta H°$ (H_2O)[b]	$\Delta S°$ (H_2O)[b]	ΔH_i (Me_2SO)[c]	ΔS_i (Me_2SO)[d]
CH_3NO_2	5.9 ± 1	−27 ± 2	20.15	−11
$MeCH_2NO_2$	2.4 ± 1	−31 ± 2	18.3	−15
Me_2CHNO_2	0.1 ± 1	−35 ± 2	19.9	−11

[a] ΔH in kcal/mol; ΔS in eu. [b] T. Matsui and L. G. Hepler, *Can. J. Chem.*, **51**, 1941, 3789 (1973). [c] E. M. Arnett, unpublished results privately communicated. [d] From $\Delta S_i = (\Delta H_i - 2.3RT\ pK)/T$.

Alkyl Effects in Disubstituted Nitroalkanes, $R_1R_2CHNO_2$. In the series CH_3NO_2, $MeCH_2NO_2$, Me_2CHNO_2 the second Me effect is acidifying, but less so than the first. The lesser effect may be due to a saturation of the hyperconjugative effect,[36] or to steric hindrance to solvation. (Examination of a scalar molecular model of $Me_2C{=}NO_2^-$ indicates slight steric inhibition of rotation of Me.) From the results in Table II we can expect hyperconjugative and/or steric hindrance to solvation effects of R on the anion to de-

Table IV. Effect of Alkyl Substitution into Alkylnitromethanes, RCH_2NO_2, in 50% MeOH–H_2O

nitroalkane	registry no.	pK	ΔpK^a
$MeCH_2NO_2$		9.63	(0.0)
Me_2CHNO_2		8.85	1.08
$MeCH_2NO_2$		9.63	(0.0)
(Me)(c-Pr)$CHNO_2$	2625-38-9	8.73	1.20
(Me)(i-Pr)$CHNO_2$	2625-35-6	9.73	0.20
$EtCH_2NO_2$		9.99	(0.0)
Et_2CHNO_2	551-88-2	10.17	0.12
$PrCH_2NO_2$		9.77	(0.0)
Pr_2CHNO_2	2625-37-8	9.85	0.22
i-$PrCH_2NO_2$	625-74-1	10.38	(0.0)
i-Pr_2CHNO_2	66291-08-5	11.0	−0.32
c-$PrCH_2NO_2$		9.41	(0.0)
c-Pr_2CHNO_2	2625-39-0	10.67	−0.96

[a] pK(RCH_2NO_2) − pK($RR'CHNO_2$) statistically corrected for the number of acidic hydrogen atoms.

crease with increasing size when a second R group is substituted for a hydrogen atom in RCH_2NO_2. The effect of i-Pr vs. Me should be acid weakening by 0.75 pK units on this basis. Examination of Table IV shows that substitution of Me for H in $MeCH_2NO_2$ increases the acidity by 0.88 pK units more than does substitution of i-Pr for H, in close agreement with the effect anticipated. Substitutions of Et for H in $EtCH_2NO_2$ or Pr for H in $PrCH_2NO_2$ are also slightly acid strengthening when statistical factors are taken into account (Table IV). On the other hand, substitution of i-Pr for H in i-$PrCH_2NO_2$ causes a slight acid-weakening effect. This is surprising, since examination of a model of i-$Pr_2C{=}NO_2^-$ does not indicate much interaction between the i-Pr groups, whereas there is severe crowding in i-Pr_2CHNO_2, which is relieved by formation of the anion. On this basis we might have expected the steric effect to be acid strengthening. Increased steric hindrance to solvation in the anion appears to be the most likely cause for the acid-weakening effect observed. The 1 pK unit lower acidity of c-Pr_2CHNO_2 vs. c-$PrCH_2NO_2$ is also surprising in view of the 1.3 pK unit *higher* acidity of (Me)(c-Pr)$CHNO_2$ vs. $MeCH_2NO_2$. Apparently there is some kind of a destabilizing interaction between the c-Pr groups in the c-$Pr_2C{=}NO_2^-$ anion. Presumably this destabilizing effect has an electronic origin, since models indicate that c-Pr is smaller than i-Pr sterically.

Experimental Section[41]

Materials. Except for some of the nitroalkanes, the compounds listed in Tables I–IV upon which measurements were made are commercially available. They were carefully purified (99+%) prior to measurements.

Nitroalkanes not available commercially were prepared from the corresponding oximes by oxidation with peroxytrifluoroacetic acid according to the method of Emmons and Pagano.[42]

Reaction times of 1.5–5 h were employed except for 2-methyl-1-nitropropane, 2,2-dimethyl-1-nitropropane, 3-methyl-2-nitrobutane, and 2,4-dimethyl-3-nitropentane, which required 24-h reaction times to obtain satisfactory yields. The nitroalkenes were prepared from the corresponding bromides or chlorides by the method of Kornblum and Ungande.[43] The purity of all compounds synthesized was at least 99% as evidenced by vapor-phase chromatography.

Aldehydes and Ketones. Cyclopropanecarboxaldehyde was prepared from reagent grade cyclopropyl cyanide by the method of Smith and Rogier.[44] Dicyclopropyl ketone was prepared from butyrolactone by the method of Hart and Curtis.[45] All other ketones and aldehydes were commercially available.

Oximes. The oxime of cyclopropanecarboxaldehyde was prepared by the method of Roberts and Chambers,[46] that of dicyclopropyl ketone by the method of Hart and Curtis,[45] and that of cyclopropyl methyl ketone by the method of Perkin and Marshall.[47] All other oximes were prepared by the method of Pearson and Burton.[48] Since the oximes of 2-methylpropanal, 2,2-dimethylpropanal, 3-methyl-2-butanone, 3-pentanone, 4-heptanone, and 2,4-dimethyl-3-pentanone are liquids, the following isolation procedure was employed for these oximes. A large portion of the ethanol was removed from the reaction mixture by distillation, and the residue was extracted with three 50-mL portions of ether. The combined ether extracts were dried ($MgSO_4$) and concentrated. The residue was distilled to yield the desired oxime.

pK Determinations. The pK's in 50% (v/v) MeOH–H_2O were determined at 23 ± 1 °C by the potentiometric partial neutralization technique described previously.[49] The pH measurements were performed on either a Sargent Model D recording titrator equipped with a Corning triple purpose glass electrode and a Corning calomel reference electrode, or on a Sargent Model DR digital readout pH meter equipped with a Corning semimicro combination electrode. A period of 1–12 h was necessary for attainment of equilibrium. The pK's in Me_2SO were determined by the indicator method described previously.[50]

Acknowledgment. We are grateful to the National Science Foundation and the National Institute of Health for support of this work. We are indebted to Walter S. Matthews and Zafra Margolin for most of the acidity measurements in Me_2SO solvent. We are also indebted to Professor Robert W. Taft for a number of helpful comments.

References and Notes

(1) National Institutes of Health Predoctoral Fellow, 1967–1970.
(2) (a) V. M. Belikov, A. Tavlik, and C. B. Korchemnaye, *Org. React.*, **2** (1), 20 (1965); (b) A. Pihl, V. Timotheus, A. Pihl, and A. Tavlik, *ibid.*, **2** (4), 25 (1965).
(3) C. D. Ritchie, *J. Phys. Chem.*, **65**, 2091 (1961); C. D. Ritchie and W. F. Sager, *Prog. Phys. Org. Chem.*, **2**, 323 (1964).
(4) A. J. Talvik and V. A. Palm, *Org. React.*, **11** (2), 287 (1974).
(5) A. J. Kresge, D. A. Drake, and Y. Chiang, *Can. J. Chem.*, **52**, 1889 (1974).
(6) V. I. Slovetskii, S. A. Shevelev, V. I. Erashko, L. I. Biryukova, A. A. Fainzil'berg, and S. S. Novikov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 655 (1966).
(7) M. E. Sitzmann, H. G. Adolph, and M. J. Kamlet, *J. Am. Chem. Soc.*, **90**, 2815 (1968).
(8) I. V. Tselinsky, A. S. Kosmynina, V. N. Dronov, and I. N. Shokhor, *Org. React.*, **7**, 65 (1970).
(9) (a) W. M. Schubert, R. B. Murphy, and J. Robbins, *Tetrahedron*, **17**, 199 (1967); for more recent discussions see: (b) M. Charton, *J. Am. Chem. Soc.*, **97**, 3691 (1975); (c) A.-J. MacPhee and J.-E. Dubois, *Tetrahedron Lett.*, 2471 (1976); (d) F. G. Bordwell and H. E. Fried, *ibid.*, 1121 (1977).
(10) R. W. Taft, "Steric Effects in Organic Chemistry", M. S. Newman, Ed., Wiley, New York, N.Y., 1956, Chapter 13.
(11) (a) Many of the examples in ref 10, pp 608–609, are of this type; (b) A. Streitwieser, "Solvolytic Displacement Reactions", McGraw-Hill, New York, N.Y., 1962, pp 122–126; (c) T. W. Bentley, S. H. Liggero, M. A. Imhoff, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **96**, 1970 (1974); (d) J.-E. Dubois and E. Goetz, *J. Chim. Phys.*, **63**, 780 (1966).
(12) J. Hine, "Structural Effects on Equilibria in Organic Chemistry", Wiley-Interscience, New York, N.Y., 1975.
(13) R. D. Gilliom, "Introduction to Physical Organic Chemistry", Addison-Wesley, Reading, Mass., 1970; J. A. Hirsch, "Concepts in Theoretical Organic Chemistry", Allyn and Bacon, Boston, Mass., 1974; J. M. Harris and C. C. Wamser, "Organic Reaction Mechanisms", Wiley, New York, N.Y., 1976; T. H. Lowry and K. S. Richardson, "Mechanism and Theory in Organic Chemistry", Harper and Row, New York, N.Y., 1976.
(14) S. Ehrenson, R. T. C. Brownlee, and R. W. Taft, *Prog. Phys. Org. Chem.*, **10**, 1 (1968).
(15) R. W. Taft, M. Taagepera, J. L. M. Abboud, J. F. Wolf, J. E. Bartmess, and R. T. McIver, Jr., unpublished results privately communicated.
(16) The importance of contributors like **1a** is indicated by the failure of the proton NMR signal at the γ-carbon atom in $CH_2{=}CHCH_2NO_2$ to be shifted upfield on conversion to its nitronate anion, $CH_2{=}CHCH{=}NO_2^-$. (See the final paper in this series.)
(17) F. G. Bordwell, N. R. Vanier, W. S. Matthews, J. B. Hendrickson, and P. L. Skipper, *J. Am. Chem. Soc.*, **97**, 7160 (1975).
(18) D. J. DeFrees, J. E. Bartmess, J. K. Kim, R. T. McIver, Jr., and W. J. Hehre, *J. Am. Chem. Soc.*, **99**, 6451 (1977).
(19) J. I. Brauman and L. K. Blair, *J. Am. Chem. Soc.*, **92**, 5986 (1970).
(20) J. F. Wolf, J. L. M. Abboud, and R. W. Taft, *J. Org. Chem.*, **42**, 3316 (1977).
(21) K. W. Egger and A. T. Cocks, *Helv. Chim. Acta*, **56**, 1516 (1973).
(22) S. Furuyama, D. M. Golden, and S. W. Benson, *Int. J. Chem. Kinet.*, **3**, 237 (1971).
(23) R. K. Solly, D. M. Golden, and S. W. Benson, *Int. J. Chem. Kinet.*, **2**, 11 (1970).
(24) R. O. C. Norman and B. C. Gilbert, *Adv. Phys. Org. Chem.*, **5**, 53 (1967).
(25) A. H. Zimmerman, K. J. Reed, and J. I. Brauman, *J. Am. Chem. Soc.*, **99**, 7203 (1977).
(26) F. Bernardi, N. D. Epiotis, W. Cherry, H. B. Schlegel, M-H. Whangbo, and S. Wolfe, *J. Am. Chem. Soc.*, **98**, 469 (1976).
(27) J. B. Cumming and P. Kebarle, *J. Am. Chem. Soc.*, **99**, 5818 (1977). We are indebted to Professor Kebarle for supplying us with a preprint of this

paper prior to publication.
(28) F. G. Bordwell and F. D. Cornforth, *J. Org. Chem.*, **43**, 1763 (1978).
(29) (a) J. E. Bartmess and R. T. McIver, Jr., *J. Am. Chem. Soc.*, **99**, 4163 (1977); (b) R. W. Taft, J. A. Abboud, and J. E. Bartmess, manuscript in preparation.
(30) Y. E. Rhodes and L. Vargas, *J. Org. Chem.*, **38**, 4077 (1973).
(31) Kinetic evidence, based on rates of deuterium exchange for $PhCH_2$-*i*-Pr and $PhCH_2$-c-Pr with *t*-BuOK–Me_2SO-d_6,[32] or relative rates of addition of *i*-PrLi in Et_2O to $PhC(R)=CH_2$,[33] suggests a somewhat greater stabilizing ability for c-Pr vs. *i*-Pr on an adjacent carbanion center. It is difficult to relate such kinetic results to carbanion stabilities, however,[34] even if we accept *i*-Pr as a good model for c-Pr.
(32) M. J. Perkins and P. Ward, *Chem. Commun.*, 1134 (1971).
(33) J. A. Landgrebe and J. D. Shoemaker, *J. Am. Chem. Soc.*, **89**, 4465 (1967).
(34) F. G. Bordwell, W. S. Matthews, and N. R. Vanier, *J. Am. Chem. Soc.*, **97**, 442 (1975).
(35) In the next paper in this series we will see that this greater negative charge density on carbon in the anion causes the equilibrium acidities of nitroalkanes of the type $GCH_2CH_2CH_2NO_2$ to be much more sensitive to the nature of the substituent, G, in Me_2SO than in 50% MeOH–H_2O. These effects are related to the changes in the acidifying effect of Ph in molecules of the type $PhCH_2G$, where G is a strongly acidifying function. Here the relative charge density on carbon in the $PhCHG^-$ anion changes with the nature of G, and the size of the phenyl-acidifying effect changes accordingly. Thus, substitution of phenyl for α-H in weak carbon acids, such as acetonitrile, causes a much larger effect than substitution for α-H in a stronger carbon acid, such as nitromethane. As one progresses from weak to strong carbon acids the progressive decrease (saturation) of the phenyl effect observed has been referred to as a resonance saturation effect.[36] Similarly, we can refer to the diminution of the substituent effects in the present instances in changing from Me_2SO to H_2O solvent as saturation of the substituent effects by solvation.
(36) (a) F. G. Bordwell, J. E. Bares, J. E. Bartmess, G. J. McCollum, M. Van Der Puy, N. R. Vanier, and S. S. Matthews, *J. Org. Chem.*, **42**, 321 (1977); (b) F. G. Bordwell and G. J. McCollum, *ibid.*, **41**, 2391 (1976).
(37) Reference 12, pp 193–199.
(38) I. M. Kolthoff, J. J. Lingane, and W. D. Larson, *J. Am. Chem. Soc.*, **60**, 2512 (1938).
(39) E. M. Arnett, *Faraday Symp. Chem. Soc.*, **No. 10** (1975).
(40) F. G. Bordwell, J. E. Bartmess, G. E. Drucker, Z. Margolin, and W. S. Matthews, *J. Am. Chem. Soc.*, **97**, 3226 (1975).
(41) Additional experimental details may be found in the Ph.D. Dissertation of J. A. Hautala (June, 1971) and J. E. Bartmess (June, 1975).
(42) W. D. Emmons and A. S. Pagano, *J. Am. Chem. Soc.*, **77**, 4557 (1955).
(43) N. Kornblum and H. E. Ungande, *Org. Synth.*, **38**, 75 (1958).
(44) L. I. Smith and E. R. Rogier, *J. Am. Chem. Soc.*, **73**, 4047 (1951).
(45) A. Hart and O. E. Curtis, *J. Am. Chem. Soc.*, **78**, 113 (1956).
(46) J. D. Roberts and V. C. Chambers, *J. Am. Chem. Soc.*, **73**, 3176 (1951).
(47) W. H. Perkin and T. R. Marshall, *J. Chem. Soc.*, 865 (1891).
(48) D. E. Pearson and J. D. Burton, *J. Org. Chem.*, **19**, 957 (1954).
(49) F. G. Bordwell, W. J. Boyle, Jr., and K. C. Yee, *J. Am. Chem. Soc.*, **92**, 5926 (1970).
(50) W. S. Matthews, J. E. Bares, J. E. Bartmess, F. G. Bordwell, F. J. Cornforth, G. E. Drucker, Z. Margolin, R. J. McCallum, G. J. McCollum, and N. R. Vanier, *J. Am. Chem. Soc.*, **97**, 7006 (1975).
(51) J. E. Bartmess and R. T. McIver, Jr., private communication.
(52) R. Yamdagni and P. Kebarle, *J. Am. Chem. Soc.*, **95**, 4050 (1973).
(53) C. K. Ingold, "Structure and Mechanism in Organic Chemistry", 2nd ed, Cornell University Press, Ithaca, N.Y., 1969.
(54) D. Turnbull and S. Maron, *J. Am. Chem. Soc.*, **65**, 212 (1943).
(55) A. Talvik, A. Pihl, H. Timotheus, A. Osa, J. Vira, and V. Timotheus, *Org. React.*, **12**, 135 (1975).
(56) J. E. Bares, Ph.D. Dissertation, Northwestern University, 1976.
(57) R. P. Bell and B. G. Cox, *J. Chem. Soc. B*, 652 (1971).
(58) J. B. Cumming, T. F. Magnera, and P. Kebarle, unpublished data privately communicated. J. E. Bartmess and R. T. McIver have observed a similar order (private communication).
(59) G. E. Drucker, Ph.D. Dissertation, Northwestern University, June, 1978.

The Taft Equation As Applied to Equilibrium Acidities of Nitroalkanes, $G(CH_2)_nNO_2$

F. G. Bordwell* and John E. Bartmess

Department of Chemistry, Northwestern University, Evanston, Illinois 60201

Received February 22, 1977

Equilibrium acidities for 25 nitroalkanes, $G(CH_2)_nNO_2$, with $n = 1, 2$, or 3, are reported in two different solvents. The acidities of nitroalkanes $G(CH_2)_3NO_2$ were found to be reasonably well correlated with Taft $\sigma^*_{CH_2CH_2G}$ constants in 50% (v/v) MeOH–H_2O ($\rho^* = 1.2$) and Me_2SO ($\rho^* = 3.4$). Reversals in acidity order from that predicted by σ^* constants were observed, however, for $PhSO_2$ vs. CN, PhS vs. PhO, CH_3CO vs. HO, and Me vs. H, and it is concluded that substituent effects in the Taft relationship vary with the geometry of the system. The five points examined for nitroalkanes $GCH_2CH_2NO_2$ all deviated widely from the Taft line, which is interpreted to mean that "methylene transmission coefficients" vary with the nature of G and the nature of the system because of changes in conformations. Points for nitroalkanes GCH_2NO_2 deviated widely from the Taft line. The general conclusion is drawn that, although $\sigma^*_{CH_2G}$ (or σ_I) constants give an approximate measure of polar effects, their size and sometimes even their relative order change as the geometry of the system is changed.

Quantitative evaluations of substituent effects on equilibria and rates in aliphatic systems in solution are fundamental to the understanding of organic chemistry, yet progress in this area has been slow. Twenty years ago Taft made an important contribution by applying a Hammett-type linear free-energy relationship based on hydrolysis rates for esters of the type $G(CH_2)_nCO_2R$ [or an equilibrium acidities in water of acids of the type $G(CH_2)_nCO_2H$] where n is 0, 1, or 2.[1] Stated in terms of equilibrium acidity constants the Taft relationship is given by the equation

$$\log (K/K_0) = \Delta pK = \sigma^*\rho^* \quad (1)$$

where σ^* represents the polar (i.e., inductive) effect of G and ρ^* represents the sensitivity of the system to structural changes.

The σ^*'s for hydrogen and alkyl points ($\sigma^*_{Me} = 0$) were derived from $G(CH_2)_nCO_2R$ systems where $n = 0$. Most of the σ^* constants for substituents containing heteroatoms (Cl, F, O, S, etc.) were derived from data where $n = 1$, but in some instances (CCl_3, CO_2Me, and $COCH_3$, as well as Ph and CH=CHMe) σ^*'s were derived from $n = 0$. In three instances ($COCH_3$, Ph, and CH=CHMe) these σ^*_G constants were shown to be related to $\sigma^*_{CH_2G}$ constants by assuming a falloff factor of 2.8, which Branch and Calvin had found useful in correlations of aliphatic acids.[2] This falloff factor (equivalent to a methylene transmission coefficient of 0.36) was also found to be suitable for relating $\sigma^*_{CH_2G}$ and $\sigma^*_{CH_2CH_2G}$ constants when G is Ph or CF_3.

Although the Taft equation has enjoyed considerable success,[3] two fundamental problems have arisen. The first relates to the question of whether or not σ^*_H, σ^*_R, and σ^*_G constants derived from data where H, R, or G is attached to an sp^2 carbon atom can be applied, as Taft did originally, to systems where these substituents are attached to an sp^3 carbon atom.[4] The second relates to the applicability of σ^* constants to systems of differing geometry and the use of methylene transmission coefficients to relate σ^*_G, $\sigma^*_{CH_2G}$, $\sigma^*_{CH_2CH_2G}$, etc., constants. The first of these questions was discussed in the

0022-3263/78/1943-3101$01.00/0

Table I. Equilibrium Acidity Constants of Nitro Compounds, GCH_2NO_2

G	registry no.	σ^* [a]	pK_a (50% MeOH–H_2O) [b]	pK_a (Me_2SO) [c]
$C(CH_3)_3$	34715-98-5	−0.30	11.66 ± 0.07	18.13
$CH(CH_3)_2$	625-74-1	−0.19	10.32	17.1 ± 0.3
$(CH_2)_2CH_3$	627-05-4	−0.115	9.77	16.83
CH_2CH_3	108-03-2	−0.10	9.93	17.01
CH_3	79-24-3	0.0	9.58	16.72
$(CH_2)_2Ph$	22818-69-5	0.08	9.79	16.36
c-Pr	2625-33-4	0.01 [d]	9.35	16.53
$(CH_2)_2OH$	25182-84-7	0.20 [e]	9.65	16.26
$(CH_2)_2COCH_3$	22020-87-7	0.21 [e]	9.60	16.41
CH_2Ph	6125-24-2	0.215	9.82	16.14
$(CH_2)_2SPh$	66291-17-6	0.24 [e]	9.43	15.66
$(CH_2)_2OPh$	66291-15-4	0.30 [e]	9.49	15.76
$CH{=}CH_2$	625-46-7	0.40 [d]	6.29	11.25
$CHPh_2$	5582-87-6	0.405	9.63	15.79
$(CH_2)_2SO_2Ph$	66291-13-2	0.46 [e]	9.28	15.33
$(CH_2)_2CN$	58763-41-0	0.46 [e]	9.33	15.21
H	75-52-5	0.49	11.05 ± 0.04	17.20
$(CH_2)_2NO_2$	6125-21-9	0.50	8.93 (10.29) [g]	14.74
CH_2OH	625-48-9	0.555	10.34	16.30
Ph	622-42-4	0.60	7.87	12.20
COPh	614-21-1	1.7 [f]	5.59	7.7 ± 0.2
SPh	60595-16-6	1.8 [e]	7.3 ± 0.1	11.93
CO_2Et	626-35-7	2.0	6.79	9.25
Br	563-70-2	2.8 [e]	8.7 ± 0.2	12.5 ± 0.1
SO_2Ph	21272-85-5	3.7 [e]	5.69	7.2 ± 0.2

[a] Reference 4. [b] At 23 ± 1 °C with nitroalkane concentrations of ~0.01 M; standard deviation ±0.02, unless otherwise stated. [c] Determined at 23 ± 1 °C by the method described in ref 7; standard deviation ±0.05, unless otherwise stated. [d] From pK(c-$PrCO_2H$) = 1.49 × 10^{-5} [G. Kortüm, W. Vogel, and K. Andrussow, *Pure Appl. Chem.*, **1**, 190 (1960)] and ρ^* = 1.72.[1] [e] Extrapolated from $\sigma^*_{CH_2G}$ using a falloff factor of 2.8.[1] [f] Estimated from σ_m(COPh) and $\sigma^*_{COCH_3}$.[1] [g] Second ionization.

preceding paper in this series. It was concluded that the σ^*_H constant *cannot* be used and that, although σ^*_R constants may represent intrinsic electron-donor properties of alkyl groups, correlations are frequently obscured by other factors. In this paper the question of the applicability of σ^*_G, $\sigma^*_{CH_2G}$, and $\sigma^*_{CH_2CH_2G}$ constants to the nitroalkane system, $G(CH_2)_nNO_2$, which differs appreciably in geometry from the $G(CH_2)_nCO_2R$ system from which these constants were derived, will be examined.

Results

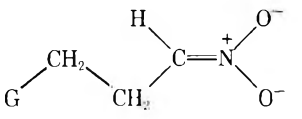
The equilibrium acidity constants were determined potentiometrically in 50% (v/v) methanol–water and by an indicator method in anhydrous dimethyl sulfoxide (Me_2SO). The constants in MeOH–H_2O were corrected for both activity coefficient and true hydrogen ion activity in the mixed aqueous solvent,[5] but not for statistical corrections. Measurements were made at ambient temperature, but since the acidities of nitroalkanes vary only slightly with temperature,[6] this introduces relatively little error. All nitro compounds gave measurements stable with time during 0.5–12 h equilibration save $BrCH_2NO_2$, $PhSCH_2NO_2$, and $PhCOCH_2NO_2$. These all gave yellow solutions and drifting of pH within minutes of the addition of base. The acidities in these cases were computed from the potentiometric measurements after 1–2 min of equilibration with base. This time was found to be sufficient for equilibration of compounds of comparable acidity. For less acidic compounds, the aliquots with differing partial neutralizations gave widely varying calculated pK's immediately upon base addition; after 0.5–2 h equilibration, the values were within 0.02 pK units.

The equilibrium acidities in Me_2SO were determined by the method described previously.[7,8] All compounds behaved well during measurements (±0.05 pK units for differing partial neutralizations) save for those listed as having larger standard deviations. For these, trends in the calculated pK's were observed; this usually indicates decomposition of the anion.

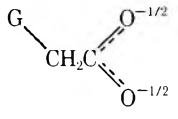
The data for equilibrium acidities in 50% (v/v) MeOH–H_2O and in Me_2SO are summarized in Table I.

Discussion

Taft Correlation. The pK's of 3-substituted nitroalkanes, $GCH_2CH_2CH_2NO_2$, in 50% (v/v) MeOH–H_2O are plotted against $\sigma^*_{CH_2CH_2G}$ constants in Figure 1 (circles). A regression analysis of the plot shows a reasonably good relationship, ρ^* = 1.18 ± 0.30 at the 95% confidence level (r = 0.956; R^2 = 0.914). The smaller size of ρ^* than that obtained for α-substituted acetic acids, GCH_2CO_2H (ρ^* = 1.72), may, at first sight, be surprising, since G is separated from the acidic proton by the same number of atoms in each instance. Examination of the structural formulas for the anions (**1** and **2**) shows,



1



2

however, that in **1** the negative charge is delocalized to oxygen, and is thereby removed two atoms further from G.

Judging from the original work of Taft,[1] and numerous apparently successful extensions,[3] one might have anticipated a better correlation. By separating G from the acidic site by two methylene groups we have minimized steric effects. Also, in plotting the data we have avoided using the original Taft σ^*'s for the hydrogen and methyl points, since these were derived from situations where these groups were attached to an sp^2 carbon atom, rather than an sp^3 carbon atom.[4] (A value of 0.0 was assumed for $\sigma^*_{CH_2CH_2R}$ when R = H, and a value of −0.05 was assumed when R = Me.) The $\sigma^*_{CH_2CH_2G}$ constants used were extrapolated from $\sigma^*_{CH_2G}$ constants, assuming a transmission coefficient (ϵ) of 0.36,[1] but the size of ϵ chosen

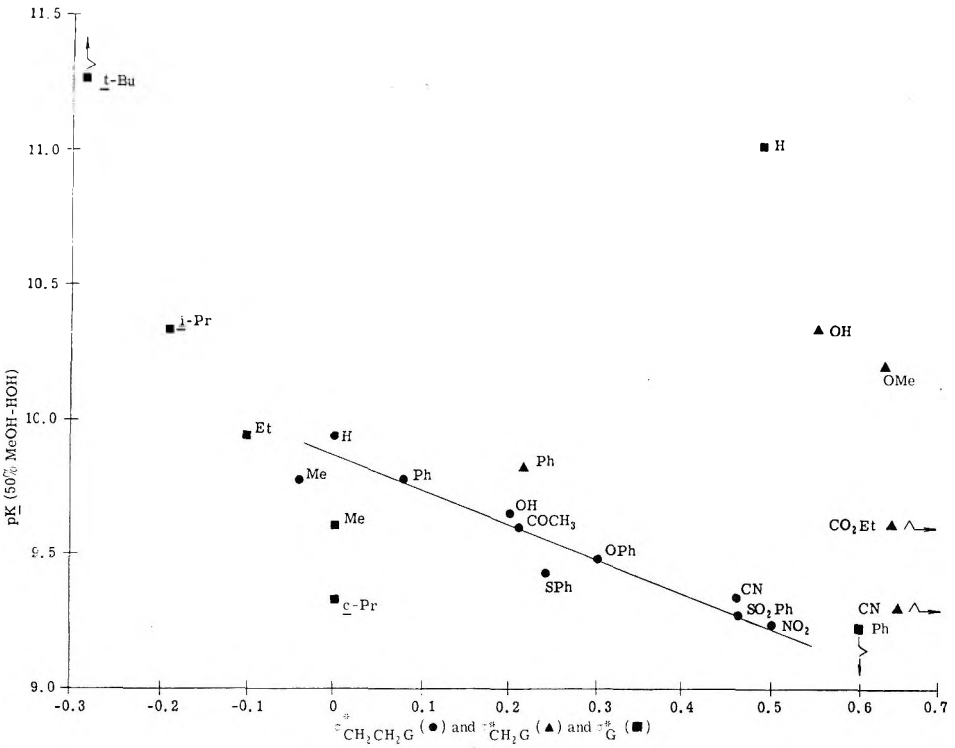


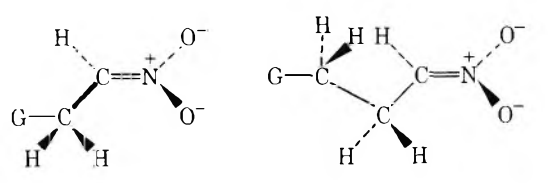
Figure 1. Taft plots of pK's in 50% (v/v) MeOH–H_2O of $GCH_2CH_2CH_2NO_2$ vs. $\sigma^*_{CH_2CH_2G}$ (●), $GCH_2CH_2NO_2$ vs. $\sigma^*_{CH_2G}$ (▲), and GCH_2NO_2 vs. σ^*_G (■). (For $\sigma^*_{CH_2CH_2R}$ a value of 0 was assumed for R = H and a value of −0.05 was assumed for R = Me.)

should not affect the linearity of the plot as long as it has a constant value. On the other hand, it is remarkable that the data fit the line as well as they do when one considers that the Taft equation fails to take into account the geometric relationships between G and the acidic site, which must differ for the $G(CH_2)_nNO_2$ system, relative to the $G(CH_2)_nCO_2R$ systems from which the Taft constants were derived.[9] Inspection of anion structures **1** and **2** shows that the relative geometric relationships of G and the centroid of charge in the anion may vary greatly, depending on the conformations of **1** and **2** to be compared. Current theory indicates that these geometric relationships are of primary importance. The variation of electrostatic effects of this type with geometry appears to be best approximated by the Kirkwood–Westheimer approach using eq 2 and an elliptical cavity model.[10]

$$\Delta pK = (\mu \cos \theta)/r^2D \qquad (2)$$

According to eq 2 the change in acidity (ΔpK) on substitution of G for a γ-hydrogen atom in **1** will depend on: (a) the dipole moment (μ) of G; (b) the cosine of the angle (θ) this dipole makes with the acidic site; (c) the inverse square of the distance, r, between G and the acidic site; and (d) the reciprocal of the effective dielectric constant, D. The high degree of significance in our Taft correlation, as revealed by the statistical analysis of the data, shows that the geometric relationships of varying substituents to the centroid of negative charge must vary in such a way that $\cos \theta/r^2$ is similar in **1** and **2** for each substituent, G. There are some reversals in the relative effects of groups, however. For the $G(CH_2)_2CH_2NO_2$ series we see from Table I that in Me_2SO the acidifying effects are in the order $PhSO_2$ > CN, PhS > PhO, CH_3CO > HO, and Me > H, whereas the reverse order for each of these pairs is observed for GCH_2CO_2H. These differences may be caused by variations in the conformations of the two systems with changes in the nature of G.

Conformational Effects. The importance of geometric relationships in determining the effect of G on acidity in nitroalkanes, $G(CH_2)_nNO_2$, is brought out by comparing substituent effects in 2- and 3-substituted nitroalkanes ($GCH_2CH_2NO_2$ vs. $GCH_2CH_2CH_2NO_2$). For the five substituents for which information is available (Ph, MeO, HO, CO_2Et, and CN) the acidities of the $G(CH_2)_3NO_2$ compounds are equal to or greater than those of the $G(CH_2)_2NO_2$ compounds *despite the presence of one less methylene group in the latter* (Table II). For the compounds of about equal acidity, i.e., those with G equal to Ph, CO_2Et, or CN, this means that the "methylene transmission coefficient" (ϵ) is ~1.0, rather than 0.36. For the $GCH_2CH_2NO_2$ compounds with lower acidities, i.e., when G is MeO or HO, ϵ would have to be negative. These five points deviate markedly from the Taft plot, of course (triangles in Figure 1; the CN and CO_2Et points are off the scale of the plot). Evidently the geometric relationship of G to the centroid of charge in the anion $GCH_2CH{=}NO_2^-$ relative to the anion $GCH_2CH_2CH{=}NO_2^-$ is quite different from the comparable geometric relationship in the $GCH_2CO_2^-$ and $GCH_2CH_2CO_2^-$ anions.[11] Examination of scalar models of the former shows that conformations are available in which the orientation of the C–G dipole and the distance, r, between G and the centroid of charge do not differ greatly (**3** and **4**).



3 **4**

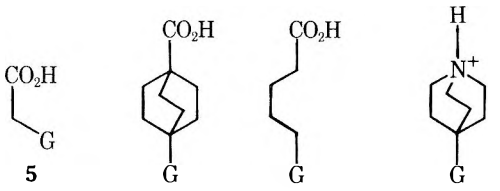
The importance of geometry in determining the size of substituent effects was considered by Taft in his original analysis of polar effects. Taft showed that there was a close correspondence between substituent effects in the acetic acids (**5**) and the 4-substituted bicyclo[2.2.2]octanecarboxylic acids (**6**), supporting his claim that σ^* constants have some generality. At the same time, this close correspondence points up the danger inherent in using "methylene transmission" coefficients. For example, the σ_I's (σ_I = 0.45 $\sigma^*_{CH_2G}$) deter-

Table II. Comparison of pK's of β- and γ-Substituted Nitroalkanes

nitroalkane	registry no.	pK(H_2O)	pK (50% MeOH)[a]	σ^*
$Ph(CH_2)_2NO_2$		8.78[b]	9.82	0.215
$Ph(CH_2)_3NO_2$			9.79	0.08
$MeO(CH_2)_2NO_2$	35461-44-0	9.26[c]	(10.2)	0.52
$MeO(CH_2)_3NO_2$	42472-01-5	8.62[d]	(9.6)	0.18
$HO(CH_2)_2NO_2$			10.34	0.555
$HO(CH_2)_3NO_2$			9.65	0.21
$EtO_2C(CH_2)_2NO_2$	3590-37-2	8.65[d]	(9.6)	0.71
$EtO_2C(CH_2)_3NO_2$	2832-16-8		(9.6)[e]	0.25
$NC(CH_2)_2NO_2$	35461-45-1	8.31[c]	(9.3)	1.3
$NC(CH_2)_3NO_2$			9.33	0.46

[a] Values in parentheses were calculated from pK(H_2O) using an equation, pK(50% MeOH) = (0.97 ± 0.04)pK(H_2O) + 1.19 ± 0.33, which was derived for RCH_2NO_2 with R = i-Pr, n-Pr, Et, Me, $PhCH_2$, H, $O_2NCH_2CH_2$, $HOCH_2$, and Ph (r = 0.995). [b] S. Hiidma, A. Pihl, and A. Talvik, *Reakts. Sposobn. Org. Soedin.*, **3**, 62 (1965). [c] A. Talvik, H. Timotheus, V. Loodmaa, V. Timotheus, T. Sarapan, A. Laht, and V. Kφφbi, *Org. React. (USSR)*, **8**, 409 (1971). [d] A. Talvik, V. Timotheus, and H. Timotheus, *ibid.*, **4**, 478 (1967). [e] Interpolated by Taft equation with ρ^* = 1.18.

mined for **5** and **6** are essentially identical (0.56 vs. 0.58), whereas the σ_I calculated for **6**, or its open-chain analogue (**7**), using σ_I for **5** and a "methylene transmission coefficient" of 0.36 is only 0.025 for **6** or **7**.



5 **6** **7** **8**

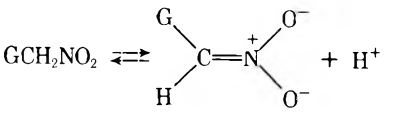
The ability of groups in **6** to exert effects comparable to groups in **5**, despite the fact that in **6** G is separated from the carboxyl group by three additional carbon atoms, is remarkable. Apparently the bulky aliphatic moiety separating G from CO_2H in **6** markedly reduces the effective dielectric constant, D, whereas in **5** (or **7**) the presence of solvent molecules in the molecular cavity leads to a much higher value for D. The favorable orientation of the C–G dipole in **6** is no doubt also a contributing factor. Since these substituent effects have been shown to be primarily field, and not bond-mediated inductive effects, the number of bridges between the substituent and the acidic site should not matter.[10] A similar effect has been observed in the 4-substituted quinuclidine system (**8**), where substituent effects are transmitted *more* readily than in the acetic acid system, despite the intervention of one additional σ bond between the substituent and the acidic site.[12]

Solvent Effects. A plot of the pK's in Me_2SO for nitroalkanes, $GCH_2CH_2CH_2NO_2$, vs. $\sigma^*_{CH_2CH_2G}$ is linear (r = 0.96) and shows about the same amount of scatter as was observed in 50% (v/v) MeOH–H_2O (r = 0.96). Comparison of the plots shows only a few minor changes in the positions of the points. The phenyl group in $Ph(CH_2)_3NO_2$ is relatively more acidifying in the Me_2SO solvent, and this is true also for the phenyl group in $Ph(CH_2)_2NO_2$. The apparent "methylene transmission coefficient" is now slightly on the positive side, rather than being negative as it is in MeOH–H_2O; $HO(CH_2)_3NO_2$ is still more acidic than $HO(CH_2)_2NO_2$ in the Me_2SO solvent, however. Hydrogen-bond effects are absent in Me_2SO, but H bonding does not appear to make the PhO more acidifying than PhS; the latter is *more* acidifying in both solvents.

Since the absolute acidities for most of the nitroalkanes listed in Table I are about 6.5 pK units lower in Me_2SO than in 50% (v/v) MeOH–H_2O, it is clear that large solvent effects are operative. The ρ^* for the $G(CH_2)_3NO_2$ series is 3.4 in Me_2SO vs. 1.2 in MeOH–H_2O, corresponding to a greater than three orders of magnitude sensitivity of the K_a's in Me_2SO to substituent effects. Both this larger ρ^* and the lower acidities in Me_2SO are due largely to the absence of H bonding between the oxygen atoms in the nitronate ion and the Me_2SO solvent. The strong H bonding of MeOH and H_2O to these negatively charged oxygen atoms stabilizes the anion and decreases the negative charge density on carbon in the $CH{=}NO_2^-$ function. In Me_2SO the greater charge density on this carbon atom greatly increases the sensitivity of the anion toward stabilization by the substituents G. [A similar solvent effect is observed in the GCH_2NO_2 series, when G = Ph or $CH_2{=}CH$ (see the preceding paper) and in comparing ρ's in H_2O and in Me_2SO for meta- and para-substituted phenols.]

Perhaps the most striking feature of the data is that, despite large differences in the type and magnitude of the solvent effects of Me_2SO and MeOH–H_2O, the *relative effects with varying substituents are remarkably similar.* Note in particular that in each solvent the PhS substituent is slightly more acidifying than the PhO substituent, although the σ^* constants predict an appreciable difference in the opposite direction. Similarity in relative substituent effects in Me_2SO and in protic solvents appears to be the general rule.[13,14,15]

α-Substituted Nitroalkanes. The points for α substituents deviate widely from the line defined for $G(CH_2)_3NO_2$ compounds in either 50% (v/v) MeOH–H_2O (Figure 1) or in Me_2SO. This is expected since: (a) it is unlikely that Taft σ^*'s derived for substituents attached to sp^3 carbon atoms can be applied to these same substituents when attached to sp^2 carbon atoms;[4] (b) steric effects are enhanced at the α position; and (c) delocalization of the negative charge in the anion by resonance is often possible. Deprotonation of nitroalkanes (or other carbon acids) differs from that of carboxylic acids with respect to a, b, and c, since the hybridization of carbon changes during deprotonation.



When G is c-Pr, Me, Et, or i-Pr the nitroalkanes are appreciably more acidic than when G is t-Bu or H (squares on Figure 1). These alkyl and hydrogen effects have been discussed in a previous paper, as have the effects for G = Ph and $CH{=}CH_2$.[13]

The order of acidifying effects for the other substituents, G, are, with a single exception, in the same order as for methane carbon acids, i.e., PhCO > $PhSO_2$ > EtO_2C > PhS > Ph (Table I). The differences in acidities in Me_2SO for the nitroalkanes, GCH_2NO_2, are much smaller than for the methane carbon acids, GCH_3, as is brought out by comparing

Table III. Comparison of Acidifying Effects in Me_2SO for Nitroalkanes, GCH_2NO_2, and Methane Carbon Acids, GCH_3

G	pK (GCH_3)[a]	ΔpK (GCH_3)	pK (GCH_2NO_2)	ΔpK (GCH_2NO_2)
H	~65[b]	(0.0)	17.2	(0.0)
Ph	~44[c]	~21	12.2	5.0
PhS	~40[d]	~25	11.9	5.3
CO_2Et	~31[e]	~34	9.2	8.0
$PhSO_2$	29.0	~36	7.2	10.0
PhCO	24.7	~40	7.7	9.5

[a] Reference 7 unless otherwise noted. [b] Based on unpublished data of D. Algrim. [c] Reference 14. [d] Estimate based on data in ref 14. [e] Based on unpublished data of H. Fried.

the ΔpK's in Table III. The much smaller ΔpK's for the GCH_2NO_2 acids than the GCH_3 acids are caused by the much smaller concentration of charge on carbon in the $GCH{=}NO_2^-$ anions (resonance saturation effect[15]). Steric effects will play a role in dictating the stabilizing effect in $GCH{=}NO_2^-$ anions, and offer a possible explanation for the reversal of the $PhSO_2$ and PhCO effects.

Summary

It is apparent from this study that the Taft relationship can be applied in only a limited sense to systems of the type $G(CH_2)_nX$, where X is a reactive function or one that activates the α-C–H bond, and G is a substituent. Taft $\sigma^*_{CH_2G}$ (or σ_I) constants can be used only when n is kept constant; they are not applicable in instances where G is attached to an sp^2 carbon atom, and cannot be related quantitatively to σ^*_G or $\sigma^*_{CH_2CH_2G}$ constants by the use of "methylene transmission coefficients". The Taft σ^*_H constant is not applicable and the small effects of alkyl groups are often strongly affected by factors other than the inductive σ^*_R effect. Finally, although $\rho^*_{CH_2G}$ (or σ_I) constants give an approximate general measure of polar effects, their size and sometimes even their relative order changes as the geometry of the sytem is changed. This last statement is strongly supported by the work of Grob and Schlageter on the 4-substituted quinuclidine system.[12]

Experimental Section

Materials. The 50% methanol solvent was made by mixing equal volumes of methanol (Fisher Certified, acetone free) and deionized water. The 50% methanol–water lyate ion solutions were made by diluting aqueous Anachemia Acculute 0.10 M NaOH solution with an equal volume of methanol, followed by further dilution with prepared 50% MeOH–H_2O solvent. The lyate ion concentration was checked by titration against standard acid. The details of Me_2SO purification and measurement of acidity constants in that solvent have been published elsewhere.[7] The pK_a's in 50% MeOH–H_2O were determined by the method of Bordwell, Boyle, and Yee[16] save that an activity coefficient correction of $-\log \gamma^{\pm} = 0.04$[5] and a true hydrogen ion activity correction[5] to the pH of −0.10 have been applied to the reported data.

All of the nitro compounds reported here were purified by fractional distillation to >99% purity, unless otherwise stated. Four of the nitroalkanes were obtained as gifts from Commercial Solvents Corp.: nitromethane (99.99% pure by VPC) and nitroethane (99.92% by VPC) were used as received, while 1-nitropropane and 1-nitrobutane were distilled. Literature methods were followed for the syntheses of 5-nitro-2-pentanone,[17] 2-phenyl-1-nitroethane,[18] 2-nitroethanol,[19] phenylnitromethane,[20] 3-nitropropene,[21] bromonitromethane,[22] benzoylnitromethane,[23] and ethyl nitroacetate.[24] Phenylnitromethane was purified by column chromatography on silica gel with CCl_4 as eluent, followed by Kugelrohr evaporative distillation [70 °C (5 mm)]. Benzoylnitromethane was twice recrystallized from hexane. 2,2-Diphenylnitroethane was a gift of C. J. M. Stirling.

3-Phenyl-1-nitropropane. Following the procedure of Kornblum,[25] 3-phenyl-1-bromopropane (Aldrich) was stirred in DMF for 3 h with 1.5 equiv of sodium nitrite and 1.5 equiv of urea. The mixture was poured into water and extracted with ether, followed by washings

Table IV. Physical Constants of Nitro Compounds, RCH_2NO_2

R	bp, °C (mm)	n^{23}_D	bp, lit., °C (mm)	n^{20}_D, lit.	ref	NMR ($CDCl_3$), δ
CH_3CH_2	131–132	1.3996	130–131.5	1.3994	38	
$CH_3CH_2CH_2$	50–51 (20)	1.4112	152–153	1.4024	39	0.7–2.2 (m, 7 H); 4.30 (t, 2 H)
$(CH_3)_2CH$	65 (50)	1.4070 (21 °C)	71 (65)	1.4069	40	0.95 (d, 6 H); 2.38 (m, 1 H); 4.17 (d, 2 H)
$(CH_3)_3C$	65 (45)	1.4132 (21 °C)	150–151	1.4099 (30 °C)	41	1.05 (s, 9 H); 4.20 (s, 2 H)
c-Pr	80 (30)	1.4375 (21 °C)	71.5–73 (25)	1.4383	42	0.5 (m, 4 H); 1.4 (m, 1 H); 4.20 (d, 2 H)
$Ph(CH_2)_2$	80–81 (0.3)	1.5181	147–148 (11)		43	2.1–2.8 (m, 4 H); 4.30 (t, 2 H); 6.9–7.5 (m, 5 H)
$HO(CH_2)_2$	72–73 (0.3)	1.4450	138–140 (32)		44	2.20 (s, 1 H); 2.23 (quintet, 2 H); 3.80 (t, 2 H); 4.52 (t, 2 H)
$CH_3C{-}O(CH_2)_2$	101–102 (4.5)	1.4420	117–120 (10)	1.4445	17	2.18 (s, 3 H); 2.0–2.6 (m, 4 H); 4.48 (t, 2 H)
$PhS(CH_2)_2$	108–110 (0.1)	1.5695				2.21 (quintet, 2 H); 2.95 (t, 2 H); 4.47 (t, 2 H); 7.0–7.4 (m, 5 H)
$PhO(CH_2)_2$	98–100 (0.3)	1.5220	171–177 (17)		45	2.40 (quintet, 2 H); 4.01 (t, 2 H); 4.56 (t, 2 H); 6.7–7.4 (m, 5 H)
$CN(CH_2)_2$	73–74 (0.1)	1.4502	160 (35)		29a	2.0–2.7 (m, 4 H); 4.45 (t, 2 H)
$PhS{-}O_2(CH_2)_2$	mp 45.0–45.5					2.40 (quintet, 2 H); 3.27 (t, 2 H); 4.57 (t, 2 H); 7.4–8.0 (m, 5 H)
$NO_2(CH_2)_2$	87–88 (0.2)	1.4630	103 (1)	1.4638	28	2.65 (quintet, 2 H); 4.55 (t, 4 H)
$PhCH_2$	85–86 (0.3)	1.5243	73–74.5 (0.15)	1.5270	18	3.20 (t, 2 H); 4.48 (t, 2 H)
$HOCH_2$	84–85 (3.5)	1.4428	94 (10)		20	2.55 (s, 1 H); 3.9–4.2 (m, 2 H); 4.35–4.60 (m, 2 H)
Ph		1.5314		1.5315	46	5.36 (s, 2 H); 7.36 (s, 5 H)
$CH_2{=}CH$	53–54 (55)	1.4270	39–40 (20)	1.4260	21	5.0 (d, 2 H); 5.3–5.5 (m, 2 H); 6.1 (m, 1 H)
Br	68–70 (42)	1.4820	70–72 (45)		22	5.72 (s)
PhCO	mp 105–105.5		mp 105.5		23	5.95 (s, 2 H); 7.5–8.0 (m, 5 H)
PhS		1.5785				5.38 (s, 2 H); 7.1–7.5 (m, 5 H)
$PhSO_2$	mp 76–77		mp 69–72		47	6.65 (s, 2 H); 7.7–8.2 (m, 5 H)
EtO_2C	79–80 (5)		94 (11)	1.4243	48	1.63 (t, 3 H); 4.40 (quartet, 2 H); 5.13 (s, 2 H)

with sodium bisulfite solution and with brine. Drying and removal of solvent gave a 60% yield (by NMR) of crude material. Two fractionations gave >99% pure material.

3-Phenoxy-1-nitropropane. As with the 3-phenyl compound, 3-phenoxy-1-bromopropane (Aldrich) was converted to crude nitro compound in 55% yield and fractionated twice.

3-Thiophenoxy-1-nitropropane. Sodium iodide (1.2 equiv) was refluxed in acetone for 24 h with 3-thiophenoxy-1-chloropropane. Workup identical with that for the 3-phenyl-1-nitropropane reaction gave a 75% yield of crude iodo sulfide. As with the 3-phenyl compound, this was converted to the nitro sulfide in 18% crude overall yield from the chloro sulfide. The dry sodium nitronate salt[26] was prepared and recrystallized from absolute ethanol containing a trace of water. Reprotonation with hydroxylamine hydrochloride,[27] followed by vacuum distillation, gave material >99% pure.

Anal. Calcd for $C_9H_{11}NO_2S$: C, 54.80; H, 5.62. Found: C, 54.95; H, 5.72.

1,3-Dinitropropane and 3-Nitro-1-propanol. As in the 3-thiophenoxy-1-nitropropane synthesis, 1-bromo-3-chloropropane was diiodinated with 2.2 equiv of sodium iodide. The crude diiodopropane was treated with silver nitrite following the method of Kispersky,[28] save that after removal of the silver salts, 1 equiv of methanol was added to hydrolyze the nitrite esters. Removal of solvent after 24 h and distillation at 1 mm gave crude yields of 28% 3-nitro-1-propanol (from hydrolysis of the nitronitrite compound), bp 80–85 °C, and 47% 1,3-dinitropropane, bp 100–116 °C.

4-Nitrobutyronitrile. Iodination of 4-chlorobutyronitrile with 1.2 equiv of sodium iodide, as for the 3-thiophenoxy compound, followed by reaction of the crude iodo compound with silver nitrite,[29] gave a 42% yield of crude product.

3-Phenylsulfonyl-1-nitropropane. The nitro sulfide (1.1 g, 5.8 mmol) and 20 mL (20 mmol) of 30% H_2O_2 were stirred for 2 h in 60 mL of glacial acetic acid at 23 °C, and for 1 h on the steam bath. It was poured into 200 mL of H_2O and extracted with ether, and the combined extracts were washed with $NaHCO_3$ solution and with brine solution. Drying and removal of solvent under reduced pressure, followed by two recrystallizations from ether, gave white prisms, mp 45.0–45.5 °C, in 42% yield.

Anal. Calcd for $C_9H_{11}NO_4S$; C, 47.15; H, 4.84. Found: C, 47.22; H, 4.78.

2-Methyl-1-nitropropane. The oxime of isobutyraldehyde (Chemical SAMPLES Co.) was prepared by the method of Pearson and Bruton,[30] save that a 24-h reflux was employed. The oxime was oxidized by trifluoroperacetic acid[20] employing a 24-h reflux to obtain 42% crude yield.

2,2-Dimethyl-1-nitropropane. As for 2-methyl-1-nitropropane, pivaldehyde (Chemical Samples Co.) was converted to its oxime, and oxidized to the nitro compound in 69% yield for the oxidation step.

Cyclopropylnitromethane. Cyclopropyl cyanide (Aldrich) was reduced to cyclopropylcarboxaldehyde with $LiAlH_4$.[31] The oxime was prepared by the method of Roberts and Chambers[32] and oxidized as for 2-methyl-1-nitropropane, save that refluxing was continued for only 5 h. A 6% overall crude yield was achieved.

Phenylthionitromethane. To 21 mL (0.21 mol) of benzenethiol in 100 mL of pentane at 0 °C was added dropwise with stirring 18 mL (0.24 mol) of sulfuryl chloride over 1 h. The red mixture was stirred 1 h more at 23 °C, then solvent and excess SO_2Cl_2 were removed under reduced pressure. Distillation gave 24 g (80% yield) of benzenesulfenyl chloride as a red liquid, bp 66 °C (4 mm) [lit.[33] 73–75 °C (9 mm)]. This was converted to phenyl benzenethiosulfinate by the addition of 1.25 equiv of sodium benzenesulfinate in small portions over 15 min to the sulfenyl chloride in CCl_4 at 0 °C, followed by 1 h at 23 °C. Filtration and removal of solvent under reduced pressure gave a viscous oil, which upon crystallization from hexane gave a 74% yield of white crystals, mp 35–37 °C [lit.[34] mp 44–46 °C]. Conversion to 4-(phenylthio)morpholine[35] was accomplished in 72% yield, mp 29–33 °C [lit.[35] 33–36 °C].

Following the general procedure of Mukaiyama,[36] in 50 mL of CH_2Cl_2 were stirred 3.9 g (38 mmol) of ethyl nitroacetate and 6.5 g (38 mmol) of 4-(phenylthio)morpholine for 3 h. Removal of solvent under reduced pressure gave a tan salt, which was heated for 45 min on the steam bath in 125 mL of 40% ethanol–water solution, 1 M in KOH. The ethanol was removed under reduced pressure, and the solution was neutralized to pH 7 with 30 mL of 10% HCl solution. To this at 0 °C was added 10 g (0.14 mol) of hydroxylamine hydrochloride in 20 mL of water over 15 min. Ether extraction afforded on workup 5 mL of yellow oil, which was 92% product and 8% diphenyl disulfide by NMR and VPC. Column chromatography on 50 g of silica gel, eluting with CCl_4, gave material >99% pure in the fourth column volume of eluent.

Anal. Calcd for $C_7H_7NO_2S$: C, 49.69; H, 4.17. Found: C, 49.64; H, 4.23.

All attempts at direct benzenesulfenation of nitromethane or nitroethane with Mukaiyama's reagents[36] were unsuccessful.

Phenylsulfonylnitromethane. Acetic acid (10 mL) containing 1.0 g (5.9 mmol) of phenylthionitriomethane and 5 mL (50 mmol) of 30% H_2O_2 was refluxed 1 h. Removal of solvent under reduced pressure followed by crystallization from ethanol–water gave 0.3 g of crystals (25% yield). Recrystallization from hexane gave white needles, mp 78.0–78.5 °C.

Anal. Calcd for $C_7H_7NO_4S$: C, 41.79; H, 3.51. Found: C, 41.66; H, 3.49.

Truce[37] reports this as the product of nitration of phenyl methyl sulfone with amyl nitrate and potassium amide in ammonia: mp 150–150.5 °C. Of his two literature references for mp 151 °C, neither reports this compound, but rather *p*-tolylsulfonylnitromethane, mp 115 °C.

Acknowledgment. We are grateful to the National Science Foundation (GP-32725X) for support of this research. We are indebted to Judith A. Hautala for the preparation of the aliphatic nitroalkanes, RCH_2NO_2, and for the acidity measurements made with these in 50% MeOH–H_2O.

Registry No.—3-Phenyl-1-bromopropane, 637-59-2; 3-phenoxy-1-bromopropane, 588-63-6; 3-thiophenoxy-1-chloropropane, 4911-65-3; 1-bromo-3-chloropropane, 109-70-6; 1,3-diiodopropane, 627-31-6; 4-chlorobutyronitrile, 628-20-6; 4-iodobutyronitrile, 6727-73-7; isobutyraldehyde oxime, 151-00-8; pivaldehyde, 630-19-3; pivaldehyde oxime, 637-91-2; cyclopropylcarboxaldehyde oxime, 66291-30-3; benzenethiol, 108-98-5; benzenesulfenyl chloride, 931-59-9; phenyl benzenethiosulfinate, 1208-20-4; 4-(phenylthio)morpholine, 4837-31-4.

References and Notes

(1) R. W. Taft, "Steric Effects in Organic Chemistry", M. S. Newman, Ed., Wiley, New York, N.Y., 1956, Chapter 13.
(2) G. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry", Prentice-Hall, Englewood Cliffs, N.J., 1941.
(3) J. Shorter, "Advances in Linear Free Energy Relationships", N. B. Chapman and J. Shorter, Eds., Plenum Press, New York, N.Y., 1972, Chapter 2 (221 references).
(4) See J. Hine, "Structural Effects on Equilibria in Organic Chemistry", Wiley-Interscience, New York, N.Y., 1975, pp 89–99, for a lucid presentation.
(5) R. G. Bates, M. Paako, and R. H. Robinson, *J. Phys. Chem.*, **67**, 1833 (1963).
(6) D. Turnbull and S. H. Maron, *J. Am. Chem. Soc.*, **65**, 212 (1943).
(7) W. S. Matthews, J. E. Bares, J. E. Bartmess, F. G. Bordwell, F. J. Cornforth, G. E. Drucker, Z. Margolin, R. J. McCallum, G. J. McCollum, and N. R. Vanier, *J. Am. Chem. Soc.*, **97**, 7006 (1975).
(8) We are indebted to Zafra Margolin and W. S. Matthews for carrying out these measurements.
(9) At the time the Taft relationship was derived the importance of the geometric relationship between G and the acidic site was not apparent, since the polar effect of G was thought to be transmitted mainly through the σ-bond framework. It now appears that very little of the effect is transmitted in this way.[10]
(10) See L. Stock, *J. Chem. Educ.*, **49**, 400 (1972), and references cited therein; S. Ehrenson, *J. Am. Chem. Soc.*, **98**, 7510 (1976).
(11) It must be kept in mind, however, that the constancy of the methylene transmission coefficient $\sigma^*_{CH_2CH_2G}/\sigma^*_{CH_2G}$ was tested by Taft for only three groups (Ph, 0.37; CH=CHMe, 0.36; $COCH_3$, 0.36). Using the data on acetic acids supplied by Charton, together with Taft's data,[1] suggests considerable variation (CF_3, 0.33; Cl, 0.32; Br, 0.40; I, 0.42; MeO, 0.28; CN, 0.32; CO_2Et, 0.38): M. Charton, *J. Org. Chem.*, **29**, 1222 (1964).
(12) C. A. Grob and M. G. Schlageter, *Helv. Chim Acta*, **59**, 264 (1976).
(13) F. G. Bordwell, J. E. Bartmess, and J. A. Hautala, *J. Org. Chem.*, companion paper in this issue (paper 1 in this series); F. G. Bordwell and F. D. Cornforth, *J. Org. Chem.*, **43**, 1763 (1978); unpublished data from this laboratory.
(14) (a) F. G. Bordwell, J. E. Bares, J. E. Bartmess, G. J. McCollum, M. Van Der Puy, N. R. Vanier, and W. S. Matthews, *J. Org Chem.*, **42**, 312 (1977); (b) F. G. Bordwell, J. E. Bares, J. E. Bartmess, G. E. Drucker, J. Gerhold, G. J. McCollum, M. Van Der Puy, N. R. Vanier, and W. S. Matthews, *ibid.*, **42**, 326 (1977); (c) F. G. Bordwell and D. Algrim, *ibid.*, **42**, 1817 (1977).
(15) See ref 14a and 14b and F. G. Bordwell and G. J. McCollum, *J. Org. Chem.*, **41**, 2391 (1976), for examples and discussion of the resonance saturation effect.
(16) F. G. Bordwell, W. J. Boyle, Jr., and K. C. Yee, *J Am. Chem. Soc.*, **92**, 5926 (1970).
(17) H. Shechter, D. E. Ley, and L. Zeldiv, *J. Am. Chem. Soc.*, **76**, 3664 (1954).
(18) H. Shechter, D. E. Ley, and E. B. Roberson, Jr., *J Am. Chem. Soc.*, **78**, 4984 (1956).
(19) A. S. Sopova, V. V. Perekalin, V. M. Lebednova, and O. A. Yurchenko, *Zh. Obshch. Khim.*, **34**, 1185 (1964).
(20) W. D. Emmons and A. S. Pagano, *J. Am. Chem. Soc.*, **77**, 4557 (1955).
(21) N. Kornblum and D. C. Iffland, unpublished work reported in *Org. React.*,

12, 131 (1962).
(22) H. R. Slagh, U.S. Patent 2 632 776; *Chem. Abstr.*, **48**, 1412 (1954).
(23) M. M. Holleman, *Recl. Trav. Chim. Pays-Bas*, **23**, 299 (1904).
(24) V. M. Rodionov, I. M. Machinskaya, and V. M. Belikov, *Zh. Obshch. Khim.*, **18**, 917 (1948); *Chem. Abstr.*, **43**, 127 (1949).
(25) N. Kornblum, H. O. Larsen, R. K. Blackwood, D. D. Mooberry, E. P. Oliveto, and G. E. Graham, *J. Am. Chem. Soc.*, **78**, 1497 (1956).
(26) A. A. Griswold and P. S. Starcher, *J. Org. Chem.*, **30**, 1687 (1965).
(27) N. Kornblum and G. E. Graham, *J. Am. Chem. Soc.*, **73**, 4041 (1951).
(28) J. P. Kispersky, H. B. Hass, and D. E. Holcomb, *J. Am. Chem. Soc.*, **71**, 516 (1949).
(29) (a) L. Henry, *Bull. Acad. R. Belg.*, **36**, 149 (1898); *J. Chem. Soc., Abstr.*, 251 (1899); (b) N. Kornblum and H. E. Ungnade, *Org. Synth.*, **38**, 75 (1958).
(30) D. E. Pearson and J. D. Bruton, *J. Org. Chem.*, **19**, 957 (1954).
(31) L. I. Smith and E. R. Rogier, *J. Am. Chem. Soc.*, **73**, 4047 (1951).
(32) J. D. Roberts and V. C. Chambers, *J. Am. Chem. Soc.*, **73**, 3176 (1951).
(33) H. Lecher and F. Holschneider, *Ber. Dtsch. Chem. Ges.*, **57**, 755 (1924).
(34) F. Klivenyi, *Magy. Kem. Folyoirat*, **64**, 121 (1958); *Chem. Abstr.*, **54**, 16416e (1959).
(35) J. E. Dunbar and J. H. Rodgers, *J. Org. Chem.*, **31**, 2842 (1966).
(36) T. Mukaiyama, *Tetrahedron Lett.*, 5115 (1970).
(37) W. E. Truce, T. C. Klinger, J. E. Parr, H. Feuer, and D. K. Wu, *J. Org. Chem.*, **34**, 3104 (1969).
(38) R. R. Dreisbach and R. A. Martin, *Ind. Eng. Chem.*, **41**, 2876 (1949).
(39) J. G. Miller and H. S. Angel, *J. Am. Chem. Soc.*, **68**, 2358 (1946).
(40) N. Kornblum, B. Taub, and H. E. Ungnade, *J. Am. Chem. Soc.*, **76**, 3209 (1954).
(41) A. P. Howe and H. B. Hass, *Ind. Eng. Chem.*, **38**, 251 (1946).
(42) F. T. Williams, Ph.D. Thesis, The Ohio State University, Columbus, Ohio, 1958, p 65.
(43) J. V. Braun and O. Kruber, *Ber. Dtsch. Chem. Ges.*, **45**, 395 (1912).
(44) L. Henry, *Rec. Trav. Chim. Pays-Bas*, **16**, 193 (1897).
(45) J. V. Braun, H. Deutsch, and A. Schmatlock, *Ber. Dtsch. Chem. Ges.*, **45**, 1252 (1912).
(46) N. Kornblum and W. M. Weaver, *J. Am. Chem. Soc.*, **80**, 4333 (1958).
(47) J. Tröger and E. Nolte, *J. Prakt. Chem.*, [2], **101**, 136 (1920).
(48) K. v. Auwers and L. Harres, *Ber. Dtsch. Chem. Ges.*, **62**, 2287 (1929).

Kinetic and Equilibrium Acidities for Nitroalkanes

F. G. Bordwell,* John E. Bartmess, and Judith A. Hautala[1]

Department of Chemistry, Northwestern University, Evanston, Illinois 60201

Received March 14, 1977

Rates of deprotonation for 20 nitroalkanes, $G(CH_2)_nNO_2$, where n is 1, 2, or 3, catalyzed by lyate ion or by pyridine were measured in 50% (v/v) MeOH–H_2O. The rates were correlated reasonably well by the Taft relationship, but this is believed to be fortuitous for n = 1 or 2. A Brønsted plot for lyate rates vs. equilibrium acidities for n = 3 gave a slope of 1.67 and for pyridine rates gave a slope of 1.89. Rates of deprotonation by lyate ion of seven secondary nitroalkanes, $RR'CHNO_2$, with R or R′ = Me, Et, Pr, *i*-Pr, or c-Pr, were measured in 50% (v/v) MeOH–H_2O. Changes in R (or R′) caused larger effects in kinetic acidities than in equilibrium acidities; these effects were frequently in inverse directions. A three-step mechanism involving a singly H-bonded anion intermediate or a virtual intermediate is postulated to account for the large k_H/k_D isotope effects and "anomalous" Brønsted coefficients observed for the deprotonation of nitroalkanes in protic solvents. Six examples are given from kinetic and equilibrium acidity data where the order of polar effects is PhS > PhO, which is opposite to the order of Taft σ_I constants.

Although there is a wealth of information concerning rates of deprotonation of simple nitroalkanes with varied bases (HO^-, AcO^-, pyridine, etc.),[2-4] relatively little information concerning the effect of introducing heteroatom substituents into the alkyl groups is available. We now present data for rates of deprotonation of nitroalkanes, $G(CH_2)_nNO_2$, where G is a heteroatom substituent and where n = 1, 2, or 3, with lyate ion in 50% (v/v) MeOH–H_2O and with pyridine in 50% (v/v) MeOH–H_2O. These results, together with those on the effect of alkyl substitution into nitromethane, are then compared with the equilibrium acidity data[5] for these compounds in the same solvent.

Results

Rates of deprotonation by lyate ion in 50% (v/v) methanol–water at 15 °C of 20 nitroalkanes of the type $G(CH_2)_nNO_2$, where n is 1, 2, or 3 and G is hydrogen, methyl, or a functional group, were measured by observance under pseudo-first-order conditions of the appearance of nitronate ion absorbance at 225–240 nm. Excellent kinetics were obtained in most instances with correlation coefficients of >0.999 for each run (Table I). The behavior of 3-chloro-1-nitropropane was exceptional in that the infinity absorbance slowly decreased with time, probably due to cyclization to form isoxazoline oxide. Lyate rates were also measured for a number of secondary nitroalkanes, $RR'CHNO_2$. The data are summarized in Table III.

A Taft plot (Figure 1) constructed from the lyate rates for 3-substituted-1-nitropropanes, $G(CH_2)_3NO_2$, vs. $\sigma^*_{CH_2CH_2G}$, with G = H, Ph, OH, SPh, $COCH_3$, OPh, Cl, SO_2Ph, and CN, gave ρ^* = 2.09 ± 0.17 (r = 0.975; R^2 = 0.950; SD = ±0.39 at 95% confidence level). Points for $GCH_2CH_2NO_2$ and GCH_2NO_2 compounds vs. $\sigma^*_{CH_2G}$ and σ^*_G, respectively, are also included in Figure 1, but were not used in the least-squares plot to determine ρ^*.

The rates of deprotonation of the $G(CH_2)_nNO_2$ compounds with pyridine base in 50% MeOH–H_2O were determined by a buffer dilution method, using triiodide ion as a scavenger for the nitronate ion[6a] (Table I). The zero-order disappearance of triiodide is the actual kinetic variable. Iodination of the nitroalkanes does not go to completion,[6b] but is extensive enough to allow successful measurement of rate constants. For 3-substituted-1-nitropropanes, $GCH_2CH_2CH_2NO_2$, with G = H, Ph, OH, OPh, SO_2Ph, and CN, a Taft plot gave ρ^* = 2.27 ± 0.26 (r = 0.957; R^2 = 0.916; SD = ±0.62 at 92% confidence level). Points for 1,3-dinitropropane and 5-nitro-2-pentanone were not included because of complications due to side reactions. The distribution of the other points (Table I) along the line was similar to that shown in Figure 1.

A Brønsted plot (Figure 2) for lyate ion deprotonation in 50% MeOH–H_2O (at 15 °C) vs. equilibrium acidities in 50% MeOH–H_2O (at 25 °C) for $GCH_2CH_2CH_2NO_2$ compounds, with G = H, Ph, OH, $COCH_3$, OPh, SPh, SO_2Ph, and CN, gave α = 1.67 ± 0.19 (r = 0.957). Since the temperature dependence for pK's for nitroalkanes is known to be small,[7] and should be similar for a series such as $G(CH_2)_3NO_2$, the fact that the kinetic and equilibrium measurements were made at temperatures 10 °C apart should not affect α appreciably. The Brønsted α for a plot of pyridine deprotonation rates in 50% MeOH–H_2O (at 25 °C) vs. pK's in 50% MeOH–H_2O (at 25 °C) was 1.89 ± 0.19 (r = 0.965).

The correlations of the (calculated) rates of protonation of

0022-3263/78/1943-3107$01.00/0

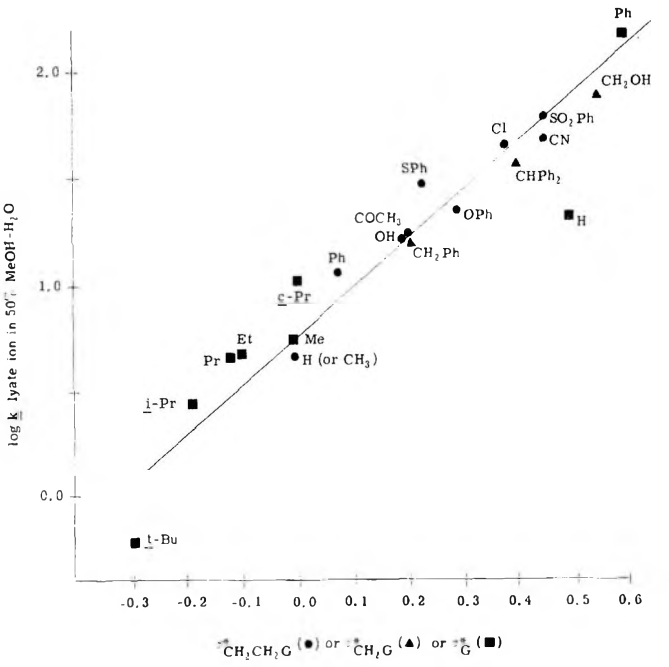


Figure 1. Plot of the logarithm of the rates of deprotonation by lyate ion in 50% MeOH–H_2O at 15 °C for 3-substituted 1-nitropropanes, $GCH_2CH_2CH_2NO_2$, vs. $\sigma^*_{CH_2CH_2G}$ (●). Points for $GCH_2CH_2NO_2$ vs. $\sigma^*_{CH_2G}$ (▲) and GCH_2NO_2 vs. σ^*_G (■) are also shown, but were not used to determine ρ^*.

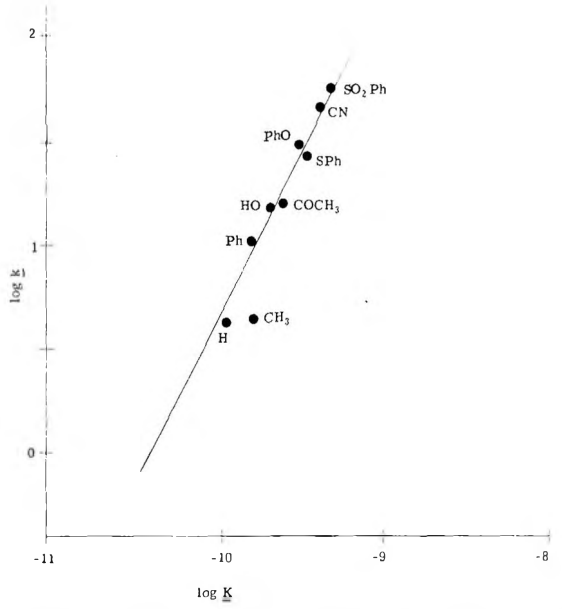


Figure 2. Brønsted plot of the rates of deprotonation by lyate ion vs. pK's for 3-substituted nitroalkanes, $GCH_2CH_2CH_2NO_2$, in 50% (v/v) MeOH–H_2O.

$GCH_2CH_2CH{=}NO_2^-$ on carbon by solvent are less satisfactory than those in the opposite direction. Examination of Table II shows that for protonations of $ArCH{=}NO_2^-$ on carbon there is a general trend for electron-withdrawing groups to accelerate the rate, in agreement with the calculated ρ of 0.45, but that the acceleration is irregular and generally smaller than expected. In particular, we note that the protonation of m-$ClC_6H_4CH{=}NO_2^-$ is as rapid as that of m-$NO_2C_6H_4CH{=}NO_2^-$, despite a sizable difference in the electron-withdrawing power of these two groups. Also, m-$CF_3C_6H_4CH{=}NO_2^-$ is protonated at almost the same rate as $C_6H_5CH{=}NO_2^-$, despite the moderately strong electron-withdrawing properties of the CF_3 group. Similar discontinuities of this type have been observed in protonation of $ArCH{=}NO_2^-$ by the conjugate acids of amine bases.[8] In protonations of $GCH_2CH_2CH{=}NO_2^-$ on carbon we note that, despite the calculated ρ^* of 0.81, there is little or no change in rate for G = Ph, OH, CH_3CO, or PhO for a change in Taft constants of over 0.2 unit. We do not propose to interpret these results except to note that they are consistent with a complex mechanism for the forward and reverse reactions, involving solvent reorganization, such as presented herein.

Table I. Deprotonation Rates of Nitroalkanes, GCH_2NO_2, by Lyate Ion and Pyridine in 50% (v/v) Methanol–Water

G	registry no.	k, $M^{-1}\ s^{-1}$ [a]	10^5k, k, $M^{-1}\ s^{-1}$ [b]
t-Bu	34715-98-5	0.63	0.182
i-Pr	625-74-1	3.3	1.35
n-Pr	627-05-4	4.6	2.68
Et	108-03-2	4.7	2.17
Me	79-24-3	5.5	2.83
$(CH_2)_2Ph$	22818-69-5	10.9	4.08
c-Pr	2625-33-4	10.6	3.95
$(CH_2)_2OH$	25182-84-7	15.4	6.25
$(CH_2)_2COCH_3$	22020-87-7	16.4	
CH_2Ph	6125-24-2	16.3	6.05
$(CH_2)_2SPh$	66291-17-6	27.8	12.2
$(CH_2)_2OPh$	66291-15-4	21.3	9.61
$CHPh_2$	5582-87-6	36.6	
$(CH_2)_2Cl$	16694-52-3	43.8	
$(CH_2)_2SO_2Ph$	66291-13-2	58.5	24.6
$(CH_2)_2CN$	58763-41-0	45.2	21.6
H	75-52-5	30[c]	8.04
$(CH_2)_2NO_2$	6125-21-9		68
CH_2OH	625-48-9	79.3	11.4
Ph	622-42-4	144	147

[a] At 15 °C, with lyate ion as the base; reproducible to ±5%. [b] At 25 °C, with pyridine as the base; reproducible to ±5%. [c] Extrapolated from the rate with hydroxide in water.

Discussion

Taft and Brønsted Correlations for $G(CH_2)_3NO_2$ Nitroalkanes. Let us look first at the data for $G(CH_2)_3NO_2$ nitroalkanes, a system where steric effects appear to be relatively constant, judging from the success of the Taft and Brønsted correlations (Figures 1 and 2). The pyridine rates correlate well with the lyate rates for these compounds (slope = 0.950 ± 0.053 for ten points; r = 0.991). It is noteworthy that the pyridine rates have about the same sensitivity to the effect of the substituent, G, as do the lyate rates, despite the fact that the pyridine rates are over five powers of ten slower. This result is similar to that observed in the deprotonation of $ArCH_2NO_2$ and $ArCH(Me)CH_2NO_2$ systems, where the Hammett ρ values were slightly *larger* for deprotonation by hydroxide ion in water than by amine bases in water.[8] These results can be rationalized, since with amine bases the negative charge developing on carbon in the transition state is offset by the positive charge developing on the nitrogen of the amine base. Furthermore, if H–C bond breaking is greater in the transition state for deprotonation by the amine base, as seems likely (Hammond postulate), more of the negative charge in this transition state (see 2) may be delocalized to the nitro group, making the reaction less sensitive to changes in the nature of G or to substituent effects in Ar.

The Brønsted α for $ArCH_2NO_2$ and $GCH_2CH_2CH_2NO_2$ nitroalkane systems can be expressed in terms of Hammett ρ and Taft ρ^* values,

$$\alpha = \rho_{k_B}/\rho_{K_a} \text{ and } \alpha^* = \rho^*_{k_B}/\rho^*_{K_a}$$

where ρ_{k_B} and $\rho^*_{k_B}$ refer to the sensitivity of the rates of deprotonation in the series of nitroalkanes by a given base, B,

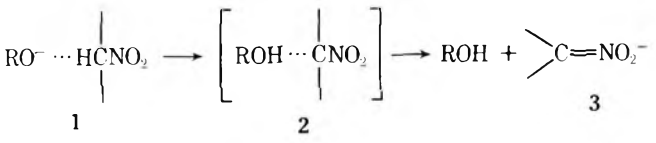
Table II. Relative Rates of Protonation on Carbon of $GC_6H_4CH{=}NO_2^-$ by Solvent Water and of $GCH_2CH_2CH{=}NO_2^-$ by Solvent 50% MeOH–HOH

$GC_6H_4CH{=}NO_2^-$				$GCH_2CH_2CH{=}NO_2^-$			
G	registry no.	σ	$(k/k°)^a$	G	registry no.	$\sigma^*_{CH_2CH_2G}$	$(k/k°)^b$
m-CH_3	66291-11-0	−0.07	1.01	CH_3	34430-24-5	−0.04	0.66
H	12413-18-2	(0.0)	(1.0)	H	25590-60-7	(0.0)	(1.0)
m-F	66322-97-2	0.34	1.01_4	Ph	66291-18-7	0.080	1.69
m-Cl	66291-22-3	0.37	1.25	HO	66291-16-5	0.20	1.73
m-CF_3	66291-21-2	0.43	1.03_5	CH_3CO	66291-14-3	0.21_6	1.64
m-NO_2	66291-20-1	0.71	1.26	PhO	66291-12-1	0.30_6	1.66
p-NO_2	66291-19-8	0.78	1.20_5	CN	66291-10-9	0.46_8	2.40
				$PhSO_2$	66291-09-6	0.47_5	2.80

[a] Calculated from data in ref 8. [b] Calculated from data in the present paper.

to substituent effects, and ρ_{K_a} and $\rho^*_{K_a}$ refer to the sensitivity of the equilibrium acidities in the same nitroalkane series to changes in substituent effects. The same pattern of response is observed in each series, the kinetic acidities being more sensitive to changes in remote substituent effects than are the equilibrium acidities, causing α and α^* to be >1.

For deprotonation by lyate ion $\alpha^* = 2.09/1.25 = 1.67$. For deprotonation by pyridine $\alpha^* = 2.27/1.25 = 1.8$. A simulated reaction coordinate diagram comparing the rates of deprotonation of a nitroalkane, $GCH_2CH_2CH_2NO_2$, and a more acidic nitroalkane, $G'CH_2CH_2CH_2NO_2$, by lyate ion is shown in Figure 3. It is assumed in Figure 3 that substitution of substituent, G, by a more powerful electron-withdrawing substituent, G′, will have essentially no effect on the ground-state energy of the nitroalkane (reactant), but will lower the energy of the transition state and the ground-state energy of the nitronate ion (product). A noteworthy feature of Figure 3 is that the effect of the substitution is *greater* in lowering the transition-state energy than in lowering the energy of the products. The assumption of a greater substituent effect on the transition-state than on the ground-state energies, which presumably correspond to the ground-state energies in the equilibrium, is necessary to explain the greater sensitivity of the kinetic acidity ($\rho^*_{k_1}$) than the equilibrium acidity ($\rho^*_{K_a}$) to substituent changes. The greater sensitivity of rates to substituent changes is understandable in terms of transition state **2** for lyate ion (RO^-; R = H or Me) depro-



1 2 3

tonation, since in **2** the negative charge is developing primarily on carbon, whereas in the reactant ground state (**1**) the negative charge is primarily on the lyate ion base (RO^-), and in the product ground state (**3**) it is primarily on the oxygen atoms of the nitronate ion, two atoms further removed.

In the reverse reaction, protonation of **3** on carbon by solvent, the greater lowering of transition-state energy than product ground-state energy by substitution of a more powerful electron-withdrawing substituent, G′, requires that electron withdrawal in nitronate ion **3** *accelerate* the rate. (A similar situation arises for protonation of $ArCH{=}NO_2^-$ by solvent.[4]) This too is understandable in terms of the formulas **3** and **2**, since protonation on carbon requires that in the transition state negative charge be concentrated on carbon. Electron withdrawal from oxygen in **3** by the substituent will assist this operation.

The most important feature of this analysis is that it is contrary to the assumption of Leffler and Grunwald that in the generalized rate-equilibrium equation

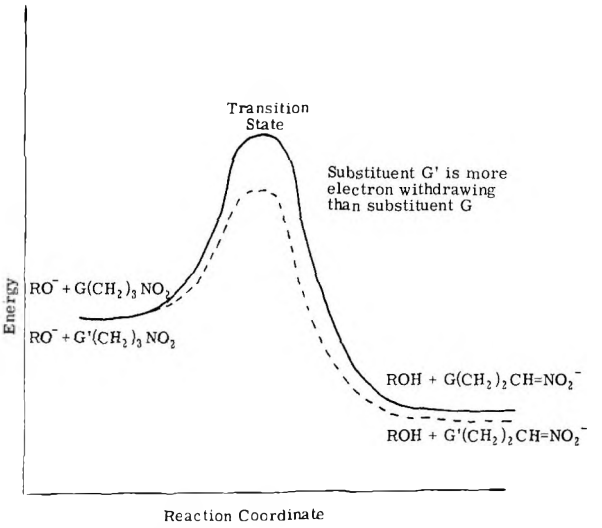


Figure 3. Simulated effect of a substituent, G (solid line), and a more electron-withdrawing substituent, G′ (dashed line), on the rate of deprotonation of a nitroalkane by lyate ion (RO^-). (The assignment of the same ground-state energies for the reactants is arbitrary.)

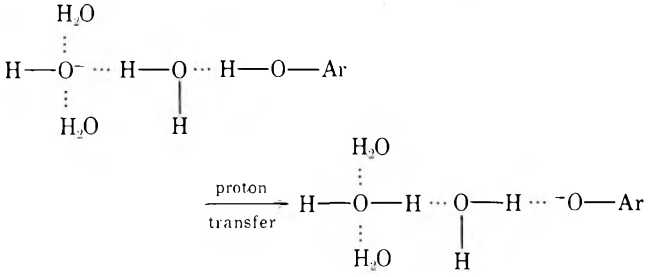
$$\delta\Delta G^{\ddagger} = \alpha\delta\Delta G° \quad (1)$$

the effect of a substituent change, δ, on the transition-state energy will be *intermediate* to the effect of the substituent change on the energies of the reactant and product.[9] As Kresge has pointed out,[10] it is this assumption that constrains the value of the coefficient α to the limits of 0 and 1.0. It seems clear that this assumption is not correct for deprotonations of nitroalkanes. It follows that, at least for nitroalkanes, the size of α does *not* provide an index of the extent of proton transfer to the base in the transition state for deprotonation. Replacement of a substituent, G, by G′ in other carbon acids of the type $G(CH_2)_nA$ and $GC_6H_4(CH_2)_nA$, where A is an acidifying function such as COR, SO_2R, CN, Ph, and the like, should lead to effects on deprotonation rates similar to those depicted in Figure 3. In deprotonation of systems of the type $GC_6H_4CH_2A$ one might expect, as a first approximation, that the size of α will decrease with the ability of A to delocalize the negative charge in the anion, i.e., NO_2 > COR > CO_2R > CN, SO_2R, etc. It may turn out, then, that in most systems of this type α will be less than 1.0. This does not mean, however, that such α's provide a good index of the extent of proton transfer in the transition state.

The presentations of proton transfers in Figure 3 or by reaction **1** → **3** are oversimplified in that they ignore the role of the solvent. It now seems likely that such deprotonation reactions may involve an intermediate or virtual intermediate, rather than a single transition state.[4,11,12] We will show in the next section that such mechanisms can accommodate

"anomalous" Brønsted coefficients and the surprisingly large k_H/k_D isotope effects for exoenergetic nitroalkane deprotonations.

Mechanisms of Proton-Transfer Reactions. The Eigen mechanism for proton transfer with oxygen and nitrogen acids ("normal acids") visualizes a three-step mechanism:[13] (1) formation of an "encounter complex"; (2) proton transfer; and (3) separation of the new "encounter complex" generated in the proton transfer. All three steps in this mechanism are very rapid. Proton transfer, for example deprotonation of phenol by hydroxide ion, can occur through one or more solvent molecules.[14] In the representation shown the hydroxide ion is pictured as being solvated by three ("inner solvation sphere") water molecules, one of which is hydrogen bonded

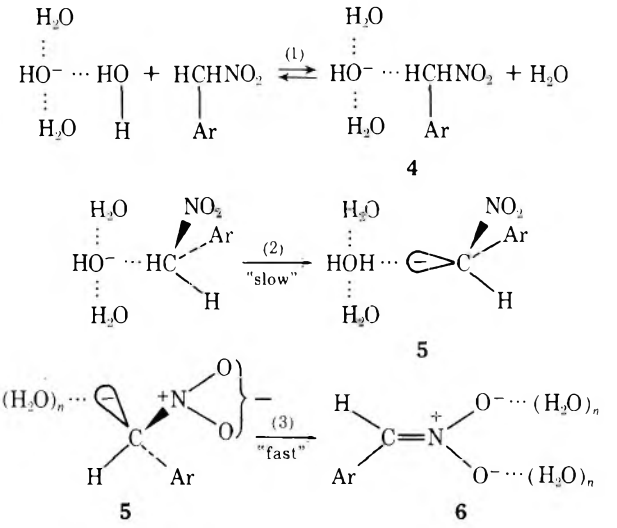


to a phenol molecule. The activation energy for this (exoenergetic) proton transfer is low and the transition state is expected to be reactant-like (Hammond postulate). Substituent changes that increase the acidity of the phenol are expected to result in a small Brønsted coefficient (approaching zero),[10] and the k_H/k_D isotope effect is expected to be small and to decrease as ArOH becomes more acidic.[15] In the reverse (endoenergetic) proton transfer the transition state is expected to be product-like, resulting in a Brønsted coefficient approaching one and a small k_H/k_D isotope effect increasing as the basicity of ArO^- decreases.

This "normal" behavior, wherein the activation energies for proton transfers are low and the Brønsted coefficient changes abruptly from zero to one with a relatively small change in $\Delta G°$, differs sharply from the proton transfer to hydroxide ion from a carbon acid of acidity comparable to that of a phenol, e.g., a nitroalkane such as $GCH_2CH_2CH_2NO_2$ or $ArCH_2NO_2$. Here the activation energy is relatively high, and the Brønsted coefficient and k_H/k_D isotope effects are large. There is good reason to believe that the high activation energies for such proton transfers are associated to a considerable degree with desolvation of the hydroxide ion. It was pointed out many years ago that the reaction of an anion with an alkyl halide requires essentially replacing one solvent molecule of the anion with an alkyl halide molecule,[16] and that the entire activation energy for the reaction of hydroxide ion with methyl iodide in water could be attributed to partial desolvation of the hydroxide ion.[17] The essential correctness of this view as applied to proton transfers is supported by the much lower activation barriers and faster rates observed in dipolar aprotic solvents wherein the anions are not hydrogen bonded to the solvent. For example, deprotonation of triphenylmethane by alkoxide ions is roughly 10^6 faster in dipolar aprotic (dimethyl sulfoxide) solutions than in protic solutions.[18] This large rate acceleration can be attributed to the absence of hydrogen-bonding protic solvent molecules surrounding the ethoxide ions.[17] Evidently carbon acids, which form very weak hydrogen bonds, if any, are unable to utilize the Eigen mechanism for proton transfer.

The Eigen mechanism has been modified in a number of ways to take account of the appreciable solvent reorganization that occurs when a carbon acid is deprotonated by a base. Kreevoy has introduced an additional step in the mechanism to accommodate proper orientation and solvent reorganization.[12] Albery has discussed the mechanism in terms of the Marcus equation by dividing the Marcus work term, ω^r,[19] into two parts, one of which represents solvent reorganization.[11] According to the Albery mechanism, rate-determining proton transfer from a nitroalkane to a base gives a relatively strongly basic pyramidal anion with much of the charge concentrated on carbon. Solvent reorganization then helps to transform this anion to the planar nitronate ion, in which the charge is concentrated on oxygen. This mechanism is comparable to one that evolved in our laboratory at about the same time.[4] An elaboration of this mechanism, which takes specific account of the need to desolvate the attacking base, is presented in Scheme I. (The mechanism is illustrated using $ArCH_2NO_2$, but would, of course, apply equally well to other nitroalkanes or other carbon acids.)

Scheme I



In step 1 of this mechanism one of the three solvent molecules surrounding the hydroxide ion is replaced by a nitroalkane molecule,[20] and complex **4** is formed. The proton transfer in step 2 is visualized as being comparable to that in the Eigen mechanism, but the activation barrier is larger because the hydrogen bond in the encounter complex (**4**) is very weak, and because some structural and solvent reorganization accompanies the proton transfer to form the "essentially pyramidal", "singly-solvated" carbanion **5**. Carbanion **5** must be partially rehybridized, but, for reasons to be presented shortly, the major part of the rehybridization (and solvent reorganization) of **5** is believed to occur in step 3. The mechanism presented in Scheme I has been devised to account for: (a) the slow proton transfers observed for nitroalkanes in protic solvents; (b) the high k_H/k_D isotope effects observed for nitroalkane deprotonations; and (c) the "anomalous" Brønsted coefficients observed for nitroalkanes.

The rapid proton transfers to hydroxide ion from oxygen acids, such as phenols, have been explained by Eigen as being due to the ability of ArOH to fit into the hydrogen-bonded network surrounding the hydroxide ion.[13] Carbon acids of comparable acidity, such as nitroalkanes, form only very weak hydrogen bonds, if any. They cannot fit into this network, and require a much larger activation barrier for proton transfer. Scheme I pictures this high barrier as consisting of a separate, reversible step (1) with a sizable barrier needed to desolvate the hydroxide ion, and a second step (2) with a second barrier for the actual proton transfer. If proton transfer is viewed as occurring without intervention of an intermediate, as in Figure 3, complex **4** would be converted in one step to the rehybridized nitronate ion **6**. This reaction would be highly exoenergetic, however, and is not consistent with the large k_H/k_D isotope effect observed for nitroalkane deprotonations. On the other hand, intermediate (or virtual intermediate[22]) **5** has

Table III. Equilibrium and Kinetic Acidities for Nitroalkanes, $RR'CHNO_2$, in 50% MeOH–H_2O

R	R′	registry no.	pK	ΔpK^a	k^b	log $(k_0/k)^c$
H	H		11.11		30[d]	
H	Me		9.63	(0.00)	5.6	(0.00)
Me	Me	79-46-9	8.85	−1.08	0.26	1.24
H	Et		9.99	(0.00)	4.7	(0.00)
Et	Et	551-88-2	10.17	−0.12	0.039	1.78
H	Pr		9.77	(0.00)	4.6	(0.00)
Pr	Pr	2625-37-8	9.85	−0.52	0.034	1.83
H	*i*-Pr		10.38	(0.00)	3.3	(0.00)
i-Pr	*i*-Pr	66291-08-5	11.0	0.32	0.00061	3.35
H	c-Pr		9.41	(0.00)	10.6	(0.00)
c-Pr	c-Pr	2625-39-0	10.65	0.94	0.079	1.84
H	*t*-Bu		11.4		0.63	
Me	*i*-Pr	595-42-6	9.73		0.095	
Me	c-Pr	2625-38-9	8.73		0.22	

[a] $\Delta pK = pK - pK_0$ (statistically corrected). [b] Lyate rates. [c] Statistically corrected. [d] Estimated from the hydroxide rate in water.

a much higher energy than does product **6**, and step 2 should have a transition state nearer to the point along the reaction coordinate at which the proton is half transferred. A large k_H/k_D isotope effect is therefore reasonable according to this mechanism.

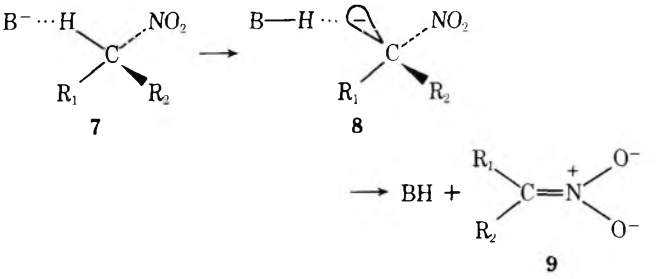
Intermediate **5** would appear as a saddle point in the curve in Figure 3 if it is an actual intermediate, or as a discontinuity in the curve if it is a virtual intermediate; see the three-dimensional representation given by Albery in ref 12. Kurz and Kurz conclude from a detailed analysis of solvent effects that all proton transfers in which solute–solvent coupling is relatively weak, as would be expected here, should occur by an uncoupled mechanism in which virtual intermediates *must* be present.[23] Kresge has obtained evidence for an intermediate (**7a**) similar in structure to **5** in the detritiation of phenylacetylene by an amine base, B. In this reaction detritiation occurs to form an ion-pair intermediate (**7a**) and the "slow" step is exchange of the cation partner of this ion pair to form ion pair **7b**.[24]

$$\underset{\textbf{7a}}{PhC{\equiv}C^-\cdots TB^+} + HB^+ \xrightarrow{\text{"slow"}} \underset{\textbf{7b}}{PhC{\equiv}C^-\cdots HB^+} + TB^+$$

These results indicate that a localized carbanion can indeed form a strong hydrogen bond, as we have postulated in formulating intermediate **5**.

The Brønsted coefficient larger than 1.0 observed for deprotonation of $ArCH_2NO_2$ (or $GCH_2CH_2CH_2NO_2$) systems is accounted for according to Scheme I by the fact that the substituent effects on rates and equilibria change in a different manner.[10] Referring to Figure 3 we see that in the deprotonation step the electron-withdrawing group, G′, lowers both the transition-state energy and energy of the nitronate ion appreciably. (G′ is assumed to have no effect on the ground-state energy of the nitroalkane.) The lowering of the transition-state energy is *greater* than the lowering of the ground-state energy of the nitronate ion, causing the Brønsted α to be larger than 1.0. In the reverse reaction, protonation of the nitronate on carbon, the electron-withdrawing group, G′, *lowers* the transition-state energy appreciably but *increases* the difference in ground-state energies between the nitronate ion and the nitroalkane, causing the Brønsted α to be negative.

α-Alkyl Effect. Anomalous Brønsted Coefficients. Substitution of R for H in HCH_2NO_2 generally increases the equilibrium acidity in either aqueous or Me_2SO solvents due to the stabilizing influence of R in the $RCH{=}NO_2^-$ anion.[5a] A similar effect is observed in 50% MeOH–H_2O for substitution of H by R in RCH_2NO_2 when R is Me, Et, or Pr (Table III). On the other hand, these substitutions cause retardation of the rates of deprotonation in 50% MeOH–H_2O (Table III). Analysis of these data in terms of the simplest representation, **1** → **2** → **3**, requires that the stabilizing influence of R on the product (**3**) be overshadowed in the transition state (**2**) by a destabilizing influence. The abrupt rate decrease of over three powers of ten from *i*-$PrCH_2NO_2$ to *i*-Pr_2CHNO_2 (Table III) suggests that this is a steric effect of some kind, presumably steric hindrance to solvation. These inverse effects of alkyl substitution on rates and equilibria provide further examples wherein the effect of a substituent change, δ, on the transition-state energy is not intermediate to the effect of the substituent change on the energies of the reactant and product, as is required if α in eq 1 is to be confined to the limits of 0–1.0. The lack of correspondence in substituent effects on rates and equilibria may be explained in terms of a reactant-like transition state,[4a] or by assuming that the substituent interactions develop at different rates as the system moves along the reaction coordinate.[10] It is difficult to explain the large k_H/k_D isotope ratios in this way, however, since they show that H–C bond breaking is *extensive* in the transition state. Alternatively, one can postulate the formation of an intermediate[4b,4c] or a virtual intermediate.[11,12] If a more detailed mechanistic representation such as that shown in Scheme I is adopted, intermediates **7** and **8** can be assumed to be formed along the reaction pathway (Figure 4).



The advantage of assuming the presence of intermediate **8** is that we do not expect changes in the stabilities of the planar nitronate ion product **9** caused by substituent changes to influence the rates. Instead, the rate of deprotonation will be determined only by the height of the barrier leading to the singly H-bonded, essentially tetrahedral intermediate, **8** (**8a** or **8b** in Figure 4). For example, the substituent change from H_2CHNO_2 to *i*-Pr_2CHNO_2, which leads to a 5×10^4 decrease in rate of deprotonation by lyate ion in 50% MeOH–H_2O with essentially no change in equilibrium acidity (Table III), can be rationalized in terms of Figure 4 by assuming that a higher barrier must be surmounted to produce intermediate **8b** ($R_1 = R_2 =$ *i*-Pr) than to produce intermediate **8a** ($R_1 = R_2 =$ H). There need be little or no change in the equilibrium acidity,

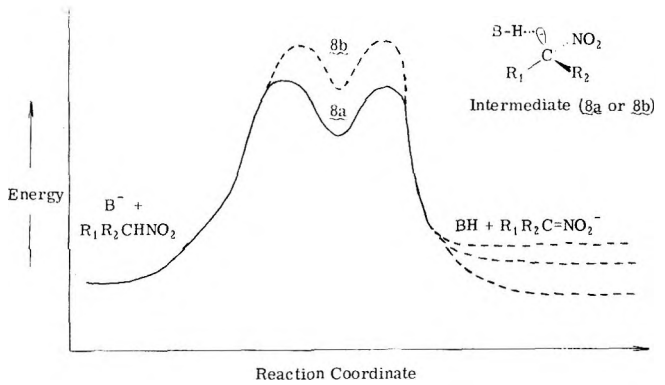


Figure 4. Simulated effect of one or two alkyl substituents (R_1 and R_2) on the rate of deprotonation of a nitroalkane by a base (B^-). (The substitution of R_1 and/or R_2 for H generally decreases the rate and increases the stability of the product, see text.)

however, because there need be little or no change in the relative ground-state energies of nitroalkane and nitronate ion product. Furthermore, a large k_H/k_D ratio is reasonable for this mechanism, since formation of either **8a** or **8b** is endoenergetic.

Substitution of Me for α-H generally produces acid-strengthening effects on the equilibrium acidities of simple nitroalkanes and ketones, but acid-weakening effects for simple nitriles and sulfones.[5a] The difference appears to arise from the degree of delocalization of charge made possible by the two types of functions. On the other hand, substitution of Me for α-H decreases the kinetic acidities of all four types of carbon acids. We can anticipate, then, that in protic solvents, ketones, like nitroalkanes, will give "anomalous" Brønsted coefficients, whereas nitriles and sulfones will not. (Unfortunately, this prediction is not easily tested, since equilibrium acidities of simple ketones, nitriles, and sulfones can be determined only in dipolar aprotic solvents.) The observation of "normal" Brønsted coefficients for the latter does not necessarily mean, however, that the transition-state structure is "intermediate" between that of reactants and products.[9] It could just as well mean that there happens to be a correspondence in substituent effects on the transition state and the product. We conclude that the size of such Brønsted coefficients is a poor guide to transition-state structures of deprotonation reactions.

Limitations of the Taft Equation. In the preceding paper we concluded that the Taft relationship can be applied in only a limited sense to systems such as $G(CH_2)_nNO_2$, where n = 1, 2, or 3, because: (a) σ^*_G constants (n = 1) cannot be mixed with $\sigma^*_{CH_2G}$ constants (n = 2(: (b) "methylene transmission coefficients", which relate $\sigma^*_{CH_2G}$ to $\sigma^*_{CH_2CH_2G}$, vary with geometry; and (c) σ^* constants in general give only a rough measure of polar effects because they are dependent on geometry.[5b] The Taft plot in Figure 1 for the kinetic acidities of $G(CH_2)_nNO_2$ appears to contradict these first two conclusions, however, since many of the σ^*_G points (squares) and $\sigma^*_{CH_2G}$ points (triangles) fit the line almost as well as do the points for $\sigma^*_{CH_2CH_2G}$ constants, which were used to define the line (circles). In contrast, the σ^*_G and $\sigma^*_{CH_2G}$ points deviate widely from the Taft plot for equilibrium acidities.[5b] (This represents another example of the lack of correspondence between kinetic and equilibrium acidities that have been discussed in earlier sections of this paper.) We believe that the apparent fit in Figure 1 is fortuitous, however, and that it is a consequence of the approximate nature of the Taft relationship. Note that there is appreciable scatter of the $\sigma^*_{CH_2CH_2G}$ points in Figure 1, and that the PhO and PhS points fit poorly. The deviations of these two points offer a good illustration of the dependence of the Taft relationship on geometry. The relative order of polar effects PhO > PhS appears to be firmly established by ester hydrolysis data, which indicate a substantial difference in $\sigma^*_{CH_2G}$ constants (0.85 for PhO[26] and 0.66 for PhS[27]). This order is confirmed by using the pK's of carboxylic acids, GCH_2CO_2H, as an alternative source of σ^* constants (0.92 and 0.71, respectively).[28] Hammett σ_m constants also indicate PhO >PhS to be the correct polar order (σ_m^{PhO} = 0.25; σ_m^{PhS} = 0.18[29]). On the other hand, all of the data on the $G(CH_2)_3NO_2$ system point to an *opposite* order for the relative polar effects of PhO and PhS. Equilibrium acidities in both Me_2SO and MeOH–H_2O give the order PhS > PhO, as do kinetic acidities using either lyate ion or pyridine in MeOH–H_2O (Table I). The deviations are substantial as may be judged by the fact that $\sigma^*_{CH_2G}$ constants give a calculated rate ratio, k^{PhO}/k^{PhS}, for lyate ion deprotonation in 50% MeOH–H_2O of 426, whereas the observed ratio is 0.77. The equilibrium acidities $PhO(CH_2)_3SO_2Ph$ and $PhS(CH_2)_2SO_2Ph$ are also in an order opposite to that predicted by Taft $\sigma^*_{CH_2G}$ constants.[30] One might have expected the order for equilibrium acidities of the carboxamides $PhOCH_2CONH_2$ and $PhSCH_2CONH_2$ to follow the Taft order, since carboxamides are closely related in structure to the carboxylic esters, GCH_2CO_2Et, from which the Taft $\sigma^*_{CH_2G}$ constants were derived. Here too, however, a reverse order is observed.[31] It would appear that the polar effects of PhO and PhS substituents are strongly dependent on the geometry of the system used for the measurements. These results are reminiscent of those of Grob, who finds that the halogen order for the equilibrium acidities of 4-haloquinuclidinium ions in water is Br > F > Cl > I instead of the "inductive order" F > Cl > Br > I.[32]

Experimental Section

Materials. The substituted nitroalkanes were prepared as previously reported,[5] save for 3-chloro-1-nitropropane. This was synthesized by the procedure of Lampman, Horne and Hager,[33] giving a 28% yield of crude product, along with 45% starting material and 14% 3-nitroisoxazoline as a high-boiling byproduct. Refractionation of the product gave material >99% by VPC: bp 66–67 °C (4 mm) [lit.[33] bp 98–110 °C (22 mm)]; n^{23}_D 1.453; NMR ($CDCl_3$) δ 2.47 (quintet, 2 H), 3.70 (triplet, 2 H), 4.58 (triplet, 2 H).

Kinetic Measurements. The procedure followed by lyate rates was that of Bordwell, Boyle, and Yee[34] save that data were collected with a Beckman Kintrac VII UV-visible spectrophotometer providing digital output through a Beckman 3108 Intercoupler attached to a Teletype Corp. Teletypewriter. The cell block was thermostated at 15.0 ± 0.1 °C.

The pyridine rates were determined essentially by the method of Barnes and Bell[6] as modified in this Laboratory by Dr. R. J. Scriven. In a typical run, a solution consisting of 2 mL of weak buffer base solution (0.03–0.0002 M), 1 mL of nitroalkane solution (0.02–0.0004 M), and 0.1 M KCl were allowed to equilibrate in the Kintrac cell block. Measurement was initiated by addition of 20 μL of triiodide solution (0.01–0.001 equiv, relative to nitroalkane) to the cell with an Eppendorf Microliter Pipette, and the change in absorbance at 353 nm was followed as a function of time. The observed pseudo-order rate constants, k_{obsd}, were evaluated on the CDC 6400 computer at Northwestern's Vogelback Computing Center, using a least-squares program written by Dr. A. C. Knipe, which discards the worst 10% of the data. The first-order rate constants, k_1, were calculated with the equation

$$k_1 = k_{obsd}/n[\text{nitroalkane}]\epsilon$$

where ϵ = 33 150, the extinction coefficient of triiodide in 50% MeOH–H_2O at 353 nm, and n is the number of equivalents of iodide taken up by the nitroalkane. Attempts to determine n by isolation of product proved unsuccessful, and a value n = 1 was assumed, as has been done previously.[6]

Any values of k_{obsd} with $r < 0.999$ were rejected. All buffer dilution plots consisted of at least three runs, each with at least three different base strengths. The background reaction of the weak base buffer with the triiodide solution was negligible at all concentrations. Rates were reproducible to within ±5%.

Acknowledgment. We are grateful to the National Science Foundation and the National Institutes of Health for support of this research. Comments of a referee and of Professor A. J. Kresge were helpful in preparing a revised version of this manuscript.

References and Notes

(1) National Institutes of Health Fellow, 1967–1970.
(2) R. P. Bell and D. M. Goodall, *Proc. R. Soc. London, Ser. A*, **294**, 273 (1966); D. J. Barnes and R. P. Bell, *ibid.*, **318**, 421 (1970); R. P. Bell and B. J. Cox, *J. Chem. Soc. B*, 194 (1970).
(3) V. M. Belikov, A. Talvik, and C. B. Korchemnaya, *Org. React. (USSR)*, **2** (1), 10 (1965); A. Talvik et al., *ibid.*, **3** (2), 179 (1966); **3** (4), 7 (1966); **4**, 494, 822 (1967); **6**, 468, 743, 882 (1969); **7**, 1194, 1206 (1970).
(4) (a) F. G. Bordwell and W. J. Boyle, *J. Am. Chem. Soc.*, **93**, 512 (1971); (b) F. G. Bordwell and W. J. Boyle, *ibid.*, **97**, 3447 (1975), and references cited therein; (c) F. G. Bordwell, *Faraday Symp. Chem. Soc.*, **No. 10**, 100 (1975).
(5) (a) F. G. Bordwell, J. E. Bartmess, and J. A. Hautala, *J. Org. Chem.*, companion paper in this issue; (b) F. G. Bordwell and J. E. Bartmess, *ibid.*, companion paper in this issue. (These are papers 1 and 2 in this series.)
(6) (a) D. J. Barnes and R. P. Bell, *Proc. Ry. Soc. London, Ser. A*, **318**, 421 (1970); (b) R. P. Bell and E. Gelles, *ibid.*, **210**, 310 (1952).
(7) D. Turnbull and S. H. Maron, *J. Am. Chem. Soc.*, **65**, 212 (1943).
(8) F. G. Bordwell and W. J. Boyle, *J. Am. Chem. Soc.*, **94**, 3907 (1972).
(9) J. E. Leffler, *Science*, **117**, 340 (1953); J. E. Leffler and E. Grunwald, "Rates and Equilibria in Organic Reactions", Wiley, New York, N.Y., 1963, p 153.
(10) A. J. Kresge, "Proton-Transfer Reactions", E. F. Caldin and V. Gold, Eds., Chapman and Hall, London, 1975, Chapter 7.
(11) W. J. Albery, A. N. Campbell-Crawford, and J. S. Curran, *J. Chem. Soc., Perkin Trans. 2*, 2206 (1972).
(12) A. I. Hassid, M. M. Kreevoy, and T-M. Laing, *Faraday Symp. Chem. Soc.*, **No. 10**, 69 (1975).
(13) M. Eigen, *Angew, Chem., Int. Ed. Engl.*, **3**, 1 (1964).
(14) E. Grunwald and D. Eustace, ref 10, Chapter 4, have shown that usually one or two water molecules separate the reactants in proton transfers of this type.
(15) R. A. More O'Ferrall, ref 10, Chapter 8.
(16) R. A. Ogg and M. Polyani, *Trans. Faraday Soc.*, **31**, 604 (1935).
(17) E. A. Moelwyn-Hughes and D. Glen, *Proc. R. Soc. London, Ser. A.*, **212**, 260 (1952).
(18) C. D. Ritchie, "Solute–Solvent Interations", J. F. Coetzee and C. D. Ritchie, Eds., Marcel Dekker, New York, N.Y., 1969, Chapter 4, pp 266–268.
(19) R. A. Marcus, *J. Phys. Chem.*, **72**, 891 (1968).
(20) Hydroxide (or alkoxide) ions are believed to be solvated by three tightly bound (inner sphere) water molecules. [The additional (outer sphere) water molecules that are also present are not shown.] Judging from the energy liberated on solvation of a gas-phase chloride ion by one or two protic solvent molecules,[21] we can expect removal of one solvent molecule from $HO^-(H_2O)_3$ to require a minimum energy of about 5 kcal/mol.
(21) P. Kebarle, "Ions and Ion Pairs in Organic Reactions", Vol. 1., M. Szwarc, Ed., Wiley, New York, N.Y., Chapter 2, p 75.
(22) As a virtual intermediate 5 would appear as a discontinuity on the potential energy curve, rather than as a potential energy minimum.[11,12]
(23) J. L. Kurz and L. C. Kurz, *J. Am. Chem. Soc.*, **94**, 4451 (1972).
(24) A. J. Kresge, *Acc. Chem. Res.*, **8**, 354 (1975).
(25) F. G. Bordwell, W. J. Boyle, J. A. Hautala, and K. C. Yee, *J. Am. Chem. Soc.*, **91**, 4002 (1969).
(26) R. W. Taft, "Steric Effects in Organic Chemistry", M. S. Newman, Ed., Wiley, New York, N.Y., 1956, p 619.
(27) A. Chambers and C. J. M. Stirling, *J. Chem. Soc. B*, 4558 (1965).
(28) M. Charton, *J. Org. Chem.*, **29**, 1222 (1964).
(29) C. Y. Meyers, *Gazz. Chim. Ital.*, **93**, 1206 (1963) (based on acidities of phenols).
(30) N. R. Vanier, Ph.D. Dissertation, Northwestern University, 1977.
(31) H. E. Fried, unpublished results.
(32) C. A. Grob and M. G. Schlageter, *Helv. Chim. Acta*, **59**, 264 (1976).
(33) G. D. Lampman, D. A. Horne, and G. D. Hager, *J. Chem. Eng. Data*, **14**, 396 (1969).
(34) F. G. Bordwell, W. J. Boyle, Jr., and K. C. Yee, *J. Am. Chem. Soc.*, **92**, 5926 (1970).

Kinetic and Equilibrium Acidities of Nitrocycloalkanes

F. G. Bordwell,* John E. Bartmess, and Judith A. Hautala[1]

Department of Chemistry, Northwestern University, Evanston, Illinois 60201

Received March 14, 1977

Rates of deprotonation by lyate ion in 50% (v/v) MeOH–H_2O were determined for C_3–C_8 and C_{12} nitrocycloalkanes. Equilibrium acidities in this solvent were also determined for C_4–C_8 and C_{12} nitrocycloalkanes and were determined in Me_2SO for C_3–C_7 nitrocycloalkanes. Equilibrium acidities in the two solvents showed a remarkable similarity in their variation with ring size, despite a (constant) difference of 7.75 pK units in the acidity constants. The equilibrium acidity of nitrocyclopropane was found to be over 10^8 times smaller than that for nitrocyclobutane, and its kinetic acidity in water was found to be over 10^3 times smaller. The correspondence in the relative order of equilibrium and kinetic acidities between the C_8 and the C_4 nitrocycloalkanes is contrasted with the lack of correspondence between the equilibrium and kinetic acidities of the C_4 and the C_5 nitrocycloalkanes. This is explained by assuming a different mechanism for deprotonation of nitrocyclopropane as compared to other nitroalkanes.

In the preceding paper we discussed the "anomalous" Brønsted coefficients observed for the deprotonation of acyclic nitroalkanes in protic solvents. A lack of the "expected" correlation between kinetic and equilibrium acidities of certain nitrocycloalkanes has also been apparent for some time.[2,3] The relative rates of deprotonation for nitrocycloalkanes by hydroxide ion in water and by lyate ion in a variety of other protic solvents has been found to vary with ring size in the order: $4 > 5 > 7 > 8 > 6 \gg 3$.[3] (Nitrocyclopropane failed to react.) In contrast, the order of equilibrium acidities in 33% (w/w) MeOH–H_2O for nitrocycloalkanes was found to vary with ring size in the order: $8 > 7 > 5 > 6 > 4 \gg 3$.[3] (The acidity constant for nitrocyclopropane was too small to measure.) Studies of kinetic and equilibrium acidities of nitrocycloalkanes in 50% (v/v) MeOH–H_2O were in progress at the time these data were published. The work was continued, since it seemed worthwhile to obtain kinetic and equilibrium measurements in the same solvent.[4] The equilibrium acidity studies have now been extended to dimethyl sulfoxide (Me_2SO) solution, and rate and equilibrium data for nitrocyclopropane have been obtained.

Results

Equilibrium Acidities for Nitrocycloalkanes. The relative values for the equilibrium acidities obtained potentiometrically in 50% (v/v) MeOH–H_2O (Table I) agreed reasonably well with those determined conductometrically in 33% (w/w) MeOH–H_2O,[3] except for nitrocyclohexane, for which a higher relative value was found. Repetition of this measurement in 33% (w/w) MeOH–H_2O gave, in our hands, a pK of 9.58, instead of the value reported (8.92). (On the other hand, we were able to check the values reported for nitrocyclopentane and nitrocycloheptane in 33% MeOH–H_2O to within 0.1 pK unit.) The value of 9.58 appears to be correct, since it places the pK of nitrocyclohexane within a few tenths of a unit of that reported for nitrocyclobutane (pK = 9.53),[3] and we have observed a close correspondence between the pK's for these two nitrocycloalkanes in: (a) water (8.56 and

0022-3263/78/1943-3113$01.00/0

Table I. Equilibrium Acidities of Nitrocycloalkanes in 50% (v/v) MeOH-HOH and in Dimethyl Sulfoxide (Me_2SO) at 25 °C

registry no.	ring size	pK (50% MeOH–HOH)[a]	pK (Me_2SO)[b]
13021-02-8	3	>18[c]	26.9 ± 0.2[d]
2625-41-4	4	10.05 ± 0.03	17.82 ± 0.05
2562-38-1	5	8.15 ± 0.02	16.00 ± 0.05
1122-60-7	6	10.07 ± 0.01	17.90 ± 0.05
2562-40-5	7	8.15 ± 0.01	15.80 ± 0.05
24509-62-4	8	7.37 ± 0.03	
1781-70-0	12	9.6 ± 0.1[e]	
79-46-9	Me_2CHNO_2	8.85 ± 0.02	16.89 ± 0.05
551-88-2	Et_2CHNO_2	10.17 ± 0.03	

[a] Determined potentiometrically. [b] Determined by the indicator method described by W. S. Matthews et al., *J. Am. Chem. Soc.*, **97**, 7006 (1975). [c] Based on the absence of UV absorption typical of $>C{=}NO_2^-$ in 1 M aqueous NaOH. [d] Decomposition occurs. [e] Extrapolated from data in 75% (v/v) MeOH–H_2O.

Table II. Rates of Deprotonation of Nitroalkanes by Lyate Ion in 50% (v/v) MeOH–H_2O (k_2) at 25 °C

ring size	k_2, $M^{-1}\,s^{-1}$ [a]	k_2 rel	k_{-2} rel[b]
3	0.002[c]	0.0072	~10^5
4	5.4	19	18
5	1.4	5	0.059
6	0.28	(1.0)	(1.0)
7	0.87	3.1	0.037
8	0.65	2.3	0.0045
12	0.13	0.46	0.15
Me_2CHNO_2	0.26	0.93	0.055

[a] Determined spectrophotometrically unless otherwise noted; the reproducibility of runs was better than ±5%. [b] Relative rate of protonation of $C{=}NO_2^-$ on carbon calculated from the equation $k'_{-2}/k_{-2} = K_{HA}k'_2/K'_{HA}k_2$. [c] Rate of deuterium exchange catalyzed by DO^- in D_2O; reproducible to ±5%. The rate for *trans*-2-methyl-1-nitrocyclopropane was the same, within experimental error, while that for the cis isomer was about tenfold faster.

8.61); (b) 50% (v/v) MeOH–H_2O (10.05 and 10.07); and (c) 50% (v/v) dioxane–H_2O (10.88 and 11.16). Our value for nitrocyclohexane in water is 0.3 pK unit above that reported in another investigation,[5] but agrees with a value we have extrapolated into water from measurements in aqueous dioxane (using 50, 40, 25, and 10% of dioxane).[4]

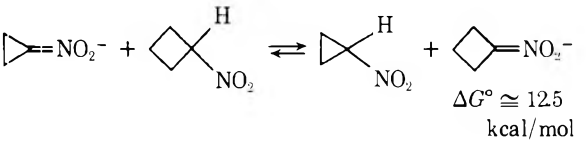
Comparison of the equilibrium acidities in Me_2SO with those in 50% MeOH–HOH for the C_4–C_7 nitrocycloalkanes shows that they differ by an almost constant amount (7.75 ± 0.1 pK unit). Acyclic nitroalkanes show a similar behavior, but the differences are not quite so constant.[6a,b]

Contrary to the report that *trans*-2-ethylnitrocyclopropane fails to undergo base-catalyzed deuterium exchange even under strenuous conditions,[3] we found that nitrocyclopropane (and *cis*- or *trans*-2-methylnitrocyclopropanes) underwent deuterium exchange readily with either 0.1 N NaOD–D_2O or 0.1 N lyate ion in 50% (v/v) MeOD–D_2O. The rate of deprotonation for nitrocyclopropane is over 100 times slower than that of nitrocyclohexane or an open-chain analogue, 2-nitropropane, however, and is over 2500 times slower than that of nitrocyclobutane (Table II). For deuterioxide exchange of the protio compound in D_2O, $\Delta H^{\ddagger}$ is 13 ± 1 kcal/mol, which is the same as that of nitrocyclohexane in 50% dioxane–water;[3] $\Delta S^{\ddagger}$ for deprotonation of nitrocyclopropane is, however, −27 ± 2 eu, a value much lower than that reported for nitrocyclohexane (−14.5 eu).[3]

In comparing the deuterium exchange rates for nitrocyclopropane with the rates for appearance of the nitronate ions (determined spectrophotometrically) for the other nitrocycloalkanes, one must consider the possibility that the rate of deuterium exchange is complicated by internal return.[7] This does not appear to be a major factor, judging from "mixed" kinetic isotope effect, $k_{H(D_2O)}/k_{D(H_2O)}$, of 9.1 observed for nitrocyclopropane. The "mixed" isotope effect is the product of the "normal" substrate isotope effect, k_H/k_D (both in H_2O), and the solvent isotope effect (k_{D_2O}/k_{H_2O}) (both with the protio compound). For 2-nitropropane, the "normal" isotope effect has been found to be 7.6 ± 0.2, and k_{D_2O}/k_{H_2O} has been found to be 1.36.[8] Solvent isotope effects for carbon acids generally fall in the range 1.2–1.6.[9] Judging from these data, the k_H/k_D isotope effect for nitrocyclopropane in water at 25 °C will be about 6.5, which would appear to rule out internal return as a major factor.

Discussion

Variation of Equilibrium Acidities of Nitrocycloalkanes with Ring Size. Examination of Table I shows that the relative order of equilibrium acidities observed in protic solvents for nitrocycloalkanes, namely, 5, 7 > 4, 6 ≫ 3, is observed also in Me_2SO solution. The changes in equilibrium position with changes in ring size are evidently independent of solvent and depend only on the nature of the ring. The changes in these equilibrium constants for the C_4–C_8 and C_{12} ring sizes in 50% MeOH–H_2O are in the same order as the equilibrium constants for formation of ketones from cyanohydrins in 95% EtOH, namely, $C_4 < C_5 > C_6 < C_7 < C_8 > C_{12} \simeq R_2C{=}O$.[10] The major effects determining the position of the cyanohydrin equilibria are believed to be angle strain in the C_4 compound and torsional strains in the C_5, C_7, and C_8 compounds.[10] Adopting this analysis, the unfavorable dissociation constant for nitrocyclobutane, relative to C_5, C_7, and C_8 nitrocycloalkanes (Table I), can be explained by assuming that angle strain in the C_4 nitronate ion overshadows torsional strain in the C_4 nitroalkane. Similarly, the remarkably low dissociation constant for nitrocyclopropane (9 pK units lower than nitrocyclobutane in Me_2SO) can be attributed largely to strain in the C_3 nitronate ion. Introduction of one trigonal center into cyclopropane has been estimated to increase the total strain energy by 13 kcal/mol, as compared to only about 1 kcal/mol for cyclobutane.[11]



$\Delta G^{\circ} \cong 12.5$ kcal/mol

The greater degree of dissociation of the C_5, C_7, and C_8 nitrocycloalkanes as compared to the C_6 or C_{12} nitrocycloalkanes (Table I) can be attributed to the presence of torsional strains in the nitrocycloalkanes, which are partially relieved in forming the corresponding nitronate ions.[10]

Comparison of Equilibrium and Kinetic Acidities for Nitrocycloalkanes. The rates of deprotonation of nitrocycloalkanes by lyate ion in protic solvents follow the relative order 4 > 5 > 7, 8 > 6, 12, acyclic ≫ 3 (see Table I and ref 3). (The reversal in the order of the relative rates and equilibrium constants for the C_4 and C_5 nitrocycloalkanes has been commented on earlier as an example of an anomalous Brønsted relationship.[2]) The relative order of kinetic acidities of the C_4, C_5, and C_6 nitrocycloalkanes obtained in this way are 19: 5.0:1.0, which corresponds closely to the relative order of kinetic acidities of cycloalkanes determined by cesium cyclohex-

ylamide catalyzed tritium exchange in cyclohexylamine, CHA (28:5.7:1.0).[12] The similarity in these rate patterns may seem surprising when one considers that, although the rate-limiting step is presumably formation of a carbanion in each reaction, in one instance carbanion formation is a highly endoenergetic reaction, whereas in the other it is an exoenergetic reaction (formation of a nitronate ion). In the preceding paper in this series we pointed out, however, that as a *general rule,* rates of deprotonation of acyclic nitroalkanes are *not* governed by nitronate ion stabilities.[6c] The failure of the strain in the (developing) cyclobutane nitronate ion to produce an observable increase in transition state energy is therefore consistent with this general pattern of behavior.[6c] This result can be rationalized by assuming a reactant-like transition state, but this is not consistent with the large k_H/k_D isotope ratios observed; k_H/k_D = 8.4 for nitrocyclobutane, 8.3 for nitrocyclopentane, and 8.8 for nitrocyclohexane in aqueous dioxane.[3] For this reason we favor a mechanism involving the formation, in the rate-limiting step, of an essentially pyramidal, singly H-bonded intermediate (**2** in this instance).[6c]

1 **2** **3**

According to this mechanism the rate-limiting step is the (endoenergetic) conversion of **1** to **2.** The extent of H–C bond breaking can be appreciable (large k_H/k_D) and some relief of torsional strain can occur (leading to rate acceleration for deprotonation of nitrocyclobutane relative to nitrocyclopentane) without much increase in angle strain. (See Figure 4 in ref 6c and the accompanying discussion for more details.)

The rates of protonation of the nitronate ions on carbon by MeOH–H_2O solvent (k_{-2}^{rel}) can be calculated from the deprotonation rates and the equilibrium constants (Table II). The order observed, C_4, $C_6 > C_5$, C_7, is similar to that for the rate of reduction of the corresponding cycloalkanones by sodium borohydride,[13a] and follows Brown's rule[13b] that the ease of transformation of sp^2 to sp^3 carbon atoms in carbocyclic ring systems is greater for four- an six-membered rings than for five- and seven-membered rings.[14] If we assume that this order of rates holds also for protonation on carbon by the conjugate acids of the solvent, it would account for the relative orders of equilibrium acidities observed; the protonation rates rather than the deprotonation rates would then control the relative equilibrium acidities.

The rate pattern for deprotonation of nitrocycloalkanes with 7, 8, and 12 members, i.e., 7 > 8 > 12 (Table II), is also the same as that for cycloalkanes,[12] although the order of rates relative to the six-membered ring compound differ slightly in the two systems. The mechanism outlined for deprotonation of nitrocyclobutane, i.e., **1** → **2** → **3,** appears appropriate also for these nitrocycloalkanes. On the other hand, the rate of deprotonation for nitrocyclopropane, relative to the rates for other nitroalkanes, shows an opposite behavior from that for the rate for cyclopropane, relative to the rates for other cycloalkanes.

Cyclopropane is deprotonated by cesium cyclohexylamide in CHA at a rate about 2500 times faster than is cyclobutane.[12] These rates, as well as those for C_5–C_8 cycloalkanes, correlate linearly with ^{13}C–H NMR coupling constants, which indicates that the amount of s character in the C–H bond is the dominant factor controlling cycloalkane kinetic acidities.[12,15] Theoretical calculations also indicate that the C–H bond in cyclopropane has appreciably more s character than do the C–H bonds in higher cycloalkanes.[16] Apparently this factor is overshadowed completely in determining the kinetic acidity of the H–C bonds in nitrocyclopropane, since it is deprotonated in protic solvents at a rate about 2500 times *slower* than is nitrocyclobutane (Table II). Remarkably enough, the major part of the rate difference appears to be in the $\Delta S^{\ddagger}$ term, judging from the comparison of the activation parameters made in the Results. These data suggest a mechanistic change for deprotonation of nitrocyclopropane as compared to other nitroalkanes. The deprotonation of nitrocyclopropane is uphill, as compared to other nitrocycloalkanes and acyclic nitroalkanes, by at least 11 kcal/mol. It has been suggested by Albery that in exoenergetic reactions, such as the deprotonation of C_4–C_8 nitrocycloalkanes by hydroxide ion, the major part of solvent reorganization may follow C–H bond breaking as in the mechanism shown for conversion of **1** to **3.**[17] However, for endoenergetic reactions, such as deprotonation of nitrocyclopropane by hydroxide ion, solvent reorganization may accompany C—H bond breaking. This would account for the unusually large negative $\Delta S^{\ddagger}$ for deprotonation of nitrocyclopropane. In terms of the mechanism shown, it could mean that nitrocyclopropane is converted directly to its nitronate ion in the rate-limiting step without intervention of an intermediate analogous to **2.** In this transition state the large strain energy in the (developing) C_3 nitronate ion can provide a strong destabilizing effect. The rate of base-catalyzed deuterium exchange for nitrocyclopropane, as compared to the rate of deprotonation of nitrocyclobutane, is 6×10^6 slower than expected on the basis of the relative rates of base-catalyzed deuterium exchange of the C_3 vs. the C_4 cycloalkane. The 12 kcal/mol greater strain in the C_3 vs. the C_4 nitronate ion, which corresponds to a rate ratio of about 10^9, is sufficient to account for this.

Experimental Section

Reagents. Partially aqueous solvents were prepared by combining measured volumes of water and either methanol or dioxane to achieve the desired volume/volume percentage composition. Reagent-grade dioxane was refluxed with molten sodium for at least 24 h and then distilled. Baker and Adamson reagent-grade (ACS Code 1212) absolute methanol was used without further purification. Sodium hydroxide solutions were either standardized against Banco Standardized or Fischer Certified standard hydrochloric acid to a phenolphthalein end point or prepared from Anachemia Acculute solutions. The basic solutions in mixed solvents were prepared by combining appropriate volumes of aqueous sodium hydroxide and the organic component and diluting with mixed solvent to the desired volume.

Kinetic Procedure. The rates of deprotonation from the nitroalkanes by lyate ion in 50% (v/v) aqueous methanol at 15 °C, other than nitrocyclopropane, were determined spectrophotometrically by following the appearance of the nitronate ion absorption in the ultraviolet region (λ_{max} 225–245 nm: ϵ_{max} 9000–14000), as previously described.[18] The measurements were performed either on the Cary Model 15 or the Beckman Kintrac VII recording spectrophotometers. When a clear infinity value could not be obtained experimentally due to decomposition or side reactions, infinity absorbances were calculated by a Kezdy treatment of the data obtained over 3–4 half lives.[19]

Deuterium exchange rates for nitrocyclopropanes were determined using 5–10-mg aliquots in 4-mL vials containing 3 mL of ~1 M NaOD/D_2O. After shaking to promote dissolution, the vials were allowed to remain in a constant temperature bath for appropriate times. For analysis, the contents of the vial was extracted with 0.5 mL of carbon tetrachloride, and the ratio of the peak areas for the α proton (δ 3.9–4.4) and the β protons (δ 0.5–2.5) were determined by NMR. Rate constants were determined from the equation, $\ln [A - A_\infty] = kt$, where A is the ratio at time t. The accuracy of the method is limited by the low solubility of nitrocyclopropane (~5–10 mg/mL of D_2O), and the rates are probably accurate to no better than ±10%. For nitrocyclopropane in D_2O k at 25 °C was 3.9×10^{-3} M^{-1} s^{-1}, and for nitrocyclopropane-d_1 in H_2O k at 25 °C was 0.43×10^{-3} M^{-1} s^{-1}. The rate constant for *trans*-2-methyl-1-nitrocyclopropane in D_2 was identical, within experimental error, to that for nitrocyclopropane itself. For *cis*-2-methyl-1-nitrocyclopropane in D_2O k at 25 °C was ~4×10^{-3} M^{-1} s^{-1}.

Rate constants for nitrocyclopropane in D_2O were determined at

15 and 35 °C by monitoring the appearance of the OH peak in the solvent by NMR. For this purpose 100 mg of nitrocyclopropane was placed in an NMR tube and 0.5 mL of ~1 M NaOD/D_2O added. After making sure that in a 2-h trial run that the OH peak (δ 4.8) was not saturated at 60 Hz paper width and 200-s scan, fresh samples were used to scan the OH peak as a function of time. Peak areas were determined by cut-and-weigh, and the data analyzed as first-order kinetics.

Materials. Nitrocyclohexane was obtained as a gift from the Commercial Solvents Corp. and nitrocyclooctane was obtained as a gift from Professor J. G. Traynham. Other nitrocycloalkanes, except for nitrocyclopropane, were prepared by the oxidation of the keto oximes as described previously.[6] Nitrocyclopropane was prepared by the method of Lampman, Horne, and Hager[20] and purified by GLC using a 3/8 in. × 10 ft Carbowax on acid-washed Chromosorb W column at 110 °C and 160 mL/min flow rate to give a clear liquid: $n^{23}D$ 1.4380 [lit.[20] $n^{20}D$ 1.4395]; NMR ($CDCl_3$) δ 1.10 (m, 2 H), 1.60 (m, 2 H), 4.33 (m, 1 H); IR (film) 1540, 1370 cm^{-1}. 2-Methyl-1-nitrocyclopropane was prepared in a similar manner starting from 1,3-dibromobutane. GLC analysis indicated the presence of two isomers in a ratio of 10:1. Isolation of each was accomplished by preparative GLC using a 1/4 in. × 20 ft 3% Carbowax on acid-washed Chromosorb W column at 80 °C and a flow rate of 80 mL/min. The products had similar, but slightly different NMR spectra: ($CDCl_3$) δ 1.2 (m, 6 H), 4.2 (m, 1 H). Upon treatment with aqueous 1 M NaOH for 0.5 h at 25 °C each was converted to the same 20:1 mixture of isomers (GLC analysis). The lesser product was therefore assigned the cis structure.

Acknowledgment. This research was supported by grants from the National Science Foundation and the National Institute of Health. We are indebted to Zafra Margolin for the pK measurements in Me_2SO solution.

Registry No.—*cis*-2-Methylnitrocyclopropane, 66303-44-4; *trans*-2-methylnitrocyclopropane, 15267-24-0; 1,3-dibromobutane, 107-80-2.

References and Notes

(1) National Institutes of Health Fellow, 1967–1970.
(2) F. G. Bordwell, W. J. Boyle, J. A. Hautala, and K. C. Yee, *J. Am. Chem. Soc.*, **91**, 4002 (1969).
(3) P. W. K. Flanagan, H. W. Amburn, H. W. Stone, J. G. Traynham, and H. Shechter, *J. Am. Chem. Soc.*, **91**, 2797 (1969).
(4) J. A. Hautala, Ph.D. Dissertation, Northwestern University, 1971.
(5) P. M. Zaitsev, Ya. I. Tur'yan, and Z. V. Zaitseva, *Kinet. Katal.*, **4**, 534 (1963); Y. I. Tur'yan, Yu. M. Tur'yan and P. M. Zaitsev, *Dokl. Akad. Nauk SSR*, **134**, 850 (1960).
(6) (a) F. G. Bordwell, J. E. Bartmess, and J. A. Hautala, *J. Org. Chem.*, companion paper in this issue; (b) F. G. Bordwell and J. E. Bartmess, *ibid.*, companion paper in this issue; (c) F. G. Bordwell, J. E. Bartmess, and J. A. Hautala, *ibid.*, companion paper in this issue. (These are papers 1–3 in this series.)
(7) D. J. Cram, "Fundamentals of Carbanion Chemistry", Academic Press, New York, N.Y., 1965, p 48.
(8) V. Gold and S. Grist, *J. Chem. Soc., Perkin Trans. 2*, 89 (1972).
(9) R. P. Bell, *Discuss Faraday Soc.*, **39**, 16 (1965).
(10) J. Hine, "Structural Effects on Equilibria in Organic Chemistry", Wiley-Interscience, New York, N.Y., 1975, Chapter 8.
(11) K. B. Wiberg and R. A. Fenoglio, *J. Am. Chem. Soc.*, **90**, 3395 (1968).
(12) (a) A. Streitwieser, Jr., R. A. Caldwell, and W. R. Young, *J. Am. Chem. Soc.*, **91**, 527 (1969); (b) A. Streitwieser, Jr., and W. R. Young, *ibid.*, **91**, 529 (1969).
(13) (a) H. C. Brown and K. Ichikawa, *Tetrahedron*, **1**, 221 (1957); (b) H. C. Brown and M. Borkowski, *J. Am. Chem. Soc.*, **74**, 1889 (1952).
(14) In ref 3, it was stated that the relative protonation rates did *not* follow this order, the C_5 nitronate being protonated *faster* than the C_6 nitronate. A check of the data shows, however, that there is a decimal error in the rate calculated for the C_5 nitronate ion (the relative k_{-2} should be 11.3, not 113).
(15) See also N. Muller and D. E. Pritchard, *J. Chem. Phys.*, **31**, 768, 1471 (1957); C. S. Foote, *Tetrahedron Lett.*, 579 (1963); G. L. Closs and R. B. Larrabee, *ibid.*, 287 (1965).
(16) C. A. Coulsen and W. E. Moffit, *Philos. Mag.*, **40**, 1 (1949).
(17) A. J. Albery, *Faraday Symp. Chem. Soc.*, **No. 10**, 144 (1975).
(18) F. G. Bordwell, W. J. Boyle, and K. C. Yee, *J. Am. Chem. Soc.*, **92**, 5926 (1970).
(19) F. J. Kezdy, J. Jaz, and A. Bruylants, *Bull. Soc. Chim. Belg.*, **67**, 687 (1958).
(20) G. M. Lampman, D. A. Horne, and G. D. Hagar, *J. Chem. Eng. Data*, **14**, 396 (1969).

Kinetic and Equilibrium Acidities of 3-Nitropropene and Some of Its Derivatives

F. G. Bordwell* and Judith A. Hautala[1]

Department of Chemistry, Northwestern University, Evanston, Illinois 60201

Received March 14, 1977

Rates of hydroxide ion deprotonation in water for 3-nitropropene and seven of its derivatives, $R_2R_3C{=}C(G)$-$CH(R_1)NO_2$, where R_1, R_2, and R_3 are either H or Me, and G is H, Me, Ph, or Br, have been measured and compared with their equilibrium acidities in water. These substitutions were found to cause a complex variation of kinetic and equilibrium acidities which was interpreted by assuming that the kinetic acidities were governed primarily by polar effects and steric inhibition of solvation in the transition state, whereas the equilibrium acidities were governed primarily by steric strains in the product nitronate ions. It was concluded that nitroalkane (and other carbon acids) deprotonations usually fail to conform to the Leffler–Grunwald rate–equilibrium relationship when the structural changes are made in the carbon acid. The rates of deprotonation in water for 3-nitropropene, 3-nitropropene-*3,3*-d_2, and 1-nitro-2-butene by pyridine and seven methyl-substituted pyridines were determined. The k_H/k_D isotope ratios were found to vary from 8.5 to 11.4. A Brønsted β of 0.59 was obtained. The significance of these data with respect to the mechanism of deprotonation of nitroalkanes is discussed.

In earlier papers in this series we have examined rates of deprotonation, equilibrium acidities, and isotope effects for a variety of nitroalkanes in an attempt to elucidate the mechanisms of deprotonation of carbon acids by bases.[2] It appeared to be of interest to extend the study of 3-nitropropene and some of its derivatives, since it was anticipated that these β,γ-unsaturated nitroalkanes, which are much more acidic than their saturated analogues, would provide useful information with regard to rate–equilibrium relationships and the variation in the size of k_H/k_D isotope effects with the strength of the base used in the deprotonation.

Results

Rates of proton removal from the β,γ-unsaturated nitroalkanes by hydroxide ion were measured spectrophotometrically in water at 25 °C under pseudo-first-order conditions. The kinetics were followed by stopped-flow except for 2-methyl-3-nitro-1-butene and 2-nitro-3-pentene, where the rates were measured on a Beckman Kintrac VII spectrophotometer. For 3-nitropropene, 1-nitro-2-butene, and 3-methyl-1-nitro-2-butene pK's were measured potentiometrically by a partial neutralization technique; other pK's were

0022-3263/78/1943-3116$01.00/0

Table I. Kinetic and Equilibrium Acidities of Nitroalkenes, $R_2R_3C{=}C(G)CH(R_1)NO_2$, in Water at 25 °C.

R_1	R_2	R_3	G	registry no.	k_1,[a] M^{-1} s^{-1}	pK[b]	k_{-1}[c] (rel)
H	H	H	H	625-46-7	394	5.22[d]	(1.0)
H	Me	H	H	1809-69-4	128	5.44	0.52
H	Me	Me	H	1809-65-0	77	5.55	0.41
H	H	H	Me	1606-31-1	62	7.27	17
Me	Me	H	H	1806-28-6	5.9[e]	5.35	0.019
Me	H	H	Me	19031-81-3	2.5[e]	7.85	3.4
H	H	H	Ph	58502-68-4	185	7.26	50
H	H	H	Br	1809-71-8	3450	5.60	20

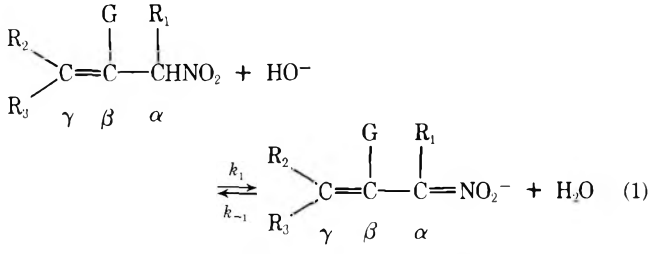
[a] Average from data on three photographs each comprising three superimposed runs on a Durrum–Gibson stopped-flow apparatus with hydroxide ion (SD < ±5%); not statistically corrected. [b] Average of two or more determinations (SD ± 0.03 pK units); activity coefficient corrections for differences in ionic strength have been applied. [c] Calculated from the equation $k'_{-2}/k_{-2} = K_{HA}k'_2/K'_{HA}k_2$. d_{pK} = 10.49 in MeOH. [e] Average of eight runs on a Beckman Kintrac VII spectrophotometer.

Table II. Rate Constants for Deprotonation of 3-Nitropropene, 3-Nitropropene-*3,3-d*$_2$, and 1-Nitro-2-butene by Pyridine Bases in Water at 25 °C

base	pK_{BH^+}[a]	3-nitropropene 10^1k_H[b]	3-nitropropene 10^2k_D	3-nitropropene k_H/k_D	1-nitro-2-butene, 10^2k,[b] M^{-1} s^{-1}
pyridine	5.22	0.567	0.577	8.5	1.60
3-picoline	5.63	1.11	1.28	8.7	3.33
2-picoline	5.96	1.82	1.56	10.2	5.6
4-picoline	5.98	1.45	1.37	9.2	
3,4-lutidine	6.46	2.92	2.74	9.2	7.97
2,4-lutidine	6.63	4.27	4.07	9.1	12.5
2,6-lutidine	6.75	1.74	1.33	11.4	5.53
2,4,6-collidine	7.59	3.37	2.72	10.8	

[a] R. J. L. Andon, J. D. Cox, and E. F. G. Herington, *Trans. Faraday Soc.*, **50**, 923 (1958). [b] Determined by the buffer dilution method; standard deviations were all <5% (units are M^{-1} s^{-1}).

measured spectrophotometrically. The pK's of propene-3-nitronic acid and 2-butene-1-nitronic acid were also measured in order to determine whether or not the pK's of the corresponding nitroalkenes should be corrected for the presence of the aci form. Since the nitronic acids were found to be ~2 pK units more acidic than the nitroalkenes, the aci form is present in low concentration and the correction is within the experimental error of the measurements for the nitroalkenes. The results summarized in Table I refer to the reaction in eq 1.

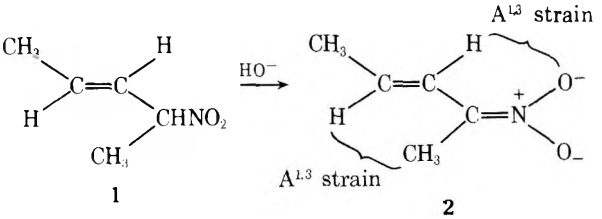


(1)

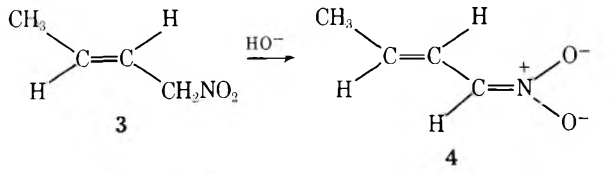
Rates of reaction of 3-nitropropene, 3-nitropropene-*3,3-d*$_2$, and 1-nitro-2-butene with a series of pyridine bases were determined in order to obtain Brønsted correlations and k_H/k_D *isotope effects* (Table II).

Discussion

Effects of Substitution on Kinetic and Equilibrium Acidities of 3-Nitropropenes. Substitution of methyl for a hydrogen atom α to the nitro group in $CH_3CH{=}CHCH_2NO_2$ (to give **1**) causes an 11-fold retardation (statistically corrected) in rate. This result is comparable to the 10.5-fold retardation observed for substitution of an α-methyl group into nitroethane, a result that has been attributed to steric inhibition of solvation by methyl in the transition state for the deprotonation reaction.[2] On the other hand, this substitution causes an increase in equilibrium acidity of only 0.09 pK unit (Table I), whereas an increase of almost 1 pK unit is observed for the change from nitroethane to 2-nitropropane. For the saturated nitroalkanes, the substantial increase in acidity is believed to be caused by stabilization of the $MeCH{=}NO_2^-$ and $Me_2C{=}NO_2^-$ nitronate ions resulting from methyl substitution.[2] In the unsaturated compounds this effect is evidently either absent or offset by other factors. The latter seems to be the case, since examination of scalar models indicates that 1,3 steric interactions between methyl and hydrogen and between O^- and hydrogen nitronate ion (**2**) ($A^{1,3}$ strains[3]) are important in destabilizing this anion.

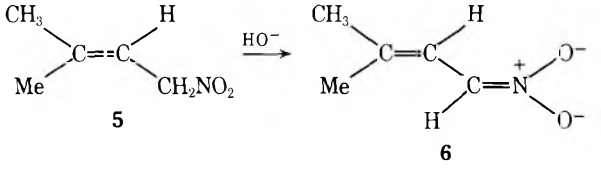


Substitution of methyl for a hydrogen atom γ to NO_2 in 3-nitropropene (to give **3**) causes a 3.1-fold decrease in kinetic acidity and a 0.2 pK unit decrease in equilibrium acidity (Table I). Methyl groups attached to sp^2 carbon atoms have electron-releasing effects, which could affect solvation in such a way as to raise the energy of the transition state in the deprotonation of **3**.[4] Since no change in hybridization at the carbon atom to which the methyl group is attached occurs when **3** is transformed to **4**, nitronate ion **4** is not stabilized, relative to **3**, by methyl substitution, as happens in the transformation of $MeCH_2NO_2$ to $MeCH{=}NO_2^-$.[2] Therefore, no appreciable change is expected in equilibrium acidities for $MeCH{=}CHCH_2NO_2$ vs. $HCH{=}CHCH_2NO_2$, and none is observed.



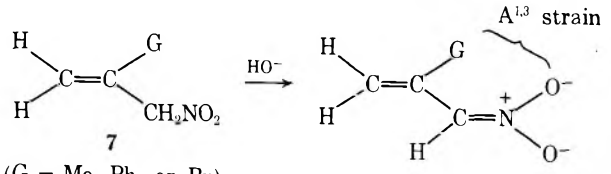
3 4

Substitution of methyl for the γ-hydrogen atom in **3** (to give **5**) introduces a cis interaction between Me and CH_2NO_2, which will destabilize **5**, relative to **3**. This interaction is also present in the nitronate ion (**6**) (comparable to $A^{1,3}$ strains in **2**). As a result, these effects balance one another, and the effect on acidity of introduction of the second methyl group differs but little from that observed for introduction of the first methyl group (Table I).



5 6

Substitution of methyl for a hydrogen atom β to NO_2 in $H_2C{=}CHCH_2NO_2$ (to give **7**, G = Me) causes a 6.4-fold decrease in kinetic acidity and a 2 pK unit decrease in equilibrium acidity (Table I). Here, the methyl effect on the kinetic acidity is similar to that for α substitution, but the methyl effect on equilibrium acidity differs markedly (2 pK unit decrease as compared to a 0.09 pK unit increase). This is understandable, since the $A^{1,3}$ steric interaction in **8** is between methyl and O^-, and is much more severe than that in **2**. This increased strain is responsible for the lowered equilibrium acidity of **7**.



7 (G = Me, Ph, or Br) 8 (G = Me, Ph, or Br)

Substitution of Ph for a β-hydrogen atom (**7**, G = Ph) causes a 2.2-fold decrease in kinetic acidity, which is accompanied by a 2 pK unit decrease in equilibrium acidity. The phenyl group in **8** must be tilted out of the plane of the C=CC=N bond system in order to relieve $A^{1,3}$ strain. Some delocalization of charge would be possible, even in this conformation, but this would be a cross-conjugation effect, and stabilization by Ph through this effect must be minimal. The sharp decrease in equilibrium acidity for β-Ph substitution is therefore understandable.

Substitution of Br for a β-hydrogen atom (**7**, G = Br) causes a ninefold *increase* in kinetic acidity, which is accompanied by a 0.4 pK unit decrease in equilibrium acidity. Apparently the much greater polar effect of Br, as compared to Me or Ph, is sufficient to override steric inhibition of solvation in the transition state for the hydroxide ion deprotonation. (A plot of σ_m vs. log k_1 for the β-Me, β-Ph, and β-Br compounds gave a linear correlation, r = 0.9999, slope = 3.8, suggesting that polar effects are influential in controlling these deprotonation rates.) The slight decrease in equilibrium acidity for $H_2C{=}C(Br)CH_2NO_2$, relative to $H_2C{=}CHCH_2NO_2$, can be explained as the result of a balance between the sizable polar effect of Br, which is acid strengthening, and the sizable steric effect of Br, which is acid weakening.

We have seen that substitution of various groups for a hydrogen atom at the α, β, and γ positions of 3-nitropropene causes a complex variation of kinetic and equilibrium acidities, including substantial decreases in kinetic acidities accompanied by little change in equilibrium acidity [$MeCH{=}CHCH(Me)NO_2$ vs. $MeCH{=}CHCH_2NO_2$], substantial increases in kinetic acidities accompanied by little change in equilibrium acidity [$CH_2{=}C(Br)CH_2NO_2$ vs. $CH_2{=}CHCH_2NO_2$], and substantial decreases in both kinetic and equilibrium acidities [$CH_2{=}C(Me)CH(Me)NO_2$ vs. $CH_2{=}CHCH_2NO_2$]. These results have been interpreted by assuming that the kinetic acidities are governed primarily by two factors, steric inhibition of solvation in the transition state and a polar factor, which are probably interrelated, and that equilibrium acidities are governed primarily by steric strains ($A^{1,3}$ strains) in the nitronate ions. These steric strains are evidently not operative in the transition state for deprotonation of these nitroalkenes by hydroxide ion.

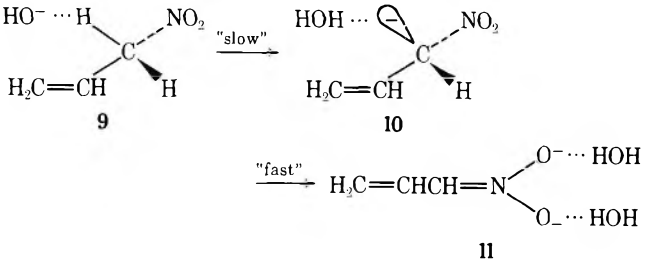
The lack of correlation between the kinetic and equilibrium acidities of alkyl-substituted 3-nitropropenes is comparable to the lack of such correlations with saturated alkyl-substituted nitroalkanes and nitrocycloalkanes.[2] These failures of the Brønsted relationship represent failures of the Leffler–Grunwald rate–equilibrium relationship (eq 2), wherein α was assumed to be confined to the limits of 0 and 1.0.[5]

$$\delta\Delta G^{\ddagger} = \alpha\delta\Delta G^{\circ} \qquad (2)$$

Failures of eq 2 are common for nitroalkanes. They are observed not only when structural changes occur near to the reactive site and are largely steric in nature, as in the examples just mentioned, but also when the substituents are remote and are largely polar in nature, as in the electronic effects of substituents, G, in $G(CH_2)_3NO_2$ and $GC_6H_4CH_2NO_2$ systems.[2] In all of these examples eq 2 fails because the substituent changes do not cause changes on the transition state energy that are *intermediate* between those caused on the reactants and products, but instead are *greater* in the transition state (either more stabilizing or more destabilizing) than in the reactants and/or products. The complex variation in kinetic and equilibrium acidities for the $R_2R_3C{=}C(G)CHR_1NO_2$ system, as R_1, R_2, R_3, and G are changed, therefore fits the general pattern of behavior observed previously for nitroalkanes. It can be accommodated by the mechanism for deprotonation discussed in the earlier papers in this series wherein formation of an essentially pyramidal, singly H-bonded intermediate is assumed (**10** in Scheme I).[2]

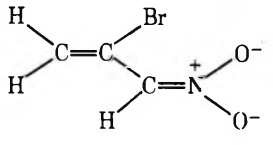
Examining the substituent changes (Table I) in light of this mechanism we see that the rate retardations observed for α-Me or β-Me substitution and the rate acceleration observed for β-Br substitution can be attributed to polar effects on the (essentially pyramidal) transition state leading to intermediate **10**, whereas the effects of these substituents on the equilibria include important contributions from steric effects, which are felt primarily in the (planar) nitronate ion product and not in the transition state. The interplay between these substituent effects on transition state and product can best be seen with the more polar substituents, Br and Ph. Substitution of a β-H atom by Br produces a nearly ninefold acceleration in the deprotonation rate, attributable to a substantial

Scheme I

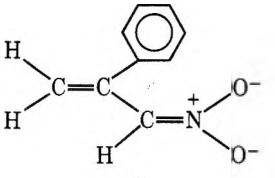


9 10 11

electron-withdrawing polar effect on the transition state leading to the intermediate. This is accompanied by a 0.4 pK unit *decrease* in equilibrium acidity, attributable to larger steric destabilization than polar stabilization of the product nitronate ion (**12**). The polar Ph group, when substituted for a β-H atom, causes a twofold retardation in the deprotonation rate accompanied by a 2 pK unit decrease in equilibrium acidity. The substantial decrease in equilibrium acidity suggests that not only is the Ph group unable to stabilize the nitronate ion **13** by a conjugative interaction, but also that it interferes with the ability of the CH_2=CH group to do so.



12



13

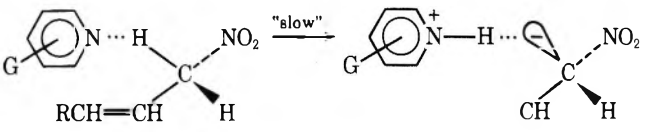
The polar effect of a β-Ph group should accelerate deprotonation of H_2C=C(Ph)CH_2NO_2 by HO^-. The observation of a twofold rate *retardation* (Table I) indicates that the large steric effect in **13** must be felt to some degree in the transition state for the intermediate believed to precede **13** along the reaction profile (Scheme I). In describing this intermediate as being "essentially pyramidal" we do not wish to imply that *no* rehybridization has occurred, but merely that rehybridization, and the accompanying solvent reorganization, is incomplete. For highly endoenergetic deprotonations, such as that of nitrocyclopropane, the evidence points to substantial rehybridization in the transition state (see the preceding paper in this issue) and, when conjugation between the developing charge on the α carbon and an α substituent can occur, rehybridization in the transition state would be expected to increase to take advantage of this stabilizing influence. On this basis we expect a greater degree of rehybridization in intermediate **10** than in comparable intermediates where an alkyl group has replaced the vinyl group at the α-carbon atom. The extent of this rehybridization in the transition state leading to **10** does not seem to be large, however, judging from the small rate retarding β-Ph effect. Also, the point for α-Ph fits reasonably well on a Taft plot constructed for deprotonation rates in 50% MeOH–H_2O for nitroalkanes of the type $G(CH_2)_nNO_2$, where n = 1, 2, or 3 (see Figure 1 in paper 3 in this series). The present data, when corrected for the change in solvent, indicate that the α-vinyl point will also fit this plot reasonably well.

Brønsted Correlations for Deprotonation with Pyridine Bases. Brønsted plots using the data in Table II for the first six bases and two nitroalkenes gave linear correlations (r = 0.990 and 0.986). The points for 2,6-lutidine and 2,4,6-collidine fell well below the lines and the k_H/k_D isotope effects were enhanced, which is usual for these sterically hindered bases.[8] The large k_H/k_D isotope ratios observed (near 9) are indicative of a transition state where H–C bond breaking is substantial and $\Delta G°$ is somewhere near zero. The broad maximum observed in k_H/k_D vs. ΔpK plots where the nature of the carbon acid and base are both changed makes it difficult to use the size of the k_H/k_D ratio as a guide to the position of the transition state along the reaction coordinate.[11a] The overall reaction, **14** → **16**, has a $\Delta G°$ near zero, but, if formation of an intermediate (**15**) is postulated, the rate-limiting step would probably be on the endoenergetic side. There is no apparent trend in the k_H/k_D ratio as ΔpK is changed, which supports the view that transition-state structures vary but little with small changes in $\Delta G°$.[11] The Brønsted β is in each instance 0.59, which is slightly smaller than that observed for the reaction of pyridine bases in water with nitroethane (β = 0.65[8a]). It is possible, as has frequently been postulated,[5,9,10] that the size of β gives a measure of the extent of proton transfer in the transition state for deprotonation reactions, but when one considers that in comparing the reactions of amine bases with such diverse carbon acid substrates as 3-nitropropene, nitroethane,[13] cyclohexanone,[12] and 3-cyclohexenone[14] β falls in the narrow range of 0.5–0.6 despite changes in $\Delta G°$ that are probably greater than 10 kcal/mol, it is clear that β cannot be a very sensitive guide to transition-state structure.

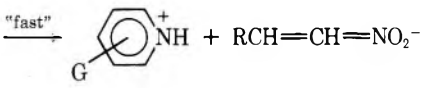
Table III. Effects on Equilibrium and Kinetic Acidities of Introducing β,γ Unsaturation into Various Carbon Acids

type of parent carbon acid	pK (Me_2SO)[a]	ΔpK (Me_2SO)[c]	log ($k_{\beta\gamma}/K$([E]
nitroalkane	~18	~5	~2
ketone	~27	~7	~3[f]
sulfone	~32	~7.5	~4[g]
alkene	~42[b]	~10[d]	~6[h]

[a] Average values for simple compounds in this class (see ref 17). [b] Taken as equal to the lowest of the values extrapolated for toluene (ref 18). [c] ΔpK = pK(RCH_2G) − pK($PhCH_2G$) unless otherwise noted. [d] Estimate based on pK($PhCH_3$) − pK($PhCH_2Ph$). [e] Rate ratio for deprotonation by HO^- (or RO^-) in H_2O (or ROH) unless otherwise noted. [f] From rate data at 0 °C for cyclohexanone (ref 20) and at 25 °C for cyclohexenone (ref 14). [g] Rate for $PrCH_2SO_2CH_3$ vs. $PrCH{=}CHCH_2SO_2CH_3$ (ref 21). [h] Rate for $CH_2{=}CHCH_2CH{=}CH_2$ vs. $CH_2{=}CHCH_2Me$ (ref 22).



14 (R = H or Me) **15** (R = H or Me)



(G = Me or diMe) **16** (R = H or Me)

Correlation of Equilibrium and Kinetic Acidities for Structural Changes in Various Weak Carbon Acids. From the data in this and the two preceding papers in this series we have concluded that deprotonations of nitroalkanes usually fail to conform to the rate–equilibrium relationships (eq 2) when structural changes in the nitroalkanes cause effects that are either primarily polar or steric in nature. This is believed to be a consequence of the extensive rehybridization and solvent reorganization in the carbon acid that accompany these deprotonations. It seems likely that most other carbon acids will behave similarly, although the lack of correlation may be less extreme and therefore less obvious. Experimental data to test this point are meager, since nitroalkanes are the only monofunctional substrates acidic enough to permit equilibrium acidities, as well as kinetic acidities, to be determined in protic media. The lower acidity of other monofunctional carbon acids means that, with a given base, deprotonations will be more endoenergetic, and the transition state will be more product-like (Leffler–Hammond postulate[15,16]). Therefore, we would expect a greater degree of rehybridization in the transition state leading to intermediates comparable to **10** or to **15**. An estimate of the relative extent of such rehybridization in weaker carbon acids can be obtained by comparing the effect on kinetic and equilibrium acidities

of introducing β,γ unsaturation into various types of carbon acids of decreasing strengths (Table III).

The estimates summarized in Table III are necessarily rough, since the data available are limited and are taken from a variety of sources in different types of solvents. (Data in solvents of the same type are not available.) The equilibrium acidities are measured or extrapolated from data in Me_2SO solvent,[17,23] while the rate data are for deprotonation rates using hydroxide or alkoxide ion as the base in protic solvents. Since substitution of either a Ph or CH_2=CH group for R in RCH_2NO_2 has an effect of the same order of magnitude on equilibrium and kinetic acidities, we have assumed that this will also be true for other carbon acids. (Substitution of Ph for Et in $EtCH_2NO_2$ increases the acidity by 4.8 pK units and a 5.8 pK unit is observed for vinyl substitution; the rate accelerations for deprotonation by RO^- in protic solvents are ~30-fold and 85-fold, respectively.[2]) Examination of Table III shows that there is a progressive decrease in the size of ΔpK from the weakest carbon acid (the alkene) to the strongest carbon acid (the nitroalkane). This corresponds to a progressive decrease in the negative charge density at the carbon atom of the acidic site in the parent acid as it becomes stronger (resonance saturation effect[19]). A similar, but smaller, effect is observed on the rates. Here the negative charge density at the carbon atom of the acidic site apparently becomes progressively greater in the transition state for the deprotonation as the acid becomes progressively weaker, in agreement with the expectation of a more product-like transition state[15,16] and a progressively greater ability of the α-Ph (or α-C=C) substituent to stabilize the charge by delocalization. Although the comparisons are crude, it would appear that rehybridization in the transition state becomes progressively greater as the acid gets weaker, and that the effect on the rate begins to approach that on the equilibrium. In other words, the Brønsted α increases in size, as anticipated by the Leffler–Grunwald rate–equilibrium equation (eq 2). The data in Table III suggests, therefore, that for deprotonation reactions that span large $\Delta G°$ ranges, variation in transition-state structures may be large enough to conform approximately to eq 2. On the other hand, for small $\Delta G°$ ranges, such as those encountered in this series of papers, where substituent effects on a single type of carbon acid are considered, the variation in transition-state structure is slight and eq 2 does not hold, even approximately. In such instances the size of α will change depending on the details of the mechanism for deprotonation, which is likely to be complex.[2] For carbon acids where deprotonation is accompanied by extensive structural and solvent reorganization, such as $ArCH_2NO_2$ or $R_1R_2CHNO_2$, we have seen that substituent effects on the transition state for deprotonation may be larger or in an opposite direction to those on the product anions, leading to Brønsted α's larger than 1.0 or negative in sign. These data have been rationalized by assuming that rehybridization of the carbon atom at the acidic site has progressed but little in the transition state. For weaker carbon acids the data in Table III suggest that rehybridization in the transition state for deprotonation becomes progressively greater as the acid becomes weaker. At the same time the extent of delocalization of the negative charge in the product anion becomes progressively less as the acid becomes weaker. We can anticipate, therefore, that for very weak carbon acids rehybridization of the carbon atom at the acidic site in the transition state for deprotonation will differ but little from that in the product anion,[15,16] and that substituent effects on the kinetic and equilibrium acidities will correspond more closely to that predicted by eq 2. This does not mean, however, that we can expect substituent effects to be intermediate to those on reactants and products or that the Brønsted α can provide more than a rough guide to the transition-state structure.

Experimental Section[24]

Instruments and Analyses. Infrared spectra were taken on either a Baird Model AB-2 or a Beckman IR 5 spectrophotometer with the polystyrene 6.243-μm band as a standard. Nuclear magnetic resonance spectra were taken on either a Varian Model A60 or Varian Model T60 instrument with tetramethylsilane as an internal standard. Analytical and preparative gas–liquid chromatography were performed on an F & M Model 5750 research chromatograph equipped with a thermal conductivity detector and a disc integrator, using helium carrier gas, an injection port temperature of 250 °C, and a detector temperature of 290 °C. The column employed for purification and analysis of the nitroalkenes was QF-1 on specially acid washed Chromosorb W.[25]

pK Determinations. 1. Potentiometric. The pK's of 3-nitropropene, 1-nitro-2-butene, and 3-methyl-1-nitro-2-butene were measured in water at 25 °C by the partial neutralization technique described previously.[2] The pH measurements were performed on a Sargent Model DR digital readout pH meter equipped with a Corning semimicro combination electrode. Equilibrium was attained in ~10 min and measurements were taken every 10 min for 1 h. After 1 h, the solutions began to decompose.

2. Spectrophotometric. The pK's of the remaining nitroalkenes were measured spectrophotometrically in water at 25 °C using a Cary Model 15 recording spectrophotometer with a brass cell block thermally controlled by an Aminco circulating water bath.

Constant ionic strength buffer solutions were prepared using reagent grade materials which were not further purified. The pH's were measured immediately prior to use and never differed by more than 0.04 units from that calculated.

In a typical experiment with nitroalkenes which do not isomerize in buffer, 3.0 mL of the appropriate solvent (water, 0.1 M sodium hydroxide or buffer) was pipetted into a cuvette. After thermal equlibration 10–40 μL of ~0.01 M nitroalkene solution in methanol (prepared as described for the potentiometric pK measurements) was injected using a 50-μL Hamilton 710N syringe. The syringe always contained 5–10 μL of methanol behind the nitroalkene solution in order to ensure complete delivery. The resulting concentration of nitroalkene in the cuvette was in the range of 5×10^{-5} to 2×10^{-4} M. The ultraviolet spectra were recorded from 350 to 220 nm.

The spectrum of nitroalkene in water (slightly acidified) was assumed to be that of the protonated species, and the spectrum in 0.1 M sodium hydroxide to be of the nitronate anion. The extinction coefficients at various wavelengths were then calculated for both forms. These extinction coefficients, rather than literature values, were used in order to eliminate errors resulting from possible differences between the actual concentration of nitroalkene and that calculated.

The spectrum of nitroalkene in buffer (the pH of which was in the region of the expected nitroalkene pK) was scanned at appropriate intervals until equilibrium was established (1–24 h) and continued for several additional hours. The pK was calculated from the equations

$$C_{HA} = T - C_{A^-} \tag{3}$$

$$A_{obsd} = C_{A^-}\epsilon_{A^-} + (T - C_{A^-})\epsilon_{HA}$$

$$C_{A^-} = (A_{obsd} - T\epsilon_{HA})/(\epsilon_{A^-} - \epsilon_{HA}) \tag{4}$$

$$pK = pH + \log(C_{HA}/C_{A^-}) - \log \gamma_{\pm} \tag{5}$$

A_{obsd} is the equilibrium absorbance value of the nitroalkene in buffer at a specified wavelength, ϵ_{HA} and ϵ_{A^-} are the extinction coefficients of the nitroalkene and its anion at that wavelength, C_{HA} and C_{A^-} are the molar concentrations of nitroalkene and anion, T is the total calculated molar concentration of substrate, $-\log \gamma_{\pm}$ is an activity coefficient correction factor which was taken to be equal to the activity coefficient of aqueous potassium chloride at the ionic strength of the buffer, and the pH is that measured for the buffer prior to the experiment. The pK was calculated in this manner at three different wavelengths, usually the λ_{max} for the nitronate anion and 15–20 nm above and below this value. The entire procedure was repeated at least twice for every pK value reported. The standard deviation was generally 0.01–0.02 pK units and never exceeded 0.05 unit.

For those nonconjugated (β,γ-unsaturated) nitroalkenes which isomerize readily in buffer solution to the conjugated (α,β-unsaturated) form a more complicated treatment was necessary. The conjugated nitroalkene (α,β isomer) was synthesized independently, and its spectrum in the buffer employed was recorded in the manner described previously. The extinction coefficients at the wavelengths used for the pK measurement were calculated from this spectrum. The spectrum in buffer was found to be identical with that in slightly

Table IV. Ultraviolet Spectra of Conjugated Nitronate Ions in Water at 25 °C[a]

nitronate ion	registry no.	μ_{max}, nm	ϵ_{max}
$CH_2{=}CHCH{=}NO_2^-$	60211-46-3	275	20 700
$MeCH{=}CHCH{=}NO_2^-$	66291-29-0	274	23 500
$CH_2{=}C(Me)CH{=}NO_2^-$	66291-28-9	276	14 570
$CH_2{=}C(Br)CH{=}NO_2^-$	66291-27-8	276	13 100
$CH_2{=}C(Ph)CH{=}NO_2^-$	66291-26-7	288	10 990

[a] Spectra of the nitroalkenes in 0.1 M NaOH; anion concentration $2\text{–}4 \times 10^{-5}$ M.

acidified water, although it decreased over long time periods and after ~24 h no observable absorbance remained. No spectral change which indicated nitronate ion formation was observed, in accordance with the expected low acidity of the conjugated nitroalkene.

The experimental procedure was identical with that described for the nonisomerizing nitroalkenes. The pK was calculated from the equations

$$A_{obsd}^{\lambda_1} = C_A - \epsilon_{A^-}^{\lambda_1} + C_{\beta\gamma}\epsilon_{\beta\gamma}^{\lambda_1} + C_{\alpha\beta}\epsilon_{\alpha\beta}^{\lambda_1} \quad (6)$$

$$A_{obsd}^{\lambda_2} = C_{A^-}\epsilon_{A^-}^{\lambda_2} + C_{\beta\gamma}\epsilon_{\beta\gamma}^{\lambda_2} + C_{\alpha\beta}\epsilon_{\alpha\beta}^{\lambda_2} \quad (7)$$

$$T = C_{A^-} + C_{\beta\gamma} + C_{\alpha\beta} \quad (8)$$

$$pK = pH + \log (C_{\beta\gamma}/C_{A^-}) - \log \gamma_{\pm} \quad (9)$$

with the aid of a Control Data 6400 computer. The terms λ_1 and λ_2 refer to two wavelengths, generally the λ_{max} of the nitronate anion and that of the α,β isomer; $A_{obsd}^{\lambda_1}$ and $A_{obsd}^{\lambda_2}$ are the absorbance values at these wavelengths of the β,γ isomer in buffer solution; $\epsilon_{A^-}^{\lambda_1}$, $\epsilon_{\beta\gamma}^{\lambda_1}$, $\epsilon_{\alpha\beta}^{\lambda_1}$, $\epsilon_{A^-}^{\lambda_2}$, $\epsilon_{\beta\gamma}^{\lambda_2}$, and $\epsilon_{\alpha\beta}^{\lambda_2}$ are the extinction coefficients of the nitronate anion, the $\beta\gamma$ isomer, and the α,β isomer at each wavelength; C_{A^-}, $C_{\beta\gamma}$, and $C_{\alpha\beta}$ are the molar concentrations of the three species; T is the total substrate concentration; pH and $-\log \gamma_{\pm}$ are the same as defined above.

The concentrations of the three species and the pK were calculated at several time intervals prior to and after attainment of equilibrium. At the outset the concentration of nitronate anion increases at the expense of the β,γ isomer, and a concentration of the α,β isomer slowly appears. After equilibrium is established, the concentration of the conjugated isomer continues to increase, while both the nitronate anion and the nonconjugated isomer decrease, but the ratio of the latter concentrations remains constant. Each pK value reported is the average of at least two determinations, with standard deviations of ~0.03 pK units (Table IV).

pK in Methanol. The pK of 3-nitropropene in methanol was measured by the spectrophotometric technique described above. An acetic acid/sodium acetate buffer in methanol was prepared as described by Belikov[26] using standardized 1.0 M acetic acid in methanol and 1.0 M sodium methoxide in methanol.

pK of Nitronic Acids. The pK values for propene-3-nitronic acid and 2-butene-1-nitronic acid were determined potentiometrically as described above except that partial neutralization was accomplished by adding increments of standard hydrochloric acid to a solution of the aci anion.

In a typical experiment, a standard solution of the aci anion (~0.01 M) in water was prepared from the sodium salt of the nitroalkane.[27] Increments (25-mL) of this solution were pipetted into wide-mouthed glass bottles with ground-glass stoppers. An increment of standard hydrochloric acid was added to effect a percentage neutralization in the range of 30–60%. Immediately after addition of the acid, the electrodes were immersed in the solution and pH readings were begun. Due to the isomerization of the liberated acid, the pH was observed to increase with time. However, since this increase with time was linear within experimental error, pH readings taken at various time intervals after addition of the acid could be extrapolated back to zero time in order to obtain the initial pH. This extrapolated pH value was used in the Henderson–Hasselbach equation to calculate the pK_{aci}. The above procedure was repeated four times for each nitronic acid using a different volume of hydrochloric acid in order to effect a different percentage neutralization. The pK_{aci} values calculated agreed within 0.03 pK units.

Kinetic Procedure. The rates of deprotonation by hydroxide ion in water at 25 °C were determined spectrophotometrically by following the appearance of the nitronate ion absorption in the ultraviolet region (λ_{max} 275–290 nm, ϵ_{max} 10 000–25 000) as previously described. The measurements for nitroalkenes were performed on a Durrum–Gibson stopped-flow spectrophotometer or on the Beckman Kintrac VII spectrophotometer.

The rates of deprotonation and dedeuteration by pyridine bases in water at 25 °C were measured spectrophotometrically by the buffer dilution method previously described.[2] The buffer pH was in all cases sufficiently high to ensure that the nitroalkene deprotonation was complete.

Preparations and Purifications. A sample of 2-methyl-3-nitrobutene prepared by Dr. E. W. Garbisch from the reaction of acetyl nitrate with 2-methyl-2-butene was redistilled and purified by vapor-phase chromatography. All other β,γ-unsaturated nitroalkanes were prepared by treatment of the allylic bromides or chlorides with silver nitrite according to the method of Kornblum and Ungnade.[28] A typical procedure is given below for 3-nitropropene. The purity of all nitroalkenes employed was at least 98% as evidenced by vapor-phase chromatography. The boiling points, refractive indices, and NMR spectral data are presented in Table V.

3-Nitropropene. The reaction was performed in a dark room equipped with a red safelight until the silver salts and nitrite esters were removed. Silver nitrite was prepared by adding a solution of 85 g of silver nitrate in 250 mL of water in several small portions with vigorous mixing to a solution of 35 g of sodium nitrite in 125 mL of water. The suspension was allowed to stand in the dark for 1 h. The yellow silver nitrite solid was separated by suction filtration, washed three times with 125 mL of water and twice with 100 mL of absolute methanol, and dried to constant weight in a vacuum desiccator over phosphorus pentoxide (36–48 h).

Eastman 3-bromopropene (34 g, 0.28 mol) was added dropwise over 1 h to a vigorously stirred suspension of 64.8 g (0.422 mol) of silver nitrite in 100 mL of anhydrous ether contained in a 500-mL three-neck flask equipped with a Teflon sleeve mechanical stirrer and a condenser protected with a drying tube. The flask was immersed in a large Dewar filled with ice–water to maintain a temperature of 0–5 °C throughout the reaction. Following the bromide addition, the solution was vigorously stirred for 12 h, at which time the supernatnat liquid gave a negative halide test (alcoholic silver nitrate).

The silver salts were removed by suction filtration and slurried three times with 75 mL of anhydrous ether. The combined ether filtrates were allowed to stand overnight in the dark with 8 mL of absolute methanol to hydrolyze the nitrite esters to the methyl ether of allyl alcohol.

The solvent was removed at atmospheric pressure using an 8 in. Vigreux column. The residue was distilled to yield 10 g (41%) of 3-nitropropene. *CAUTION:* The distillation residue must be cooled to room temperature before exposure to the atmosphere and due caution exercised in disposal, which should be done immediately following air exposure. Final purification employed gas–liquid chromatography.

3-Nitropropene-d_2. The nitroalkene dideuterated in the 3 position was prepared by the method described previously[2] using a deuterated succinic acid/sodium succinate buffer. Dideuterated succinic acid was prepared by refluxing succinic anhydride in deuterium oxide for 1 h. The isotopic purity of the nitroalkene in the 3 position was 98% (NMR).

Substituted 3-Nitropropene Derivatives. The substituted derivatives were prepared as described for 3-nitropropene above. The starting halide employed and any deviation in reaction conditions (i.e., temperature or reaction time) are given below (nitroalkene, starting halide, reaction conditions): 1-nitro-2-butene, 3-chloro-1-butene (Aldrich),[29] 12 h at 0–5 °C; 3-methyl-1-nitro-2-butene, 3-methyl-1-nitro-2-butene, 3-methyl-1-bromo-2-butene,[30] 24 h at 0–5 °C; 2-methyl-3-nitropropene, 2-methyl-3-chloropropene (Aldrich), 8 h at 0–5 °C, 24 h at 25 °C, and 36 h at reflux; 2-phenyl-3-nitropropene, 2-phenyl-3-bromopropene (prepared from α-methylstyrene by the method of Reed[31]), 48 h at 0–5 °C; 2-bromo-3-nitropropene, 2,3-dibromopropene (Aldrich), 12 h at 0–5 °C; 2-nitro-3-pentene, 2-bromo-3-pentene (prepared from Chemical Samples 3-penten-2-ol by the method of Hwa and Sims[32]), 24 h at 0–5 °C.

2-Methyl-1-nitropropene (17). The α,β-unsaturated nitroalkene was prepared from 2-methyl-3-nitropropene (7, G = Me) by triethylamine-catalyzed isomerization in hexane according to the method of Hesse et al.[33] An equilibrium mixture of 82% 17 and 18% 7 was obtained. Pure 17 was isolated by vapor-phase chromatography: UV max (C_2H_5OH) 250 nm (ϵ 8600), (H_2O) 262 nm (ϵ 8900), (*n*-hexane) 240 nm (ϵ 9000) [lit.[34] UV max (C_2H_5OH) 251 nm (ϵ 8600), (*n*-hexane) 235 nm (ϵ 10 000)]; NMR ($CDCl_3$) δ 1.98 (s, 3, methyl cis to hydrogen), 2.26 (s, 3, methyl cis to nitro), and 6.98 (s, 1 $=CHNO_2$).

2-Methyl-3-nitro-2-butene (18). The α,β-unsaturated nitroalkane was prepared from 3-nitro-2-methyl-2-butyl acetate according to the

Table V. Physical Properties of 3-Nitropropene and Its Derivatives

nitroalkene	bp, °C (mmHg)	n_D (temp, °C)	lit. n_D (temp, °C)	NMR $\delta_{Me_4Si}(CDCl_3)$, ppm
3-nitropropene	44 (27)	1.4258 (21)	1.4260 (20)[a]	4.98 (d, 2, J = 7 Hz, CH_2NO_2), 5.3–5.5 (m, 2, H_2C=), 6.1 (m, 1, =CH–)[2]
1-nitro-2-butene	60 (25)	1.4387 (21)	1.4391 (20)[b]	1.78 (d, 3, J = 5 Hz, CH_3CH=), 4.85 (d, 2, J = 6 Hz, CH_2NO_2), 5.8 (m, 2, –CH=CH)
3-methyl-1-nitro-2-butene	55 (8)	1.4490 (21)	1.4489 (20)[b]	1.75 (m, 6, $(CH_3)_2C$=), 4.90 (d, 2, J = 8 Hz, CH_2NO_2), 5.5 (t, 1, J = 8 Hz, =CH–)
2-methyl-3-nitropropene	38 (12)	1.4323 (21)	1.4331 (20)[b]	1.82 (s, 3, =$C(CH_3)$–), 4.92 (s, 2, CH_2NO_2), 5.2 (bs, 2, H_2C=
2-phenyl-3-nitropropene	84 (0.3)	1.5831 (20)		5.20 (s, 2, CH_2NO_2), 5.35, 5.65 (2s, 2, H_2C=), 7.25 (bs,5, C_6H_5
2-bromo-3-nitropropene	34 (0.3)	1.4963 (21)	1.4970 (20)[b]	5.26 (s, 2, CH_2NO_2), 5.9–6.2 (m, 2, H_2C=)
2-nitro-3-pentene	61 (30)	1.4348 (21)	1.4356 (20)[b]	1.60 (d, 3, J = 6.6 Hz, CH_3CHNO_2), 1.75 (d, 3, J = 5 Hz, CH_3CH=), 5.00 (q, 1, J = 6.5 Hz, $CHNO_2$), 5.7 (m, 2, –CH=CH–)
2-methyl-3-nitrobutene	50 (15)	1.4365 (21)	1.4352 (20)[c]	1.67 (d, 3, J = 7 Hz, CH_3CHNO_2), 1.82 (s, 3, =$C(CH_3)$–), 5.07 (q, 1, J = 7 Hz, $CHNO_2$), 5.17 (s, 2, H_2C=)

[a] N. Kornblum and D. C. Iffland, unpublished work reported in *Org. React.*, **12**, 131 (1962). [b] Yu. V. Baskov and V. V. Perekalin, *Zh. Org. Khim.*, 1, 236 (1965). [c] Reference 37.

Table VI. NMR Spectra of 3-Nitropropene and the Sodium Salt of Its Anion in D_2O and in MeOD

substrate	δ CH_2=, ppm	δ =CH–, ppm	δ CH_2NO_2, ppm
CH_2=$CHCH_2NO_2$[a]	5.45	6.15	4.97
CH_2=$CHCH$=$NO_2^-Na^+$ [b]	5.45	6.75	6.85
CH_2=$CHCH_2NO_2$[c]	5.45	6.15	5.00
CH_2=$CHCH$=$NO_2^-Na^+$ [d]	5.0	6.7	6.7

[a] Neat. [b] 5% solution in D_2O. [c] 40% solution in MeOD. [d] 5% solution in MeOD.

method of Hesse et al.[33] Final purification was by vapor-phase chromatography: bp 60 °C (15 mm); $n^{21}D$ 1.4605 [lit.[35] bp 69.2 °C (20 mm); $n^{20}D$ 1.4618]; UV max (*n*-hexane) 251 nm (ϵ 3500) [lit.[35] UV max (*n*-heptane) 250 nm (ϵ 3900)]; NMR ($CDCl_3$) δ ~1.8 (m, 6, cis methyl groups) and ~2.2 (m, 3, methyl cis to nitro).

2-Phenyl-1-nitropropene (19). The α,β-unsaturated nitroalkane was prepared by treating 2-phenyl-1-nitro-2-propyl acetate[36] (2.0 g, 0.009 mol) with 10 mL of triethylamine in 20 mL of chloroform. The solution was stirred at room temperature for 1 h and then poured into 50 mL of 3 N hydrochloric acid. The layers were separated and the aqueous layer was extracted with three 60-mL portions of chloroform. The combined chloroform layers were washed with two 50-mL portions of water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to yield 1.3 g (88%) of a mixture of 77% **19** and 23% **7** (G = Ph). The mixture was chromatographed on silica gel with dichloromethane eluent, but the highest purity obtainable was 80% **19** and 20% 2-phenyl-3-nitropropene. However, the ultraviolet spectrum of pure **19** could be obtained from this mixture, since the spectrum of pure 2-phenyl-3-nitropropene is known.

NMR Spectra. NMR data for 3-nitropropene and the sodium salt of its anion in D_2O and in MeOD are summarized in Table VI. The absence of an upfield shift of the H_2C= protons on the conversion to the nitronate ion contrasts sharply with the marked upfield shift for the H_2C= protons in allyllithium relative to allyl alcohol.[37,38] The negative charge in nitronate ions is known to be concentrated on oxygen,[27] and must remain primarily there, at least in protic solvents, even when delocalization in the carbon moiety becomes possible. The downfield shift observed for the α protons (and also the slight downfield shift for the β proton) is expected because of the change in hybridization of the α-carbon atom.

Acknowledgment. We are grateful to the National Science Foundation and the National Institutes of Health for support of this research.

Registry No.—3-Nitropropene-3,3-d_2, 66291-25-6; 3-bromopropene, 106-95-6; 2-methyl-1-nitropropene, 1606-30-0; 2-methyl-3-nitro-2-butene, 19031-80-2; 2-phenyl-1-nitropropene, 15795-70-7; 3-nitro-2-methyl-2-butyl acetate, 66291-24-5; 2-phenyl-1-nitro-2-propyl acetate, 66291-23-4.

References and Notes

(1) National Institutes of Health Predoctoral Fellow, 1967–1970.
(2) See the preceding papers in this issue, and references cited therein.
(3) F. Johnson, *Chem. Rev.*, **68**, 373 (1968).
(4) Note that $\sigma_{m\text{-}Me}$ is negative.
(5) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions", New York, N.Y., 1963, pp 156–168, 238–242.
(6) (a) R. P. Bell and D. M. Goodall, *Proc. R. Soc. London, Ser. A*, **294**, 273 (1966); (b) D. J. Barnes and R. P. Bell, *ibid.*, **318**, 421 (1970); (c) R. P. Bell and B. J. Cox, *J. Chem. Soc. B*, 194 (1970)
(7) It is amusing to note that in the series CH_2=$CHCH_2NO_2$, MeCH=CH-CH_2NO_2, and Me_2C=$CHCH_2NO_2$, where the changes in kinetic acidities and equilibrium acidities are both small, the Brønsted plot is linear (r = 0.9997) with α = 2.2.
(8) (a) R. G. Pearson and F. V. Williams, *J. Am. Chem. Soc.*, **89**, 2327 (1967); (b) E. S. Lewis and L. H. Funderburk, *ibid.*, **89**, 2322 (1967); (c) R. P. Bell and D. M. Goodall, *Proc. R. Soc. London, Ser. A*, **294**, 273 (1966).
(9) T. C. Bruice and S. J. Benkovic, "Biorganic Mechanisms", Vol. I, W. A. Benjamin, New York, N.Y., 1966, pp 37–38.
(10) A. J. Kresge, "Proton Transfer Reactions", E. F. Caldin and V. Gold, Eds., Chapman and Hall, London, 1975, Chapter 7.
(11) (a) F. G. Bordwell and W. J. Boyle, *J. Am. Chem. Soc.*, **93**, 512 (1971); (b) D. S. Kemp and M. L. Casey, *ibid.*, **95**, 6670 (1973).
(12) J. A. Feather and V. Gold, *J. Chem. Soc. B*, 1752 (1965).
(13) M. J. Gregory and T. C. Bruice, *J. Am. Chem. Soc.*, **89**, 2327 (1967); J. E. Dixon and T. C. Bruice, *ibid.*, **92**, 905 (1970).
(14) D. L. Wahlen, J. F. Weimaster, A. M. Ross, and R. Radke, *J. Am. Chem. Soc., ibid.*, **98**, 7139 (1976).
(15) J. E. Leffler, *Science*, **117**, 340 (1953).
(16) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).
(17) W. S. Matthews, J. E. Bares, J. E. Bartmess, F. G. Bordwell, F. J. Cornforth, G. E. Drucker, Z. Margolin, R. J. McCallum, G. J. McCollum, and N. R. Vanier, *J. Am. Chem. Soc.*, **97**, 7006 (1975).
(18) F. G. Bordwell, D. Algrim, and N. R. Vanier, *J. Org. Chem.*, **42**, 1817 (1977).
(19) F. G. Bordwell, J. E. Bares, J. E. Bartmess, G. J. McCollum, M. Van Der Puy, N. R. Vanier, and W. S. Matthews, *J. Org. Chem.*, **42**, 321 (1977); F. G. Bordwell and G. J. McCallum, *ibid.*, **41**, 2391 (1976).
(20) A. Schreisheim, R. J. Muller, and C. A. Rowe, *J. Am. Chem. Soc.*, **84**, 3164 (1962).
(21) C. D. Broadus, *J. Am. Chem. Soc.*, **90**, 5504 (1968).

(22) A. Schreisheim, C. A. Rowe, and L. Naslund, *J. Am. Chem. Soc.*, **85**, 2111 (1963).
(23) Unpublished data from this laboratory.
(24) Additional experimental details may be found in the Ph.D. thesis of J. A. Hautala, Northwestern University, June, 1971.
(25) Prepared according to the procedure of A. C. Huitric and W. F. Trager, *J. Org. Chem.*, **27**, 1927 (1962).
(26) Yu. N. Belikov, N. G. Faleev, and V. M. Belikov, *Bull, Akad. Sci. USSR, Div. Chem. Sci. (Engl.)*, 1039 (1969); N. G. Faleev, Yu. N. Belikov and V. M. Belikov, *ibid.*, 69 (1970).
(27) Prepared according to the method of A. A. Griswold and P. S. Starcher, *J. Org. Chem.*, **30**, 1687 (1965).
(28) N. Kornblum and H. E. Ungnade, *Org. Synth.*, **38**, 75 (1958).
(29) No 3-nitro-1-butene resulting from direct displacement of chloride was formed.
(30) We are indebted to Thomas G. Mecca for preparation of this compound.
(31) S. F. Reed, Jr., *J. Org. Chem.*, **30**, 3258 (1965).
(32) J. C. H. Hwa and H. Sims, *Org. Synth.*, **41**, 50 (1961).
(33) G. Hesse, R. Hatz, and H. Konig, *Justus Liebigs Ann. Chem.*, **709**, 79 (1967).
(34) E. A. Braude, E. R. H. Jones, and G. G. Ross, *J. Chem. Soc.*, 1104 (1947).
(35) C. A. Burkhard and J. F. Brown, Jr., *J. Org. Chem.*, **29**, 2235 (1964).
(36) We are indebted to Dr. W. J. Boyle, Jr. for preparation of this compound.
(37) P. West, J. L. Purmont, and S. V. McKinley, *J. Am. Chem. Soc.*, **90**, 797 (1968).
(38) The present result is comparable to that observed for conversion of 1-nitroindene to its nitronate ion.[39]
(39) R. C. Kerber and A. Porter, *J. Am. Chem. Soc.*, **91**, 366 (1969).

Comparison of the Acidities and Basicities of Amino-Substituted Nitrogen Heterocycles

Ross Stewart* and Madeleine G. Harris

Department of Chemistry, University of British Columbia, Vancouver, Canada V6T 1W5

Received January 27, 1978

Seventeen amino-substituted heterocycles, including pyridines, pyrimidines, cytosines, isocytosines, and adenines, have been compared with respect to acidity (pK_{HA}, deprotonation at amino) and basicity (pK_{BH^+}, protonation at ring nitrogen). Unlike the analogous deaza compounds, in which protonation and deprotonation occur at the same site, there is no correlation between pK_{HA} and pK_{BH^+}. The pK_{BH^+} for amino protonation of some of these compounds can be calculated, however, and in these cases the points fall very near the line for the deaza compounds. The displacement from this line can be regarded as a measure of the difference in basicity of the amino nitrogen atom and an aza nitrogen atom in the heterocycle in question.

The basic nature of organic amines is well known (eq 1), their acidic character much less so (eq 2).

$$RNH_3^+ \rightleftharpoons H^+ + RNH_2 \quad (1)$$

$$K_{BH^+} = [H^+][RNH_2]/[RNH_3^+]$$

$$RNH_2 \rightleftharpoons H^+ + RNH^- \quad (2)$$

$$K_{HA} = [H^+][RNH^-]/[RNH_2]$$

Recent studies of the ionization of aminoarenes[1] and aminoheterocycles[2] in basic aqueous dimethyl sulfoxide have provided us with a considerable number of pK_{HA} values (standard state, water) and we herein examine the relationship between proton gain (pK_{BH^+}) and proton loss (pK_{HA}) in such compounds.

Listed in Tables I and II are the available data for those aminoheterocycles in which a primary amino substituent NH_2 is the *acidic* center and for which both pK_{BH^+} and pK_{HA} are known. In most amino substituted nitrogen heterocycles the most *basic* center in the molecule is not the amino group but rather a ring nitrogen atom,[3] and this is so for all the heterocyclic compounds listed in the tables.

Previous work had shown that for most anilines and diphenylamines there is a linear relation between pK_{BH^+} and pK_{HA}, with the acidity, as represented by pK_{HA}, being more sensitive to substitution than basicity, as represented by pK_{BH^+}.[4] (The slope of a plot of pK_{HA} against pK_{BH^+} is 1.3.) The exceptions to this generality are those anilines and diphenylamines containing nitro groups at the ortho or para positions. The presence of one such group causes a large increase in acidity with the effect of additional nitro groups being much less. The change in *basicity*, however, is quite regular as successive nitro groups are introduced to the ortho and para positions. The net result is that a plot of pK_{HA} against pK_{BH^+} for anilines and diphenylamines has a discontinuity and a change of slope near the place where ortho and para nitroamines appear. There are two other commonly encountered –R groups in organic chemistry, cyano and carbonyl. The former does not appear to behave like nitro in the above respect, whereas there is some indication that the latter does. (Compare the effects of multiple substitution of these groups on methane acidity.[5])

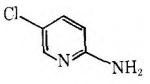
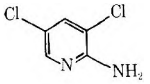
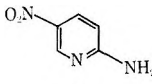
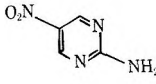
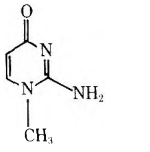
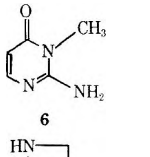
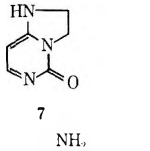
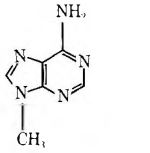
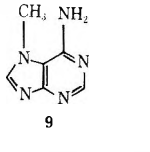
We have plotted in Figure 1 the most recently published values of pK, many of which have been obtained by extrapolative techniques.[1a] It can be seen that for compounds in which the locus of protonation and deprotonation is the amino group (anilines, filled circles) there is a fairly regular, though nonlinear, relationship.

The most acidic and least basic compound in Figure 1 is 2,4,6-trinitroaniline, whose pK_{BH^+} and pK_{HA} values are in some doubt. It is half-protonated in 96% H_2SO_4[6] and earlier literature values are more negative than that[7] used here. Its response to base, likewise, is ambiguous, since there is evidence that it forms Meisenheimer complexes by addition of base, which accompanies or precedes proton loss.[8] Any attempt to accommodate these uncertainties by displacing the point in Figure 1 would have the effect of *increasing* the degree of curvature of the line.

The amino-substituted heterocycles (open triangles) all fall well off the line in Figure 1, and in the expected direction. That is, if the amino group is not the favored site of protonation then another location (invariably a ring nitrogen atom in conjugation with the amino group) must have a more positive pK_{BH^+} and such compounds will deviate in the direction shown. Furthermore, for several of these compounds, the aminopyridines and aminopyrimidines, the pK_{BH^+} for amino protonation can be calculated using the Hammett equation.[9] When this is done and the points included in the figure (filled triangles) it is found that these compounds now fall near the line determined by the anilines. The shifts in position of these

0022-3263/78/1943-3123$01.00/0

Table I. The pK_{HA} and pK_{BH^+} Values of Amino Heterocycles[a] in Water at 25 °C

compd[b]	registry no.	pK_{BH^+} (ref)	pK_{HA}[c]
 1	1072-98-6	4.71 (22)	21.8
 2	4214-74-8	2.67 (23)	20.8
 3	4214-76-0	2.80 (24)	15.8
 4	3078-77-6	0.3 (25)	14.7
 5	2080-17-3	4.0 (26)	14.3
 6	2417-17-6	4.2 (26)	14.3
 7	63934-46-3	7.0 (27)	12.5
 8	700-00-5	3.3[d] (28)	16.7
 9	935-69-3	3.6[d] (28)	14.7

[a] Additional pK data in Table II. [b] (1) 2-amino-5-chloropyridine; (2) 2-amino-3,5-dichloropyridine; (3) 2-amino-5-nitropyridine; (4) 2-amino-5-nitropyrimidine; (5) 1-methylisocytosine; (6) 3-methylisocytosine; (7) 2,3-dihydro-1*H*-5-oxoimidazo[1,2-c]pyrimidine; (8) 9-methyladenine; (9) 7-methyladenine. [c] Reference 2. [d] Room temperature, 50% DMF–50% water.

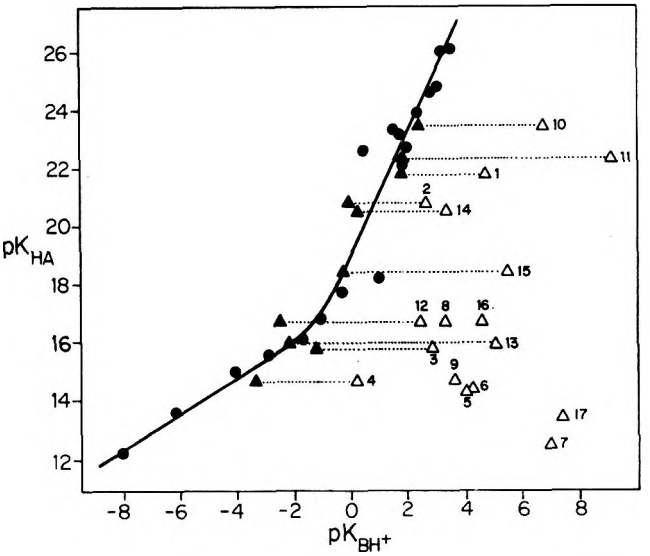


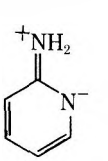
Figure 1. Plot of pK_{HA} against pK_{BH^+} for anilines (closed circles) and amino heterocycles (open triangles). Calculated points for protonation at the amino group of the latter are given by closed triangles. The numbering corresponds to that in Tables I and II. The anilines, in order of increasing pK_{HA}, with pK_{HA} and pK_{BH^+} values listed in parentheses, are 2,4,6-$(NO_2)_3$ (12.2, −8.1); 2,4-$(NO_2)_2$-6-Br (13.6, −6.2); 2,4$(NO_2)_2$ (15.0, −4.1); 4-NO_2-2,6-$(Cl)_2$ (15.6, −2.9); 4-NO_2-2,5-$(Cl)_2$ (16.1, −1.7); 2-NO_2-4-Cl (16.8, −1.1); 2-NO_2 (17.7, −0.3); 4-NO_2 (18.2, 1.0); 2,3-$(Cl)_2$ (22.1, 1.8); 2,6-$(Cl_2)_2$ (22.6, 0.4); 2,4-$(Cl)_2$ (22.7, 2.0); 4-CN (23.2, 1.7); 2,5-$(Cl)_2$ (23.3, 1.5); 3,5-$(Cl_2)_2$ (23.9, 2.4); 3-CN (24.6, 2.8); 3,4-$(Cl)_2$ (24.8, 3.0); 3-CF_3 (26.0, 3.2); 3-Cl (26.1, 3.5).

compounds are shown by dotted horizontal lines in the figure.

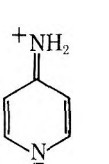
The horizontal deviation in Figure 1 for the amino heterocycles may be taken as an estimate of the difference in basicity between the amino group and the ring nitrogen atom that is the favored site. The largest deviations are found for 3-methylcytosine (**17**) and the closely related compound **7**. The latter is the only nonprimary amine considered herein; it has been included because it provides some confirmation of the extent of deviation of the cytosine.

The question arises as to whether the acidities and basicities of the amino groups in cytosines and isocytosines should conform to the relationship shown in the figure. That is, does the horizontal deviation for **17**, some 13 pK units, give an estimate of the difference in basicity between the 4-amino group and the 1-aza group in this compound? Since cytosines are not truly aromatic such an analysis may well overestimate this quantity, but, bearing in mind the similar resonance effects exerted by a 3-carbonyl group in an aminocytosine and a 4-nitro group in an aniline, the results in Figure 1 suggest that the basicity of the amino group in 3-methylcytosine is very low, indeed.[10]

One is on firmer ground in comparing ΔpK ($pK_{HA} - pK_{BH^+}$) for compounds in which the amino group is attached to an aromatic ring. Albert et al.[11] suggested some time ago that the high basicity of 4-aminopyridines is due to resonance in the neutral molecule requiring considerable charge separation, whereas that in the cation involves, of course, no separation of charge at all. The lower basicity of 2-aminopyridine is plausibly explained, then, on the basis of a smaller degree of charge separation in the resonance hybrid of the neutral compound. Since the aza group's electron-withdrawing character appears to be chiefly due to induction rather than resonance[12] the importance of the canonical structures **10′** and **11′** is uncertain. Nonetheless, the conclusion that the proximity of the aza and amino groups in the 2 compound stabilizes its neutral form more than that of its 4 isomer seems sound, since we find that 2-aza compounds are also less *acidic* than their 4-aza isomers (Table II). Indeed, for the isomeric cytosines **16** and **17** there is independent evidence showing that the neutral compounds differ in stability by approximately the amount required to produce the ΔpK differences shown in Table II.[13,2b]

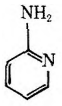
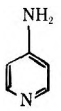
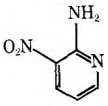
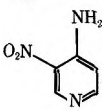
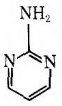
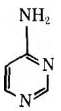
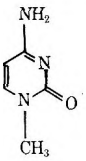
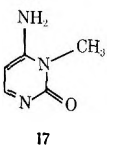


10′



11′

Table II. Effect of the Position of the Aza Group on the Acidity and Basicity of 2- and 4-Aza Amino Heterocycles[a]

2-aza compds				4-aza compds					
	registry no.	pK_{HA}[b]	pK_{BH^+}[c]		registry no.	pK_{HA}[b]	pK_{BH^+}[c]	ΔpK_{HA} ($pK_{HA}^{2\text{-aza}} - pK_{HA}^{4\text{-aza}}$)	ΔpK_{BH^+} ($pK_{BH^+}^{2\text{-aza}} - pK_{BH^+}^{4\text{-aza}}$)
 10	504-29-0	23.5	6.71	 11	504-24-5	22.3	9.15	1.2	−2.44
 12	4214-75-9	16.7	2.42	 13	1681-37-4	15.9	5.05	0.8	−2.63
 14	109-12-6	20.5	3.41	 15	591-54-8	18.4	5.58	2.1	−2.17
 16	1122-47-0	16.7	4.55	 17	4776-08-3	13.4	7.38	3.3	−2.83
							av	1.9	−2.52

[a] (10) 2-Aminopyridine; (11) 4-aminopyridine; (12) 2-amino-3-nitropyridine; (13) 4-amino-3-nitropyridine; (14) 2-aminopyrimidine; (15) 4-aminopyrimidine; (16) 1-methylcytosine; (17) 3-methylcytosine. [b] Reference 2. [c] References: compounds 10–13, ref 24; 14, and 15, ref 11b; 16 and 17, ref 27.

Calculations

The basicity of the amino group in each of the ten aminopyridines and aminopyrimidines was calculated using the Hammett equation $\log K/K_0 = \rho\sigma$ where ρ has been taken as the value for aniline 2.91.[14] For those compounds in which the 2 position (to the amino group) is either unoccupied or contains an aza substituent the calculations were done in the usual way. (The 2-aza group is known to be a well-behaved substituent.[9a,15]) The value of $\log K_0$ was taken as 4.58[14] and the following σ constants were used: $\sigma_{2N} = 0.75$ $\sigma_{4N} = 0.96$, $\sigma_{4Cl} = 0.23$, and $\sigma_{4NO_2} = 1.24$.[14] The aza substituent constants are those of Deady and Shanks et al.[15a] derived from their studies of the basic hydrolysis of methyl pyridinecarboxylates, a reaction in which no formal charge appears on the aza group. That good correlations have been obtained in the present and earlier work[2a] using these values supports the notion that these groups operate mainly by induction.

For compounds containing a non-aza group in the 2 position to the amino group the appropriate 2-substituted aniline was taken as the parent compound in the Hammett equation, the following $\log K_0$ values being used: 2,4-dichloroaniline, −2.0;[16] 2-nitroaniline, +0.30.[6] Thus, the amino group basicity in 2 is given by $(\log K) + 2.0 = 2.91 \times 0.75$, which gives for $pK_{BH^+(amino)}$ a value of −0.2.

The data for the anilines come from ref 1a (average of values obtained by the two extrapolative methods used therein), 4, 7, and 16–19. (See the caption for Figure 1 for numerical values.) A few of the pK_{BH^+} values shown in Tables I and II differ slightly from those given in the attached references because a correction has been made to convert them from 20 to 25 °C. The correction is small, −0.13 units, and is an estimate based on the results of Essery and Schofield.[20]

The ionization process that occurs in aqueous dimethyl sulfoxide between hydroxide ion and amino heterocycles appears to be proton transfer, not hydroxide addition, although the latter reaction, which tends to be time dependent, is known to take place with a number of heterocyclic compounds lacking amino groups.[21] The pattern of spectral changes accompanying ionization in base of the compounds in Tables I and II is consistent with simple proton loss, although the possibility of adduct formation cannot be unequivocally ruled out.

References and Notes

(1) (a) R. A. Cox and R. Stewart, *J. Am. Chem. Soc.*, **98**, 488 (1976); (b) A. Albagli, A. Buckley, A. M. Last, and R. Stewart, *ibid.*, **95**, 4711 (1973); (c) D. Dolman and R. Stewart, *Can. J. Chem.*, **45**, 911 (1967).
(2) (a) M. G. Harris and R. Stewart, *Can. J. Chem.*, **55**, 3800 (1977); (b) R. Stewart and M. G. Harris, *ibid.*, **55**, 3807 (1977).
(3) (a) J. H. Ridd in "Physical Methods in Heterocyclic Chemistry", A. R. Katritzky, Ed., Academic Press, New York, N.Y., 1971; (b) J. Suchy, J. J. Mieyal, G. Bantle, and H. Z. Sable, *J. Biol. Chem.*, **247**, 5905 (1972); (c) J. Riand, M. Th. Chenon, and N. Lumbroso-Bader, *J. Am. Chem. Soc.*, **99**, 6838 (1977).
(4) R. Stewart and D. Dolman, *Can. J. Chem.*, **45**, 925 (1967).
(5) D. J. Cram, "Fundamentals of Carbanion Chemistry", Academic Press, New York, N.Y., 1965, Chapter 1.
(6) M. J. Jorgenson and D. R. Hartter, *J. Am. Chem. Soc.*, **85**, 878 (1963).
(7) N. C. Marziano, G. M. Cimino, and R. C. Passerini, *J. Chem. Soc., Perkin Trans. 2*, 1915 (1973).
(8) M. R. Crampton and V. Gold, *Proc. Chem. Soc., London*, 298 (1964).
(9) (a) C. D. Johnson, "The Hammett Equation", Cambridge University Press, Cambridge, Mass., 1973; (b) P. Tomasik and C. D. Johnson in "Advances in Heterocyclic Chemistry", Vol. 20, A. R. Katritzky and A. J. Boulton, Ed., Academic Press, New York, N.Y., 1976.
(10) Abrams and Kallen have used a kinetic method to estimate the basicity of the amino groups in several adenine and cytidine derivatives. Their pK_{BH^+} values fall in the range −1.7 to −2.8 (W. R. Abrams and R. G. Kallen, *J. Am. Chem. Soc.*, **98**, 7789 (1976)).
(11) (a) A. Albert and R. Goldacre, *J. Chem. Soc.*, 706 (1946); (b) A. Albert, R. Goldacre, and J. N. Phillips, *ibid.*, 2240 (1948); (c) A. Albert in "Physical Methods in Heterocyclic Chemistry", Vol. 1, A. R. Katritzky, Ed., Academic Press, New York, N.Y., 1963.
(12) Reference 9a, p 101; reference 9b, p 7; reference 2a.
(13) (a) A. R. Katritzky and A. J. Waring, *J. Chem. Soc.*, 3046 (1963); (b) M. Dreyfus, O. Bensaude, G. Dodin, and J. E. Dubois, *J. Am. Chem. Soc.*, **98**, 6338 (1976); (c) J. Elguero, C. Marzin, A. R. Katrikzky, and P. Linda, "The Tautomerism of Heterocycles", Academic Press, New York, N.Y., 1976.
(14) T. Fujita and T. Nishioka in "Progress in Physical Organic Chemistry", Vol. 12, R. W. Taft, Ed., Wiley-Interscience, New York, N.Y., 1976, pp 64 and 56.

(15) (a) A. D. Campbell, S. Y. Chooi, L. W. Deady, and R. A. Shanks, *Aust. J. Chem.*, **23**, 203 (1970); (b) L. W. Deady, D. J. Foskey, and R. A. Shanks, *J. Chem. Soc. B*, 1962 (1971); (c) ref 9a, p 103.
(16) R. A. Robinson, *J. Res. Natl. Bur. Stand., Sect. A*, **68**, 159 (1964).
(17) R. Stewart and J. P. O'Donnell, *Can. J. Chem.*, **42**, 1681 (1964).
(18) A. I. Biggs and R. A. Robinson, *J. Chem. Soc.*, 388 (1961).
(19) W. A. Sheppard, *J. Am. Chem. Soc.*, **87**, 2410 (1965).
(20) J. M. Essery and K. Schofield, *J. Chem. Soc.*, 3939 (1961).
(21) A. Albert in "Advances in Heterocyclic Chemistry", Vol. 20, A. R. Katritzky and A. J. Boulton, Ed., Academic Press, New York, N.Y., 1976.
(22) A. El-Anani, J. Banger, G. Bianchi, S. Clementi, C. D. Johnson, and A. R. Katritzky, *J. Chem. Soc., Perkin Trans. 2*, 1065 (1973).
(23) D. J. Brown and J. S. Harper, *J. Chem. Soc.*, 5542 (1965).
(24) I. R. Bellobono and G. Favini, *J. Chem. Soc. B*, 2034 (1971).
(25) D. J. Brown and J. S. Harper, *J. Chem. Soc.*, 1276 (1963).
(26) M. Hirota, *Chem. Pharm. Bull.*, **16**, 430 (1968).
(27) T. Ueda and J. J. Fox, *J. Am. Chem. Soc.*, **85**, 4024 (1963).
(28) N. J. Leonard and J. A. Deyrup, *J. Am. Chem. Soc.*, **84**, 2148 (1962).

Friedel–Crafts Chemistry. A Mechanistic Study of the Reaction of 3-Chloro-4′-fluoro-2-methylpropiophenone with $AlCl_3$ and $AlCl_3$–CH_3NO_2

Seemon H. Pines* and Alan W. Douglas

Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey 07065

Received December 20, 1977

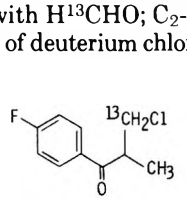
The mechanism of reaction of 3-chloro-4′-fluoro-2-methylpropiophenone (**1**) with $AlCl_3$ has been studied using both ^2H- and ^{13}C-labeled substrate. Analysis of kinetic isotope effects and of label location in the products as revealed in ^2H and ^{13}C NMR spectra allows definition of the major pathways involved. In cyclization to the 2-methylindanone **2**, an isotope rate effect supports ionization concerted with C_2–H migration as the rate-determining step. The skeletally rearranged products **3** and **4** form via initial methyl migration and not acyl migration. When the $AlCl_3$–CH_3NO_2 system is used as catalyst, no rearrangements transpire, and formation of **2** proceeds below the thermal threshold required with neat $AlCl_3$. This reaction occurs via enolization as a result of the protic nature of $AlCl_3$–CH_3NO_2 solutions. This same system possesses oxidizing power, and chloride is oxidized to chlorine which, in the enolizing medium, converts **2** to its α-chloro analogue **6**. When chloride concentration is low, competitive oxidation of **2** to isocoumarin **7** is also observed.

Reaction of 3-chloro-4′-fluoro-2-methylpropiophenone (**1**) with $AlCl_3$ was recently reported to give three products: 5-fluoro-2-methyl-1-indanone (**2**), 5-fluoro-3-methyl-1-indanone (**3**), and 2-(4′-fluorophenyl)-1-oxoniacyclopent-1-enyl cation (**4**).[2] Formation of each product was pictured, with some reservations, as having proceeded through carbenium ions which differed fundamentally from those cited in cyclialkylation of phenylalkyl halides[3] by the presence of a carbonyl group linking the aliphatic and aromatic moieties.

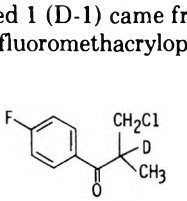
We have continued study of this reaction, and wish now to report the results of experiments using (a) both ^{13}C- and ^2H-labeled **1** and (b) nitromethane as solvent. The label studies amplify our understanding of some of the mechanistic pathways involved; the presence of nitromethane alters the outcome of the reaction entirely.

Results

Carbon-13 labeled **1** (C-1) was made via methoxymethylation[4] with $H^{13}CHO$; C_2-deuterated **1** (D-1) came from the addition of deuterium chloride to 4′-fluoromethacrylophenone (**5**).



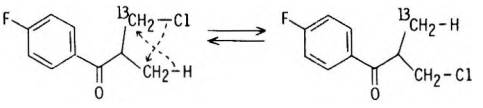
C-1



D-1

Products **2**, **3**, **4**, and "unreacted" starting material observed after reaction of C-1 with 2–3 equiv of $AlCl_3$ at 100 °C, neat, showed that scrambling had occurred in two and only two positions, as shown in Figure 1. Because this scrambling was also observed with C-1 at 70 °C, where *no* carbon–carbon bond reorganization could be discerned, the result was attributed to the equivalent of a 1,3-hydride shift in **1** as depicted in Scheme I.[5] (The C_2-attached H was not involved, as will be evident below from results with D-1.)

Scheme I[a]



[a] For clarity, complexation of $AlCl_3$ is not shown in this or the other schemes.

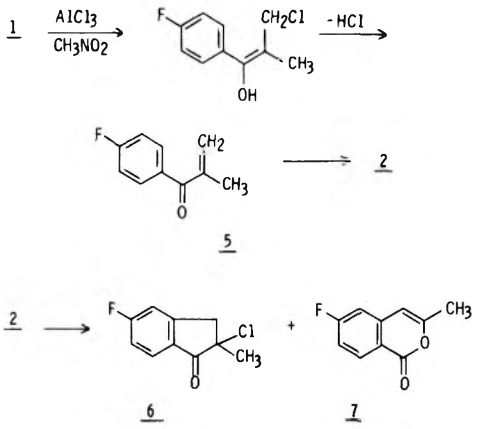
The reaction of D-1 was, overall, slower than unlabeled **1** under identical conditions. Dissection of the relative rates of the individual processes supported C_2–H (or C_2–D) bond breaking as rate determining in the formation of unrearranged indanone **2**, with $k_H/k_D = 2.5$. Negligible rate differences were seen in formation of **3** or **4**. Deuterium in CH_2D and CHD groups of **2**, **3**, and **4** was located by ^{13}C NMR spectroscopy. Integration of the signals for ^2H-split vs. solely ^1H-bearing singlet ^{13}C signals provided a semiquantitative distribution. Proton NMR showed no detectable loss nor scrambling of ^2H in the recovered D-1. Overall ^2H content in each product was also assessed by mass spectroscopy; attempts to assign its distribution in **2** and **3**, methyl group vs. indanone ring, by means of mass fragmentography[6] were not in accord with the ^{13}C NMR results.

Mechanistic suggestions are proposed on the basis of the rates and products; unfortunately, the loss of some of the deuterium, and some of its incorporation into the aromatic nucleus as ultimately shown by ^2H NMR, precludes total definition of the reactions.

Reaction of 1 M solutions of **1** in nitromethane containing 2 equiv of $AlCl_3$ occurred slowly as low at 70 °C to produce **2** without detectable formation of **3** or **4**. The medium, however, supported further reaction of **2** along two parallel paths to its α-chlorinated derivative **6** and to the isocoumarin **7** (Scheme II). The isocoumarin was not observed when the experiment was conducted in sealed tubes. These unexpected transformations are ascribed to the nature of the modified catalytic system.

0022-3263/78/1943-3126$01.00/0

Scheme II



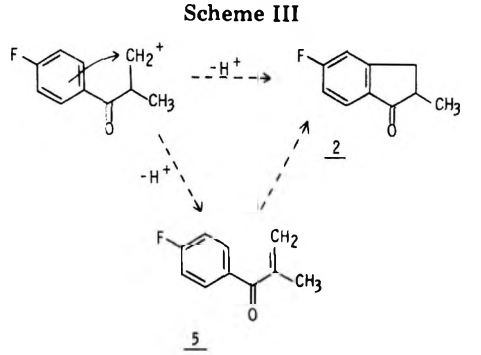
Discussion

Certain aspects of the reaction of 1 with $AlCl_3$ could not be defined with our original experimental data.[2] For instance, it was suggested[2] that 2 might arise by direct intramolecular cyclization of 1 after ionization at C_3. "Intervention of [5] is neither necessary nor excluded . . ." (Scheme III). Nucleophilic π-assisted displacement of chloride concomitant with ring formation would be an allowable alternative. Likewise, the rearrangement products **3** and **4** were rationalized in terms of rapid alkyl and hydride migrations; however, the possibility of an aroyl migration as depicted in Scheme IV was not ruled out. Publications concerning similar rearrangements are becoming increasingly frequent.[7] It was our belief that these, and other aspects, might be clarified by working with isotopically labeled **1**.

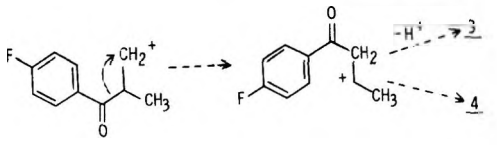
A. The Question of Methyl and Hydride Migration vs. Acyl Migration to Give 3 and 4. A clear choice between these two pathways can be made utilizing C-**1**. The latter mechanism, i.e., acyl migration (Scheme IV), would provide **3** and **4** possessing the label adjacent to the carbonyl functions, while product **2** would maintain skeletal integrity and keep its label at C_3. Moreover, the use of ^{13}C labeling would provide a highly sensitive probe; if even 1% of C-1 were to rearrange via acyl migration, the signal intensity for the α carbon would double, relative to unlabeled carbon atoms.

The products resulting from such an experiment (Figure 1) showed conclusively that acyl migration was not a contributory pathway in these rearrangements. Because of the unexpected scrambling, however, we studied the reaction under milder conditions. Nothing happened during 20 h at 50 °C. At 70 °C, the ^{13}C NMR signal for the methyl carbon grew

Scheme III



Scheme IV



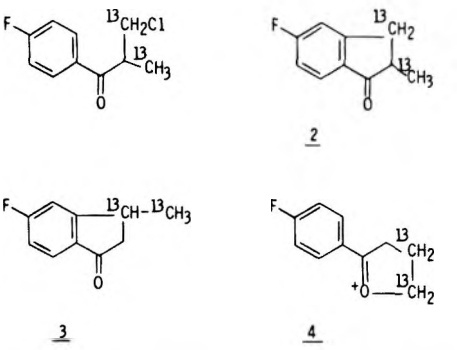


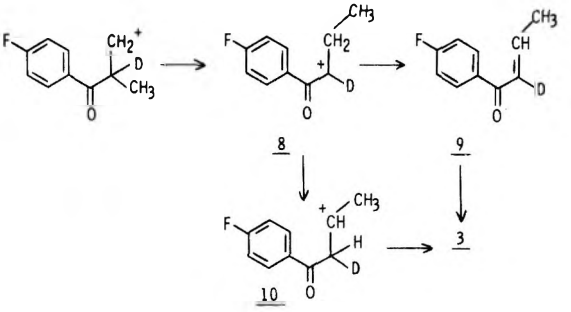
Figure 1. Labeling pattern found in products **2, 3,** and **4,** and "unconverted" starting material after reaction of C-**1** with $AlCl_3$ at 100 °C. Label was shared equally between the two positions indicated.

at the expense of the methylene signal without any indication of structural change. A 1,3-hydride–chloride shift, shown in Scheme I, accounts for these observations, and it can therefore be considered to precede any other step in the overall sequence.[5,8] The half-life for this label scrambling at 70 °C with 2.4 equiv of $AlCl_3$ was 21 h.

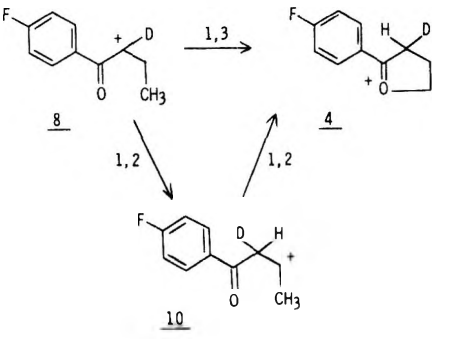
B. Inferences from Kinetic Measurements of the Reaction of D-1. Side-by-side comparison of **1** and D-**1** showed the latter to react more slowly. The stability, noninterconvertibility, and hence independent formation of **2, 3,** and **4** were verified. Reaction aliquots were examined with time and analyzed kinetically[10] in an experiment using 2.33 equiv of $AlCl_3$. In brief, half-lives of 3.2 and 5.6 h at 100 °C for **1** and D-**1,** respectively, were measured, equivalent to the first-order rate constants $\Sigma k_H = 0.22$ and $\Sigma k_D = 0.12\ h^{-1}$. Relative rate constants k_H/k_D for the individual products were calculated to be 2.5, 1.1, and 1.0 for **2, 3,** and **4,** respectively.

In the formation of **3** and **4,** since there is no significant isotope effect and since acyl migration does not occur, methyl migration to form rearranged ion **8** (Scheme V) is the probable rate-determining step. The conversion of **8** to **3** can proceed via **9** or **10,** Scheme V. Support for **9** is its characterization in the product mixture.[2] The same ion, **8,** may serve as precursor to oxonium ion **4** by means of either a 1,3-hydride shift or two 1,2 shifts in concert with attack of carbonyl oxygen at the terminal carbon (Scheme VI). A stepwise procedure to a pri-

Scheme V



Scheme VI



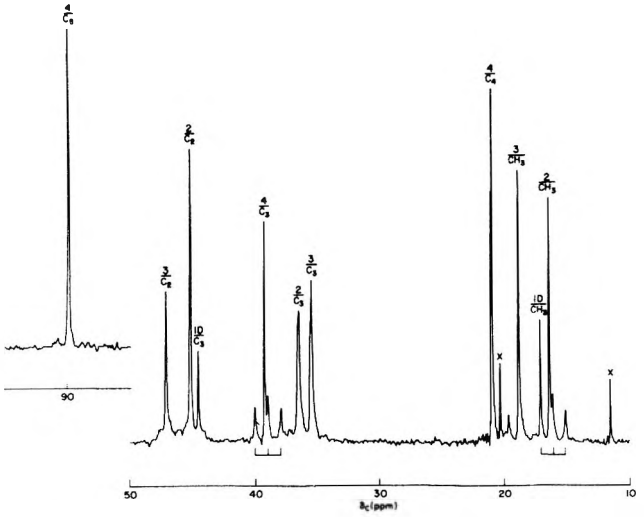


Figure 2. Partial ^{13}C NMR spectra of reaction of D-1 with neat $AlCl_3$ at 100 °C for 15.5 h. Deuterium-split triplets are indicated for the CH_2D group of **2** (one leg of which coincides with the CH_3 of D-1) at 16.2 ppm and for C_3 (C_α) of **4** at 39.1 ppm. The C_4 signal at 21 ppm is split due to a geminal deuterium isotope effect in the labeled molecules (cf. F. W. Wehrli and T. Wirthlin, "Interpretation of Carbon-13 NMR Spectra", Heyden & Son, Ltd., London, 1976, pp 107–110). Impurities from the nitromethane solvent used as diluent *after* reaction are marked "×" at 11.6 and 20.4 ppm.

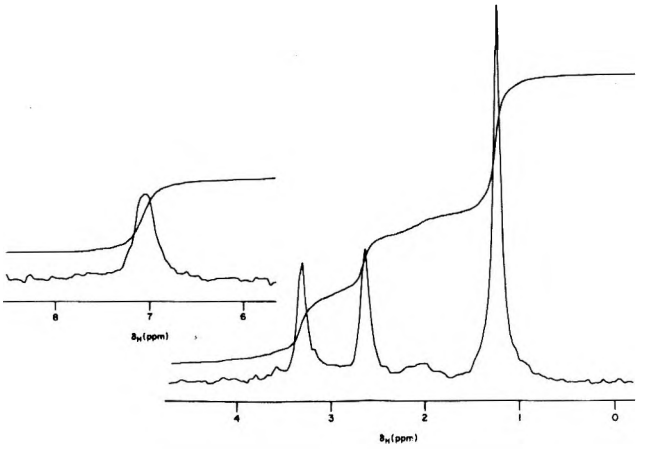


Figure 3. Deuterium NMR spectrum of **2** recovered from reaction of D-1. If ^2H were attached at C_7, its signal would be evident at ~7.7 ppm.

mary carbenium ion prior to cyclization on oxygen should be disfavored[11] even though formation of a primary carbenium ion has been recently postulated.[12] The proton-decoupled ^{13}C NMR spectrum of **4** formed from D-1 clearly shows a deuterium-coupled triplet for C_α at δ_C 39.03 ppm, with J_{CD} = 20 Hz (Figure 2). The same spectrum shows no evidence for deuterium at other positions. Of the two paths (Scheme VI) for formation of **4**, we prefer the 1,3 shift.[14]

After quench, the 4′-fluoro-4-hydroxybutyrophenone (**11**) formed from **4** shows little or no aliphatically bound deuterium by ^1H or ^{13}C NMR or mass spectroscopic analysis. This lack of deuterium at C_α suggests that reaction of **4** proceeds by attack of water at the carbonyl carbon[16] and that the ring opens via enolic **11** (Scheme VII). If the deuterium were lost in **11** by a simple enolization exchange process during the quench, then we should expect similar exchange in the case of product **3**, contrary to our experimental observations. In some experiments, the NMR spectra of purified **11** have shown ketonic **11** exclusively;[2] in others, both the ketone and hemiketal have been observed.

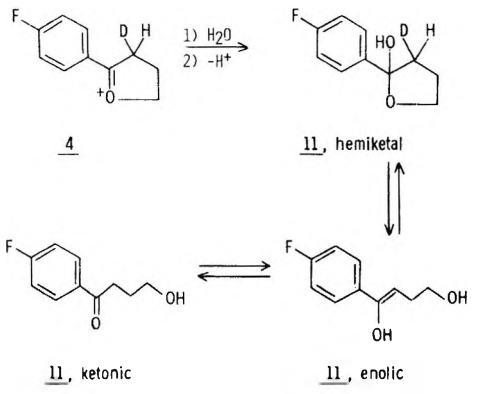
C. Does Methacrylophenone 5 Intervene in Reaction of 1 → 2? Scheme III depicts the two a priori most likely paths for conversion of **1** to **2**. Studies with D-1 were expected to ease the choice. For example, direct cyclization of a carbenium ion formed by C–Cl heterolysis of **1** should occur without isotope rate effect from D-1 and should leave C_α deuterated. Conversely, if the same ion ejects D^+ to form **5**, which is clearly the intermediate from α-halo isomers of **1**,[2] then **2** would be devoid of aliphatic-bound D. In actuality, an isotope rate effect was observed, *and* deuterium was also found in **2** (0.6 atoms) by ^{13}C NMR in both the methyl and methylene groups, but not the methine. CH_2D was favored 2:1 over CHD. Scheme VIII can account for these observations. Deuterium migration concerted[13] with ionization of the primary C–Cl bond generates the tertiary carbenium ion isotopic with one postulated from similar treatment of α-haloisobutyrophenones.[2] Proton loss to form methacrylophenone **5** leaves deuterium in either the methyl or methylene group. From **5a** is produced **2** containing label in the methylene; from **5b** comes the methyl-labeled indanone. Unlabeled **2** may arise from loss of D^+ here or during initial ionization.

Deuterium migration parallels the methyl migration which was postulated above for the rearranged products (Scheme V). It follows that the 1,3-hydride–chloride interchange established with C-1 must occur with only minimal C–Cl separation. Once C–Cl ionization occurs to initiate the first 1,2 shifts of either Scheme V or VIII, reaction must continue irreversibly to product, since none of the recovered starting material, D-**1**, shows deuterium scrambling. This observation also rules out 1,2 shifts in the behavior of C-**1** at 70 °C.[17]

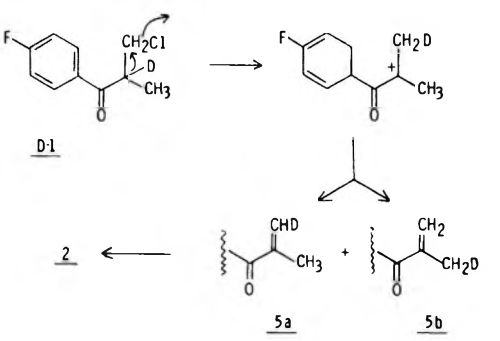
D. Other Aspects of the Overall Picture. Additional observations, some of which are briefly implied above, are worth noting. While it is not apparent from either ^2H or ^{13}C NMR spectra, ^2H NMR conclusively shows the incorporation of deuterium into the aromatic ring of indanone **2** (and **3**) from D-1 to the extent of ca. 0.1 atom.[18,19] This is not random scrambling, since none appears at C_7 (Figure 3). It is best rationalized as an electrophilic substitution by DCl.

Finally, significant discrepancy was noted between NMR and mass spectroscopic analyses of the two indanones. Our[20] interpretation assumed that $M^+ - 15$ fragment ions for both

Scheme VII



Scheme VIII



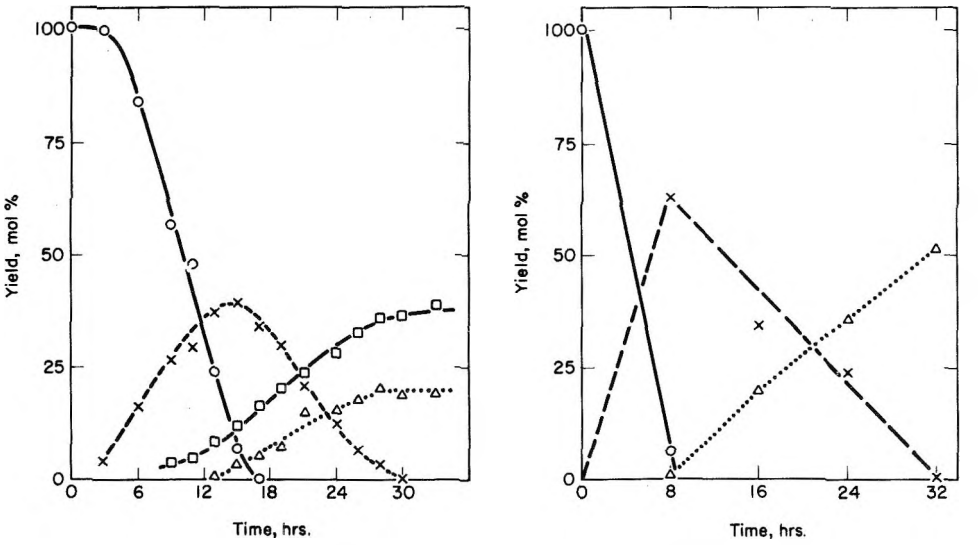


Figure 4. Transformation of **1** (○) to **2** (×), **6** (△), and **7** (□) by reaction with $AlCl_3$–CH_3NO_2 (see Experimental Section). Part A, left, represents reaction with escape of HCl; part B, right, represents reaction under autogenous HCl pressure.

2 and **3** reflect loss of the methyl group, which is likely, but nevertheless unproved. The more sensitive MS method suggests no deuterium loss from **3** in the $M^+ - 15$ ion whereas the ^2H NMR spectra show ca. 20–25% of the total ^2H on the methyl group. A lesser but real difference was also noted for **2**.

The fragmentation pathway for neither **2** nor **3** has been studied in detail, and our assumption noted above may be in error. Scrambling under electron impact is also possible,[21] and it has recently been shown that the presence of deuterium in a substrate molecule completely changed its fragmentation from that of its proteo isotope.[22]

E. The Reaction of 1 with $AlCl_3$–CH_3NO_2. Prior studies including cyclialkylation of various phenylalkyl halides have shown that not only does nitromethane moderate the activity of $AlCl_3$, but it prevents reaction of ordinary primary alkyl halides unless there is participation by neighboring aryl and/or β-alkyl groups.[3a] More recently, we showed that some ω-halophenones, i.e., primary alkyl halides, would also react with participation of the carbonyl group in the same catalyst system to form oxonium ions.[15] Although some of these rearranged to thermodynamically more stable oxonium ions, they *did not undergo carbon cyclialkylation* (except with neat $AlCl_3$).

Despite the generally accepted belief that $AlCl_3$–CH_3NO_2 is milder than $AlCl_3$ as an alkylation catalyst,[23] **1** was transformed, albeit slowly, to indanone **2** at 70 °C, a temperature at which no detectable **2** formed in the presence of $AlCl_3$ alone! Furthermore, no 3-methylindanone **3** could be seen, even when C-1 was used as substrate, nor was scrambling observed in the unreacted starting material. Inescapably, hydride and alkyl shifts were suppressed while cyclialkylation took place. With time, **2** was transformed into α-chloroindanone **6** and the isocoumarin **7**, albeit in modest yield. The reaction is pictured in Scheme II; a GLC study of the sequence may be seen in Figure 4. No other intermediates were detected spectroscopically nor from analysis of quenched aliquots. Both **2** and **6** were subjected to the same reaction conditions, and the results were found to be generally in accord with the data of Figure 4: **2** gave a mixture of **6** and **7**; **6** proved not to be a precursor of **7**.[24] In all cases, it was evident that higher molecular weight (i.e., nonvolatile, under our GLC conditions) by-products were also formed.

The very slow initiation of the reaction of **1** (note initial rate of its disappearance, Figure 4A) suggested either the intervention of an intermediate or that prior catalyst modification was involved. Paul, Kaushal, and Pahil[25] have noted the protic nature of nitromethane in the presence of Lewis acids, and they have isolated several solvent-derived salts in such systems, always with accompanying evolution of HCl. In such a modified Brønsted acid system, therefore, we may expect enolization of **1** to initiate cyclialkylation such as does H_2SO_4.[2] As for chlorination, Bauer and Foucault[26] have shown by polarography that $AlCl_3$–CH_3NO_2 exhibits a half-wave potential of 1.72 V vs. Ag–AgCl. Tables[27] of $E°$ show that 1.72 V is sufficiently high to oxidize Cl^- to $\frac{1}{2}Cl_2$ ($E° = 1.36$), granting extrapolation from water to CH_3NO_2. In the enolizing medium[25] then, chlorine should attack **2** at C_2. If the $AlCl_3$ were behaving in its usual Lewis acid sense, we should anticipate aromatic chlorination according to Pearson's procedures,[28] rather than attack at the α position.

As for oxidation of **2** to an isocoumarin, similar transformations have been recorded[29] under different conditions with different oxidants. The formation of **7** here further demonstrates the oxidizing power of the $AlCl_3$–CH_3NO_2 reagent.

The reaction of **1** was repeated in sealed tubes, under which circumstances the HCl concentration and, hence, the rate of enolization would be increased. Under these conditions, the rate of reaction of **1** essentially doubled, as did the accumulation of **2**, which reached peak concentrations in excess of 60 mol % (Figure 4B). The subsequent α-chlorination of **2** occurred this time to the exclusion of oxidation to isocoumarin **7**, also attributable to higher HCl, and hence higher H^+ and Cl_2 concentrations. From this experiment we also concluded that oxidation of **2** to **7** is a significantly slower reaction than is chlorination.

Summary

From the accumulated results of these experiments, we may assert that the conversion of **1** to **3** and **4** occurs by means of alkyl and hydride shifts and not by acyl migration. Preceding those or any other carbon bond reorganization is a degenerate 1,3-chloride–hydride transposition within the 1–$AlCl_3$ complex which is also the equivalent of a 1,3-hydride shift between methyl and methylene carbon atoms.

Once reaction begins, the sequence of alkyl and hydride shifts eludes total definition at the current state of the art; however, the label studies allow one to make inferences from which reasonable schemes have been proposed. The absence of isotope rate effects for **3** and **4** from D-1 implicate methyl migration as the rate-determining step. We believe it occurs concomitantly with irreversible C–Cl bond cleavage as the

initiating step. In the case of indanone **2**, the $k_H/k_D = 2.5$ supports initiation by a completely analogous concerted hydride (deuteride) shift.[17] Both rate effects and label position in **2** argue against a mechanism involving π-assisted ionization of the C–Cl bond and/or direct cyclization.

Deuterium NMR revealed some ^2H exchange in the aromatic ring of **2** and **3** which was not noticed by ^1H or ^{13}C NMR spectroscopy. Indiscriminate scrambling was not its cause, since C_7–H, adjacent to carbonyl, was not exchanged.

The protic nature of $AlCl_3$–NO_2 has been invoked in order to explain its catalysis of cyclialkylation of **1** to **2** under milder conditions than those needed with $AlCl_3$ alone. Furthermore, the subsequent conversion of indanone **2** to chloroindanone **6** and isocoumarin **7** attests to the little recognized oxidizing power of that catalyst system.

Experimental Section[30]

C-1. A solution of 474 mg of 20% $H^{13}CHO$ (90% ^{13}C label, MSD Canada, Ltd.), 501 mg of 4′-fluoropropiophenone (Aldrich), 36.5 mg of finely powdered potassium carbonate, and 1.9 mL of methanol was stirred at room temperature for 7 days, then concentrated in vacuo without heating.[4] It was taken up in ether, dried over sodium sulfate, then filtered into a glass Parr bomb liner. The system was closed, pressurized to 100 psig at room temperature with anhydrous HCl, then warmed 24 h at 40 °C. The residue remaining after removal of solvent was chromatographed on silica gel (C_6H_6: 0.5% MeOH) to give 475 mg of C-1 (78% overall): ^1H NMR ($CDCl_3$) δ 1.30 (t, J = 6.5 Hz, 3, CH_3), 2.1–2.82 (m, 1, $\frac{1}{2}CH_2$), 3.82 (m, 1, CH), 4.68–5.37 (m, 1, $\frac{1}{2}CH_2$), 6.8–7.35 (m, 2, $H_{2',6'}$), 7.85–8.17 (m, 2, $H_{3',5'}$). Less pure fractions were held for rechromatography.

D-1. A 10% solution of 4′-fluoromethacrylophenone (**5**)[2] in ether was saturated with anhydrous DCl (MSD Canada, Ltd.) at 0–5 °C, then held at room temperature in the stoppered flask for 24 h. Chromatography (as with C-1) gave pure D-1 in near-quantitative yield: ^1H NMR ($CDCl_3$) δ 1.3 (s, 3, CH_3), 3.78 (ABq, 2, CH_2), 6.97–7.41 (m, 2, $H_{3',5'}$), 7.9–8.26 (m, 2, $H_{2',6'}$).

Cyclialkylations with neat $AlCl_3$ were performed as before.[2] The ongoing reactions, the crude product mixtures, and chromatographically purified samples were examined by ^1H and ^{13}C NMR and mass spectroscopy. Purified **2** and **3** from D-1 were also examined by ^2H NMR in $CHCl_3$ using a Varian XL-100, also used for ^1H and ^{13}C observations. Kinetic data were obtained from experiments at 100 °C using 2.33 ± 0.4 mol of $AlCl_3$ per mol of **1** or D-1 by the internal standard GLC method as previously reported.[2]

2-Chloro-5-fluoro-2-methylindan-1-one (6). Authentic **6** was prepared by chlorination of **2** with SO_2Cl_2 in carbon tetrachloride.[31] Recrystallized from hexane, it showed: mp 70–72 °C; ^1H NMR ($CDCl_3$) δ 1.8 (s, 3, CH_3), 3.55 (ABq, 2, CH_2), 6.97–7.35 (m, 2, $H_{4,6}$), 7.73–8.03 (m, 1, H_7); mass spectrum *m/e* (rel intensity) 200 (M^+, 5), 198 (M^+, 16), 163 (100), 135 (22), 133 (36), 115 (16), 109 (14), 107 (11), 94 (9), 57 (10). Anal. Calcd for $C_{10}H_8ClFO$: C, 60.47; H, 4.06; Cl, 17.85. Found C, 60.39; H, 4.12; Cl, 17.73.

$AlCl_3$–CH_3NO_2 Cyclialkylations. To a solution of 1.33 g (10 mmol) of $AlCl_3$ in 3 mL of CH_3NO_2 was added 1.0 g (5 mmol) of **1** and ca. 300 mg of *o*-nitrotoluene as an internal GLC standard. It was diluted with CH_3NO_2 to 5.0 mL, then heated at 85 ± 1 °C in a N_2 atmosphere under a reflux condenser with stirring. Samples were taken periodically, quenched into ice water and CH_2Cl_2, and worked up in standard fashion. Replicate GLC analyses were averaged and corrected for molar detector responses and yields were calculated. The data are plotted in Figure 4A.

Portions of an identical solution were sealed in capillary tubes, heated for specified periods, worked up, and analyzed as above. The (fewer) data points are plotted in Figure 4B.

An identical reaction run in a 5-mm NMR tube, but containing 15% of C-1 with **1**, was followed by ^{13}C NMR spectroscopy for 60 h at 70 °C. Label was observed only at C_3 in the **2** produced therefrom.

Isolation of 2-Chloro-5-fluoro-2-methylindan-1-one (6) and 6-Fluoro-3-methylisocoumarin (7). After the usual extractive workup of a reaction mixture run in CH_3NO_2, chromatography on silica gel using hexane, then benzene–hexane mixtures, gave **6**, identical to an authentic sample (see above) by TLC, ^1H NMR, GLC, and MS. Slightly more polar was **7**, which was crystallized from hexane containing a little ether: mp 90–92 °C; ^1H NMR ($CDCl_3$) δ 2.26 (br s, 3, CH_3), 6.21 (br s, 1, H_4), 6.87–7.28 (m, 2, $H_{5,7}$), 8.07–8.35 (m, 1, H_8); mass spectrum *m/e* (rel intensity) 178 (M^+, 54), 163 (25), 136 (22), 107 (100), 57 (29), 43 (98). Anal. Calcd for $C_{10}H_7FO_2$: C, 67.41; H, 3.96. Found: C, 67.61; H, 3.89.

Registry No.—**1**, 58472-46-1; C-**1**, 66483-26-9; D-**1**, 66483-25-8; **2**, 41201-58-5; ^{13}C-labeled **2**, 66483-21-4; ^{13}C-labeled **3**, 66483-22-5; ^{13}C-labeled **4**, 66483-20-3; **5**, 58472-45-0; **6**, 66483-24-7; **7**, 66483-23-6; $H^{13}CHO$, 3228-27-1; 4′-fluoropropiophenone, 456-03-1; $AlCl_3$, 7446-70-0; CH_3NO_2, 75-52-5.

References and Notes

(1) Part of this work was described during the Friedel–Crafts Symposium at the 173rd National Meeting of the American Chemical Society, New Orleans, La., March 23–25, 1977.
(2) S. H. Pines and A. W. Douglas, *J. Am. Chem. Soc.*, **98**, 8119–8124 (1976).
(3) Recent reports include: (a) A. A. Khalaf, *Rev. Roum. Chim.*, **19**, 1361–1372 (1974); (b) R. M. Roberts, *Intra-Sci. Chem. Rep.*, **6**, 89–99 (1972); and (c) L. R. C. Barclay and E. C. Sanford, Can. *J. Chem.*, **46**, 3325–3331 (1968).
(4) S. H. Pines and A. W. Douglas, *J. Org. Chem.*, **42**, 2786–2787 (1977).
(5) As will be made clear later in this paper, we do not, in fact, consider that transposition of the Cl and H atoms of **1** occurs after discrete C–Cl ionization, as we have shown (for illustrative purposes) in Scheme I. Representation by valence bond pictures, or even dotted lines, leaves much to be desired.
(6) See: W. H. McFadden, "Techniques of Combined Gas Chromatography/Mass Spectrometry: Applications in Organic Chemistry", Wiley, New York, N.Y., 1973, pp 252–256, for a discussion of mass fragmentography.
(7) For some recent references to rearrangement of acyl groups to adjacent electron deficient centers, see (a) J. Kagan, D. A. Agdeppa, Jr., S. P. Singh, D. A. Mayers, C. Boyajian, C. Poorker, and B. E. Firth, *J. Am. Chem. Soc.*, **98**, 4581–4588 (1976); (b) J. M. Domagala, R. D. Bach, and J. Wemple, *ibid.*, **98**, 1975–1977 (1976); (c) J. N. Marx, J. C. Argyle, and L. R. Norman, *J. Am. Chem. Soc.*, **96**, 2121–2129 (1974); and references to older work found therein.
(8) A ring-protonated cyclopropyl ketone intermediate was ruled out earlier[2] on the basis of its reactivity. It should accumulate and be seen under these conditions. Now, an edge-protonated cyclopropane[9] may be eliminated from consideration. Such a species would have to be a special one, indeed. It would have to be present in concentrations too low to see, and it would require that the edge-attached proton not be permitted to exchange with the proton on C_α since D-**1** recovered from reaction at 100 °C is unscrambled.
(9) For useful reviews which discuss edge-protonated cyclopropanes, see: N. C. Deno in "Isotopes in Organic Chemistry", Vol. 1, E. Buncel and C. C. Lee, Ed., Elsevier, 1975, Chapter 1; J. L. Fry and G. J. Karabatsos in "Carbonium Ions", Vol. II, G. A. Olah and P. v. R. Schleyer, Ed., Wiley, 1970, p 530; and C. J. Collins, *Chem. Rev.*, **69**, 543–550 (1969).
(10) We are indebted to Dr. G. B. Smith of these laboratories for much of the kinetic analysis. The cited rate of constants and ratios represent averages from five time intervals convering a 13-h reaction span.
(11) G. J. Karabatsos and F. M. Vane, *J. Am. Chem. Soc.*, **85**, 729–732 (1963).
(12) G. A. Olah, R. J. Spear, and D. A. Forsyth, *J. Am. Chem. Soc.*, **98**, 6284–6289 (1976). Rearrangement from the ethylenebenzenium ion of this reference might also have been a process occurring in concert[13] with hydride migration such that a primary carbenium ion did not form.
(13) F. A. Carey and R. J. Sundberg, "Advanced Organic Chemistry", Part A, Plenum, New York, N.Y., 1977, p 237.
(14) Note that ion **10** was shown in Scheme V, also. We plan to examine the question of 1,3- vs. 1,2-hydride shifts in oxonium ion formation by use of properly labeled substrate. See also ref 15 for formation of oxonium ions under similar Friedel–Crafts conditions.
(15) S. H. Pines and A. W. Douglas, *Tetrahedron Lett.*, 1955–1958 (1976).
(16) For studies of hydrolysis of analogous oxonium ions and citation of the enolic form, see H. R. Ward and P. D. Sherman, Jr., *J. Am. Chem. Soc.*, **89**, 1962–63, 4222–24 (1967); **90**, 3812–3817 (1968); and D. J. Pasto and M. P. Serve, *J. Am. Chem. Soc.*, **87**, 1515–1521 (1965).
(17) A referee has postulated that **2** may arise by two paths jointly satisfying our kinetic and label data, one involving direct D^+ ejection to **5**, the other passing through a protonated cyclopropropyl ketone. "Olefin formation would of course provide DCl for scrambling purposes". Besides our earlier expressed views,[8] scrambling would require the residual labeling in methyl and methylene groups to be statistically equal. See also ref 18. The cyclopropyl route should also give C_α-labeled **2**. We do not exclude some direct elimination of DCl to form unlabeled **2**.
(18) Lewis acid catalyzed labeling studies with toluene[19] show that essentially no label enters the aliphatic side chain. In ref 19, no exchange at all was noted with, e.g., acetophenone as substrate, presumably because the small amount of Lewis acid was completely coordinated as a salt. In the present case, we use excess $AlCl_3$.
(19) M. A. Long, J. L. Garnett, and R. F. Vining, *J. Chem. Soc., Perkin Trans. 2*, 1298–1303 (1975).
(20) We are indebted to Ms. P. C. Cala of these laboratories for the considerable mass spectral experiments, data, and discussion of them.
(21) J. H. Beynon, "Mass Spectrometry and its Applications to Organic Chemistry", Elsevier, Amsterdam, 1960, pp 262–265; and R. M. Dawson and R. G. Gillis, *Org. Mass Spectrom.*, **6**, 1003–1009 (1972).
(22) J. U. R. Nielsen, S. E. Jorgensen, N. Fredricksen, R. B. Jensen, G. Schroll, and D. H. Williams, *Acta Chem. Scand., Ser. B* **31**, 227–230 (1977).
(23) $AlCl_3$-catalyzed rearrangement of a highly substituted tetralone also occurred faster in CH_3NO_2: L. R. C. Barclay, R. H. Young, K. L. Adams, and H. M. Foote, *Can. J. Chem.*, **51**, 1598–1609 (1973).

(24) Initially, we reported[1] that **6** was a precursor of **7**.
(25) R. C. Paul, R. Kaushal, and S. S. Pahil, *J. Indian Chem. Soc.*, **44**, 995–1000 (1967), and work cited therein.
(26) D. Bauer and A. Foucault, *C. R. Hebd. Seances Acad. Sci., Ser. C*, **272**, 192–194 (1971).
(27) S. Swan, Jr., in "Techniques of Organic Chemistry", Vol. II, A. Weissberger, Ed., Interscience, New York, N.Y., 1956, p 393.
(28) D. E. Pearson, H. W. Pope, W. W. Hargrove, and W. E. Stamper, *J. Org. Chem.*, **23**, 1412–1419 (1958).
(29) R. H. Carter (nee' Rayner), R. M. Colyer, R. A. Hill, and J. Staunton, *J. Chem. Soc., Perkin Trans. 1*, 1438–1441 (1976), and references cited therein. A new approach to these structures via π-olefin–metal complexes has recently been reported: D. E. Korte, L. S. Hegedus, and R. K. Wirth, *J. Org. Chem.*, **42**, 1329–1336 (1977).
(30) Melting points are uncorrected. Elemental analyses were performed under the direction of Mr. J. P. Gilbert of these laboratories. The "usual workup" involves aqueous washing of the organic solvent solutions followed by drying over sodium or magnesium sulfate then evaporation to dryness in vacuo.
(31) We thank Mr. W. E. Shearin for this preparation.

Substituent Effects on Bromodecarboxylation Reactions

Charles A. Kingsbury* and George Max

Department of Chemistry, University of Nebraska, Lincoln, Nebraska 68588

Received September 17, 1976

The reaction of ring-substituted cinnamate and α-methylcinnamate ions with bromine in water or methanol was studied. Where strongly electron-donating substituents were present, the decarboxylation products, 1-bromo-2-phenylethene or 2-bromo-1-phenyl-1-propene, were predominant. With groups of indifferent electronic character, considerable β-lactone was observed. With electron-withdrawing groups (cinnamate ions) the predominant products result from solvent capture of the intermediate ion. The effects of temperature and bromide ion concentration are discussed. The stereochemistry of the conversion to lactone and olefin is interpreted in terms of the least motion of the intermediate ion to arrive at a conformation capable of forming products. An improved synthesis of cinnamic acids is given.

The problem of interest concerns the reactions of bromine with various substituted cinnamate ions (Scheme I). The reaction very likely proceeds through the intermediate cation (e.g., **2**, Scheme I) although contributions from an electron transfer, or a free-radical pathway, cannot be entirely ruled out.[1] Subsequent reactions of the intermediate carbonium ion **2** include two variations not possible in simple solvolyses,[2] namely decarboxylation and lactonization. Previous work on cinnamic acids includes the rates of halogenation studied by James and co-workers.[3] Tarbell and Bartlett apparently were the first to observe β-lactone formation from the treatment of α,β-unsaturated acids with bromine.[4] Berman and Price studied the reactions of the isomeric α-phenylcinnamate anions with bromine and concluded that the decarboxylation was stereospecific (retention).[5] Lactonization was considered but the importance of this intermediate or product was not clarified. More recently, Johnson and co-workers studied the chlorination of various α,β-unsaturated carbonyl compounds.[6] These workers postulated a concerted chlorodecarboxylation of *trans*-cinnamate ions or, alternatively, decarboxylation passing through a very short-lived intermediate analogous to **2**, since the olefin product was formed with high stereoselectivity, whereas the other reaction products were stereochemically mixed. Lactone was not reported. On the other hand, Berman and Price observed mixed isomeric olefins from treatment of *cis*-cinnamate with bromine.

In view of other work, the absence of β-lactone seems surprising.[4,7,8] The purpose of this work was to study the effects upon the yields and stereochemistry of decarboxylation product, lactone (if any), and solvent capture products as the following parameters are varied: (1) aromatic substituent X and vinyl substituent R; (2) bromide ion concentration; (3) temperature; and (4) solvent.

α-Methylcinnamate Ions (1a); Products of Reaction. Substrate **1a** (R = CH_3) reacts with bromine in the solvents water or methanol to form products **4**, **5**, **6**, **10**, **11**, and in certain cases **12** and **13** shown in Scheme I. Tables I and II list the yields of the major products.

For substrates with strongly electron donating groups X, the predominant reaction was decarboxylation to form the olefin **4**. The yield of **4** diminishes as X becomes progressively more electron withdrawing (90% **4** for X = p-CH_3O to 2% for X = p-Cl in water as solvent). In methanol, the trend is similar.

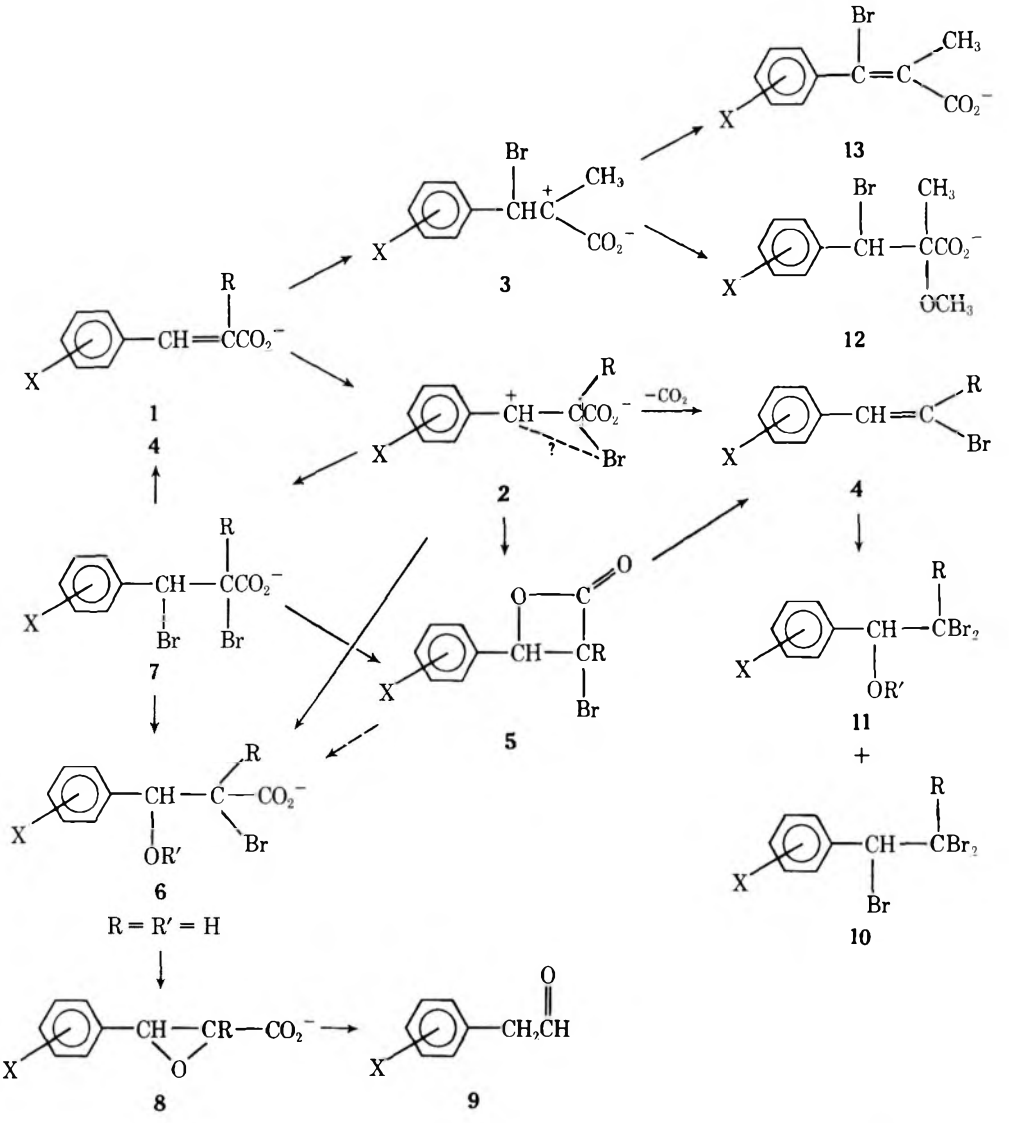
For the same substituent change, the bromohydrin or bromo ether **6** is formed in progressively higher yields (8% for X = p-CH_3O to 40% for X = p-Cl in water). Lactone **5** is definitely formed in many of these reactions. The yield of **5** is maximum for X = p-CH_3 in both solvents. The yields of **5** were rather variable in water, perhaps due to the lability of this product. No more than a trace of **5** is found where X = p-CH_3O, perhaps due to the facile reionization and subsequent decarboxylation (**5** → **2** → **4**).[9]

For compounds with electron-withdrawing groups, several additional products are observed by NMR (Figure 1), usually in very small yield. In two cases, the structure has been identified. For X = p-NO_2, an acidic product is formed in ca. 46% yield, whose NMR spectrum shows only methyl (δ 2.22) and aromatic absorptions. The olefinic structure **13** is assigned to this product which is also the product of solvolysis of **7** (free acid). For X = p-Cl and H, a second acidic product is formed, which shows methyl (δ 1.37), methoxyl (δ 3.49), and methine (δ 5.42) absorptions. The yield of this product is diminished by added bromide. The inverse addition structure **12** is assigned to this product, whose yield would be reduced by reaction of its precursor **3** with bromide. The appearance of **12** and **13** suggests that formation of ion **3** becomes competitive with formation of the benzylic ion **2**, as X becomes electron withdrawing. Solvolysis studies by Hughes and Ingold showed that ions of similar constitution as **3** (i.e., "α-lactones") enjoyed considerable stability, perhaps due to charge attraction in the zwitterion.[10,11] Reaction of the free acid of **1a** (various substituents) with bromine leads to **7** and the normal addition product **6** (no **13**), which suggests that **3** is stable as a zwitterion, but not as a simple cation.

In methanol, a sizable amount of a third material of unknown structure (labeled **6′** in Figure 1) is observed. The methyl chemical shift is very close to the bromohydrin **6** or to

0022-3263/78/1943-3131$01.00/0

Scheme I



threo-bromo ether **6** in both ^{13}C and ^{1}H spectra. This material may be the *threo*-bromohydrin that results from acyl–oxygen cleavage of the lactone, perhaps during workup.

Stereochemistry. The stereochemistry of reaction of substrate **1a** (X = CH_3O) was nonspecific. Approximately equal yields of the cis and trans olefins **4** were observed in either solvent. Mixed isomers of the bromo ethers **6** (60% erythro and 40% threo) were also found. For X = CH_3, observation of the stereochemistry of the olefin was impeded by the overlapping of NMR and GLC peaks. The lactone **5** and the bromo ether **6** were predominantly (>90%) the trans and erythro isomers, respectively. For X = H and Cl, the trans isomers of **4** and **5** and the erythro isomer of **6** were also strongly predominant. The lactone **5** formed from bromine addition to *trans*-**1a** was the same isomer as that formed in the solvolysis of *threo*-**7**. Since **7** forms lactone by intramolecular displacement of bromide, the trans configuration of **5** is indicated. The various stereochemical relationships are depicted in Scheme II.

Effect of Bromide. For X = H and Cl, addition of sodium bromide leads to the formation of ca. 20% dibromide **7** at the expense of **6** (Table I). With 0.6 M sodium bromide, both the cis and trans isomers of the olefin **4** were observed in similar yields in addition to **10** and **11** which could have been derived from either isomer.[12] Since *erythro*-**7** is also present in the reaction mixture and since **7** reacts to form *cis*-**4**, the origin of the cis isomer might be thus explained.

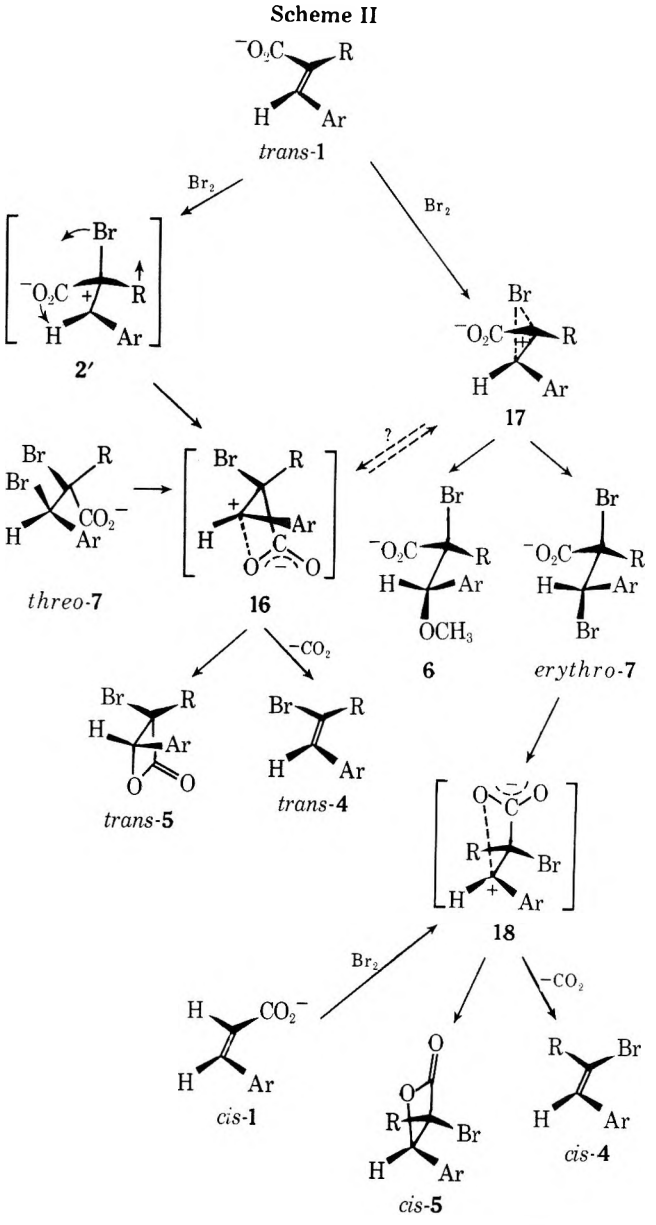
The increase in yield of the olefin **4** in the presence of bromide where X = *p*-CH_3O might thus be explained by the sequence **1** → **7** → **4**. However, the half-lives for solvolysis of **7a** (X = *p*-CH_3O, *m*-Br, H, and Cl) are 7, 88, and 104 min, respectively (at 32 °C), which are far greater than the reaction time, <3 min. On the other hand, a control experiment showed that **7a** (X = *p*-CH_3O, *m*-Br) was definitely reactive in less than 1 min in methanol solutions in the presence of bromine. It is noteworthy that Brown and Russell reported that bromine acts as a Lewis acid catalyst in certain situations, and this property may accelerate the reaction of **7a**.[13]

It is rather difficult to assess the effect of bromide on the yields of the olefin **4** and the lactone **5**, as the changes are about the same as experimental error. At best, a small reduction of yield is observed, especially in the case of electron withdrawing groups X.

Effect of Temperature. The effect of temperature on product yields is recorded in Table IV. At higher temperature, the yield of olefin **4** is increased. The temperature effect on the yields of **5** and **6** is irregular, but the sum of the two changes inversely as the olefin yield. At lower temperature, **4a** (X = H) appears to approach a minimum value, ~9%.

Cinnamate Ions (1b): Products of Reaction. The reactions of **1b** (R = H) are much less satisfactory on a quantitative basis than reactions of **1a**. Acceptable mass balances were difficult to achieve in methanol and impossible in water. The yields appear to be sensitive to seemingly minor variations in

Scheme II



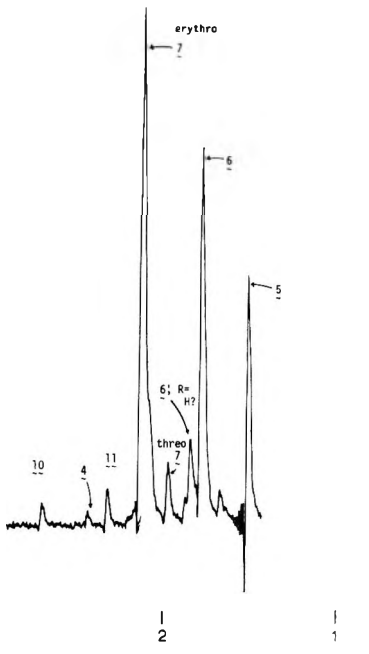


Figure 1. Partial 100 MHz NMR spectrum of the reaction products from treatment of **1a** (X = H) with bromine in methanol as solvent in the presence of NaBr.

procedure. The yields quoted below are applicable for the specific procedure given in the Experimental Section. These data are included because of the availability of the cis isomer (X = *o*-Cl). The point we wish to emphasize in reporting these data is that the stereochemistry of reaction is similar to that of **1a,** despite the presence of a less sterically demanding group, R = H. The trends in the product yields are also rather similar to those from **1a** in most respects.

In methanol, the yield of **4** again diminishes as X becomes increasingly electron withdrawing (73% for X = *p*-CH_3O to 0% for X = *m*-NO_2). Similar trends occur for reactions in water, although the yields are about 20% lower for substrates that from **4.** For the same substituent change, the bromo ether **6** is found in progressively higher yields (21% for *p*-CH_3O to 63% for *m*-NO_2). In water, the bromohydrin **6** is inefficiently removed from the aqueous layer in the workup procedure and yields cannot be quoted.

The lactone **5** is once again definitely formed, although the yields are much smaller than in the case of **1a.** In water, the maximum yield occurred for X = H (18%), whereas in methanol, very little lactone was found for this substrate. In methanol, the maximum yield of **5** was found for X = *o*-Cl (12%). In our hands, the highest yields of **5b** are observed for reactions in ethanol as solvent (26% for X = H and 20% for X = *o*-Cl). The lower ionizing power of ethanol may inhibit opening of the lactone to reform the zwitterion **2.** The relatively high yields in water, which has high ionizing power, may be due to the presence of carbon tetrachloride as a separate phase. The lactone dissolves in CCl_4 upon formation, which may protect it in part from destruction. The reaction time is also very short in water (<1 min). Yields are lower where carbon tetrachloride is omitted. A control experiment showed that a suspension of **5** and **4** (19 and 21% respectively of the amount of **1b** (X = H)) formed 2% **5** and 35% **4** on stirring in water at room temperature for ca. 25 min. Because of the lability of **5,** temperature effects were not extensively investigated (cf. Table IV).

In more highly basic solutions in water (pH ~9 rather than pH ~7), substantial yields of the epoxide **8** were observed (e.g., 40% **8,** where X = *o*-Cl).[14] Phenylacetaldehyde was also observed in certain cases (e.g., 10–13% for X = H). This product is probably formed from the epoxide **8** by a Darzens reaction during workup. This product was rarely observed in reactions run at the lower pH in which epoxides were absent.

Stereochemistry. The steric course of the reactions of **1b** was selective in nature. For *trans*-**1b** (all substituents), only the trans isomer of **4** was observed. In one large-scale run (X = H), the NMR spectrum of a neat sample of the neutral products of reactions showed no observable *cis*-**4.** However, for X = *p*-CH_3O and CH_3, considerable tribromide **10** was observed. Since the more reactive *cis*-**4** would have preferentially formed **10,** no decision about stereochemistry is possible for these substrates. The lactone **5,** where observed, was the trans isomer. The bromo ether **6** was the erythro isomer to the limits of detection, except in the case of X = CH_3O, where similar amounts of *erythro*- and *threo*-**6** were observed. This represents one of the major differences between this study and the chlorine additions reported by Cabaliero and Johnson where mixed products analogous to **6** were found for various substituents X.[6]

For *cis*-**1b** (X = o-Cl), reaction with bromine yielded observable amounts of only the cis isomer of the olefin **4** in low yield in both solvents. The cis lactone **5** was also observed in about 6% yield along with traces of *trans*-**5.** The *threo*-bromo ether **6** was dominant (*erythro*-**6,** <5%). There was slight isomerization of the starting material during the course of the reaction.[15]

Table I. Product Yields (%) from Reaction of α-Methylcinnamate Ions 1a with Bromine in Water at 28 ± 3 °C, pH 7.0–8.0

X (salt)[d]	no. of runs	olefin 4[a]	lactone 5	bromohydrin 6	other
p-CH_3O	3	90 ± 1[e]	trace	8 ± 2	
p-CH_3O (Br^-)[d]	1	90		9	
p-CH_3	2	19 ± 1	57 ± 2	22 ± 4	
p-CH_3 (Br^-)	1	16	58	12	3% **7**
H	5	6 ± 3	42 ± 10	31 ± 9	
H (Br^-)	2	7 ± 1[b]	46 ± 11	14 ± 10	14 ± 2% **7**
p-Cl	2	2 ± 1	41 ± 1	40 ± 2	
p-Cl (Br^-)	2	7 ± 2[c]	38 ± 7	7 ± 3	19% **7**, 5% **12**
o-Cl	4	8 ± 3	25 ± 7	39 ± 12	8 ± 3% **12**

[a] Includes **10** and **11** which are derived from **4**. [b] Ca. 50% *cis*- and 50% *trans*-**4** were observed. [c] Ca. 60% *cis*- and 40% *trans*-**4** were observed. [d] 0.6 M sodium bromide present. [e] In this table, and in Tables II–IV, the error term indicates the maximum range of yields between individual runs.

Table II. Product Yields (%) from Reaction of α-Methylcinnamate Ions (1a) with Bromine in Methanol at 28 ± 3 °C

X (salt)[e]	no. of runs	olefin[a] 4	lactone 5	bromo ether 6	other
p-CH_3O	4	77 ± 5	trace	22 ± 5	
p-CH_3O (Br^-)[e]	1	90		10	
p-CH_3	3	16 ± 1	47 ± 3	35 ± 3	
p-CH_3 (Br^-)	1	27	49	11	12% **7**
H	4	12 ± 5	23 ± 3	55 ± 8	ca. 6% **12**
H (0.6 M Br^-)[f]	1	12[b]	16	31	35% **7**, ca. 2% **12**
H (1.2 M Br^-)	1	9	18	20	45% **7**[g]
p-Cl	3	12 ± 3	17 ± 1	45 ± 4	ca. 12% **12**, ca. 3% **13**
p-Cl (Br^-)[f]	3	7 ± 1[c]	17 ± 2	25 ± 5	20 ± 1% **7**, ca. 1% **13**, ca. 4% **12**
p-NO_2[d]	2	trace	3 ± 3	8 ± 3	46 ± 10% **13**, 18 ± 10% **12**

[a] Includes **10** and **11**. [b] 67% *cis*- and 33% *trans*-**4**. [c] 50% *cis*- and 50% *trans*-**4**. [d] Lack of reactivity led to difficultly reproducible data. [e] 0.6 M sodium bromide present. [f] In some runs, a trace of *threo*-**7** appeared to be present. The very small yields (<5%) made positive identification difficult. [g] Ca. 10% threo and 90% erythro isomers.

Table III. Product Yields (%) from Reaction of Cinnamate Ion (1b) and Bromine in Methanol at 28 ± 3 °C

X (salt)[c]	no. of runs	olefin 4[a]	lactone 5	bromo ether 6	dibromide 7
p-CH_3O	3	73 ± 4		21 ± 2	
p-CH_3O (Br^-)[c]	1	89		4	
o-CH_3O	2	58 ± 5		26 ± 8	
o-CH_3O (Br^-)	2	65 ± 5		30 ± 5	
p-CH_3	3	47 ± 1	trace	55 ± 3	
p-CH_3 (Br^-)	1	41		49	2
H	2	23 ± 2	trace	63 ± 2	
H (Br^-)	3	20 ± 4	trace	40 ± 6	19 ± 4
p-Cl	3	14 ± 4	3 ± 1	62 ± 4	
p-Cl (Br^-)	1	19		41	36
trans-*o*-Cl	2	trace	12 ± 3	56 ± 5	4 ± 2
trans-*o*-Cl (Br^-)	3	2 ± 2	9 ± 2	25 ± 3	41 ± 11
cis-*o*-Cl	2	6 ± 2	6 ± 2[b]	70 ± 5	
cis-*o*-Cl (Br^-)	1	9	6	17	43
m-NO_2	2		2 ± 2	63 ± 2	28 ± 8

[a] Includes **10** and **11** which are derived from **4**. [b] Total of two isomeric structures. [c] 0.6 M sodium bromide present.

Effect of Bromide. Addition of sodium bromide again reduced the yields of the bromo ethers **6** by 17–30% (Table III) for X = CH_3, H, and *p*-Cl. In the case of X = *p*-CH_3O, the yield of olefin **4** was again increased by added bromide. Control experiments showed that the dibromide **7** was labile under the reaction conditions. Otherwise, the effect of bromide on olefin **4** and lactone **5** yields is at best a slight reduction, although the changes are usually within experimental error.

Discussion. Generally, the results of this study are in agreement with the findings of Berman and Price who observed retention of configuration in bromodecarboxylation,[5] with the added feature that predominant "retention" in lactone formation is also observed (e.g., *trans*-**1b** forms *trans*-**5b**). The chief exception to this specificity is where strongly stabilized ions (e.g., **2**, X = *p*-CH_3O) undergo internal rotation prior to decarboxylation. The ensuing discussion excludes *p*-CH_3O substituents.

The effect of added bromide ion on the yields of olefin **4** and lactone **5** is small and much less than the effect on the yields of bromo ether **6**. These data are in agreement with the findings of Cabaliero and Johnson, who suggested a concerted or very rapid stepwise process for the formation of **4b**.[6] Thus, bromide does not appear to be able to intercept the precursor of **4** or **5**. However, the high stereospecificity with which **6** is formed shows that the precursor does not attain rotational equilibrium, although the precursor is sufficiently long lived

Table IV. Effect of Temperature on Product Yields (%) in Methanol Solvent

substrate	X	no. of runs	temp,[a]	olefin 4	lactone 5	6	other
1a	p-CH_3O	3	28	77 ± 5	trace	22 ± 5	
	p-CH_3O	1	0	73		27	
	p-CH_3O	1	−77	52		48	
1a	H	2	67	27 ± 2	22 ± 5	33 ± 8	8 ± 3% 13
	H	4	28	12 ± 5	23 ± 3	55 ± 8	6 ± 4% 13
	H	2	−3	9 ± 1	19 ± 3	52 ± 3	5 ± 1% 13
	H	2	−75	9 ± 2	35 ± 5	47 ± 14	7 ± 4% 13
1a	p-Cl	2	67	16 ± 1	28 ± 1	46 ± 7	12 ± 5% 13
	p-Cl	3	28	12 ± 3	17 ± 1	45 ± 4	12 ± 6% 13
	p-Cl	2	−4	11 ± 2	23 ± 2	61 ± 6	13 ± 5% 13
	p-Cl	1	−75	unreactive			
1b	p-CH_3O	3	28	73 ± 4		21 ± 2	
	p-CH_3O	1	2	73		20	
1b	H	2	65	33 ± 1		57 ± 7	
	H	2	28	23 ± 2	trace	63 ± 2	
	H	2	2	22 ± 3	3 ± 2	67 ± 2	

[a] Temperature limit ±3 °C.

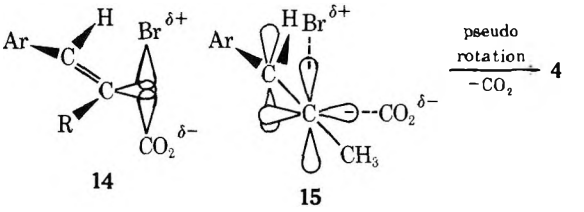
to selectively react with bromide to form **7** rather than react with one of the large number of solvent molecules present. A bridged bromonium ion (**17**) is highly likely, especially in cases where X is electron withdrawing.[16] The poorer neighboring group, chlorine, does not maintain stereochemistry in Johnson's cases.[6]

The question remains concerning the identity of the precursor of the olefin **4**. The main difficulty with a concerted mechanism may be intellectual, and not chemical; namely, it is difficult to envision an adequate concerted mechanism. One possibility is **14**, which displays a three-center two-electron bond.[12a,17] However, this transition state does not account for the effect of X. An alternative intermediate or transition state, **15**, displays effective sp^1 hybridization at the carbon undergoing covalency change.[18] This structure does not account for the stereospecificity, as pseudorotation in either direction may occur. Neither **14** nor **15** readily explain the similar stereochemistry and (lack of) sensitivity to bromide in the formation of **4** and **5**. Thus, rapid stepwise mechanisms must be considered as alternatives to try to identify common intermediates that link the **1** → **4** and **1** → **5** processes (cf. Scheme II).

The precursor of **4** and **5** is considered to be an ion basically similar to **2** (Scheme I). To explain the stereospecificity of formation of **4** and **5**, this ion must be able to preserve stereochemistry, but in a different way than **17**. The ion **16** is believed to be stabilized by electrostatic participation and possibly a degree of covalent bonding between COO^- and the β carbon. Vaughan and co-workers have quite conclusively demonstrated the importance of such electrostatic participation.[10b]

As bromine approaches and bonds to **1** (possibly via a π complex),[16f] charge attraction develops between the COO^- and the position of greatest positive charge density (the β carbon). This attraction leads to a "least-motion" process[19] in which a 60° rotation of the α carbon occurs (Scheme II) placing the COO^- in an optimum orientation for electrostatic participation. No products from the alternative ion **18** were observable, and thus the alternative 120° rotation is apparently disfavored.

The rapid reaction of **16**, despite the fact that this ion must be more stable than **17** for certain substituents, is explicable in terms of the idea that the orientation of COO^- that is optimum for electrostatic participation (**16**) is also optimum for decarboxylation and/or ring closure to form the lactone. These unimolecular processes may be intrinsically more rapid than

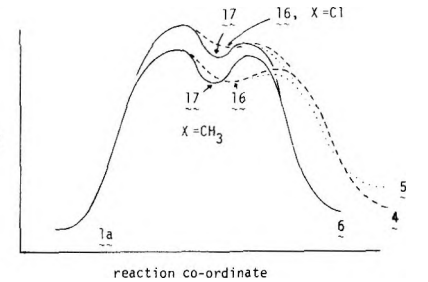


capture of **16** by a molecule of solvent to form *threo*-**6**. The low barrier for the **16** → **4** and **16** → **5** processes[20] and the relative energies of **16** and **17** as X varies are shown in Scheme III.

Reactions of α-Methylcinnamate Dibromides (7a). The reactions of **7a** are of interest since many of the same intermediates are possible as in the bromination of **1a**.[21] In addition, a concerted E2-like debromodecarboxylation may also occur.[22,23] A time study of the reaction of *threo*-**7a** (X = H) is given in Figure 2. A trans lactone intermediate (**5**) is observed, which builds up to a maximum level of 16% of the total integration then decays to zero. The major product is *trans*-**4** (81%), plus some bromo ether **6** (ca. 3%) and an unknown material (ca. 9%). The appearance of the unknown material is suppressed by running the reaction in the presence of LiBr. The chemical shifts of the unknown are rather similar to **12**, discussed earlier. The unknown may be the other diastereomer, presumably *threo*-**12**.

Direct observation of the course of reaction of *erythro*-**7a** (X = p-CH_3, H, or p-Cl) in methanol, or preferably, methanol-d_4, showed the rise and decay of peaks at δ 2.16 (CH_3) and δ 5.64 (CH) which can be ascribed to the cis lactone **5**. The chemical shifts for methyl of *cis*- and *trans*-**5** bear the same relationship to one another as the authentic cis and trans lactones (H replacing Br in **5**) prepared by Noyce and Banitt.[9b] For X = p-CH_3, **5** builds up to a maximum of about 10% of the total. The product mixture is again rich in **4** (~80% *cis*-**4** for

Scheme III



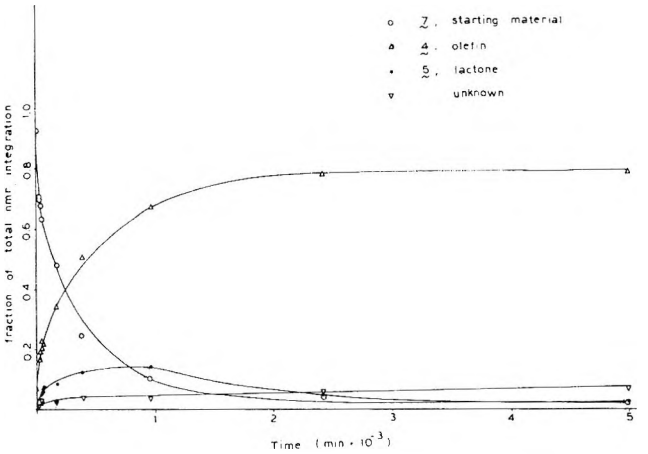


Figure 2. Time study of the solvolysis of *threo*-**7a** (X = H) in methanol-d_4 at room temperature as observed by NMR.

most substrates). Some **1a** appears very early in the reaction sequence and its level does not thereafter change.

The debromodecarboxylation of **7b** was studied earlier by Bordwell and Knipe, who cautiously disfavored the E2 process and preferred the E1 process, which proceeds through a zwitterion similar to **2**.[24] This preference resulted from a rate dependence upon σ^+ parameters and a similarity of **7b** in activation and Hammett ρ parameters to a substrate that could react only by a zwitterionic intermediate. No evidence could be found for two primary processes.[22] Earlier, Trumbull and co-workers found that electron-withdrawing groups in **7b** led to formation of *cis*-**4**, particularly in solvents of low ionizing power, whereas electron-donating groups X led to formation of the more stable *trans*-**4**.[22] These results were interpreted in terms of a dual mechanism originally proposed by Cristol and Norris (i.e., mostly E1 for X = p-CH_3O and mostly E2 for X = p-NO_2).[14] Bordwell and Knipe interpreted these results in terms of an E1 process in which electrostatic participation by carboxylate was tight or loose (permitting internal rotation) depending on X and solvent.

In the case of **7a**, neither Hammett σ nor Brown–Okamoto σ^+ parameters gave linear plots vs. log k (Table VI).[1b] Moving from methanol as solvent to 60% dimethyl sulfoxide (Me_2SO)–40% methanol resulted in a rate increase of 200, 330, and 710 for X = H, p-Cl, and p-NO_2, respectively. Thus the p-Cl compound surpasses X = H in reactivity. The substrate with X = p-NO_2 also approaches X = H in reactivity, but X = p-NO_2 undergoes a mechanism change giving ca. 80% **13** in 60% Me_2SO. The substrate with X = p-Cl also forms some **13** (ca. 13%) but still mostly **4** in 60% Me_2SO. Me_2SO, as solvent, does not readily support carbonium ion reactions, although many types of anionic (e.g., E2) reactions occur at markedly increased rates in Me_2SO mixtures.[26] The really definitive test of mechanism, however, would appear to be the presence or absence of a ^{13}C isotope effect for debromodecarboxylation.[27] We will defer judgment concerning mechanism until this experiment is performed.

The main question concerns the different stereochemistry in the reactions of **7a** in contrast to the bromine additions to **1a** and the higher level of olefin **4a** in the former reaction. To recapitulate, addition of bromine to *trans*-**1a** forms *trans*-**4**, *trans*-**5**, and *erythro*-**6** (or **7**). Reaction of the *erythro*-dibromide **7a** yields *cis*-**4** and *cis*-**5**. Presuming Bordwell's ideas concerning electrostatic participation to be correct, the stereochemistry of reaction of **7a** to form *cis*-**4** and **5** seems best explained in terms of the intermediate ion **18** (Scheme II). The approach of carboxylate from the other side of the molecule (to form **16**) is blocked by the leaving group. Therein lies the major difference between **7a** and the least-motion process in bromine addition to **1a** in which **16** is directly formed.

Table V

substrate	X	yield, %	mp, °C	lit. mp, °C (ref)
1a	p-CH_3O	26	158–159	157 (30)
	p-CH_3	41	169–171	169–170 (31)
	H	86	79–80	78 (31)
	p-Cl	45	168–172	168–169 (32)
	p-NO_2	33	208–210	208 (33)
1b	p-CH_3O	96	172–174	173 (35)
	o-CH_3O	86	181–183	185 (35)
	p-CH_3	92	197–198	198 (36)
	H	90	131–132	133 (34)
	o-Cl	93	201–204	211 (37)
	m-NO_2	80	201–208	203 (38)
	p-NO_2	88	287–289	286 (38)

Experimental Section

α-Methylcinnamic Acids (1a). The various substrates **1a** were prepared by the Perkin reaction.[29] A list of the substrates prepared and other data are given in Table V, including **1b** discussed below.

Cinnamic Acids (1b). An improvement on the Doebner modification of the Knoevenagel reaction is indicated below, making cinnamic acids one of the simplest preparations known.[29] To a mixture of 10.0 g (0.072 mol) of p-chlorobenzaldehyde and 0.83 g (0.08 mol) of malonic acid dissolved in 25 mL of dimethyl sulfoxide, 1 mL of piperidine was added. After an initial exothermic reaction subsided, the mixture was heated on a steam bath (ca. 80 °C) overnight (ca. 10 h). The mixture was poured onto 200 g of ice, and the resulting slurry was acidified with 6 N HCl. After the ice melted, the mixture was filtered and the solid cinnamic acid was washed repeatedly with water. If an odor was apparent, the solid product was also washed with petroleum ether. The product was air dried, yielding 11.4 g (87%) of **1a** (X = p-Cl), mp 246–248 °C (lit.[34] mp 250 °C). No impurities were evident in the NMR spectrum. The product was usually pure enough to be used directly, although in some preparations a single recrystallization was necessary.

Various commercial brands of dimethyl sulfoxide were used as received; these resulted in similar yields of product. It is important not to let the temperature of the reaction go too high, as evil smelling decomposition products of Me_2SO will adhere to the product. The yield may be improved slightly by using an excess of malonic acid, but the advantage does not outweigh the cost. Piperidine appeared to be the best of the bases tried. In no case was any trace of benzalmalonic acid found.

***cis-o*-Chlorocinnamic acid** was prepared by photolyzing the trans isomer in a quartz flask with a 100 W Hanovia lamp for ca. 1 week. The solvent was dichloromethane and the solution was under nitrogen. The solvent was partially evaporated, and the mixture was crystallized in a sacrificial manner, rejecting the trans isomer that preferentially crystallized. The resulting product showed traces of the trans isomer, mp 136–137 °C (lit.[38] mp 138–139 °C).

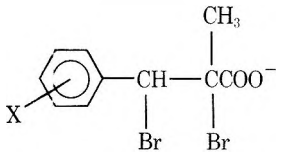
α-Methylcinnamic Acid Dibromides (7a). These were prepared by the Sudborough procedure[39] (A) or by the Trumbull procedure[24a] (B). The p-methoxy-m-bromocinnamic acid dibromide was prepared by procedure A, by placing the p-methoxy acid (11.5 g., 0.06 mol) in a desiccator, along with a beaker of H_2SO_4 and a beaker of bromine. The solid p-methoxy acid was removed at intervals and weighed. When it had reacted with the theoretical quantity of bromine vapor, it was removed and recrystallized from chloroform–pentane, mp 196–197 °C, 17 g (67% yield). This acid was found to have brominated in the aromatic ring, as shown by the ABX aromatic proton NMR pattern and the analysis.

Anal. Calcd for $C_{11}H_{11}Br_3O_3$: C, 30.66; H, 2.57. Found, C, 31.00; H, 2.89.

Unsubstituted α-methylcinnamic acid dibromide was prepared by procedure B by treating 12.7 g of α-methylcinnamic acid (0.08 mol) in 250 mL of glacial acetic acid with bromine (12.5 g, 0.08 mol). The mixture was heated to gentle reflux and stirred for 4 h. About half of the solvent was removed by rotary evaporation and the remainder was poured into water. The precipitate was quickly filtered and recrystallized from chloroform–pentane, after drying ($MgSO_4$), mp 141–143 °C (lit.[40] mp 137 °C), yielding 12.2 g (48%).

The p-methyl acid was prepared by procedure A in 96% yield, mp 160–161 °C.

Table VI. Rates of Reactions of the Anions of 7a in Methanol



erythro

X	registry no.	temp, °C	$k \times 10^4$, s^{-1}
p-CH_3O, *m*-Br	66482-02-8	0.0	0.0836 ± 0.010
		32.73	16.7 ± 0.2
p-CH_3	66482-03-9	0.0	0.00917 ± 0.00003
		32.73	2.86 ± 0.04
H	66482-04-0	32.73	1.31 ± 0.02
		49.85	13.5 ± 0.5
p-Cl	66482-05-1	32.73	1.11 ± 0.01
		49.85	12.5 ± 0.1
p-NO_2	66482-07-3	32.73	0.362 ± 0.002
		49.85	5.22 ± 0.07

Anal. Calcd for $C_{11}H_{12}Br_2O_2$: C, 39.34; H, 3.57. Found: C, 39.40; H, 3.68.

The *p*-Cl acid was prepared by B: mp 184–185 °C; MS (70 eV) *m/e* (formula; rel intensity) 357.8649 ($C_{10}H_9{}^{79}Br^{81}Br^{37}ClO_2$ and $C_{10}H_9{}^{81}Br_2{}^{35}ClO_2$, 0 9), 355.8655 ($C_{10}H_9{}^{79}Br_2{}^{37}ClO_2$, and $C_{10}H_9{}^{79}Br^{81}Br^{35}ClO_2$, 1.4), 277 (16.8), 276 (12), 201 (62.3), 198 (47.6), 181 (47.1), 130 (77.9), 127 (75.9), 113 (84.7), and 111 (100).

The *p*-NO_2 acid was also prepared by B in 86% yield: mp 179–180 °C; MS (70 eV) *m/e* (formula, rel intensity) 287.9692 ($C_{10}H_9{}^{81}BrNO_4$, 26.7), 285.9727 ($C_{10}H_9{}^{79}BrNO_4$, 27.9), 207.0539 ($C_{10}H_9NO_4$, 75.4), 206.0450 ($C_{10}H_8NO_4$, 35.5), 190 (52), 162 (41.3), 161 (86.4), 160 (56.2), 116 (90), 115 (100).

The threo unsubstituted dibromo acid was available from another study, mp 108.5–109.5 °C.

Procedure for Kinetics. The requisite amount of 0.0966 N methoxide was added to a 50-mL volumetric flask and this was filled nearly to the calibration mark with pure methanol. The flask was thermostated. The weighed amount of 7 (equivalent to the methoxide concentration) was added as a solid and the total volume was adjusted to 50 mL. Aliquots were withdrawn at intervals. These were acidified and extracted twice with ether. The ether layer was extracted twice with water and the combined aqueous layers were assayed for bromide by titration with thiosulfate. Rates were run in duplicate. Table VI lists the data obtained.

Procedure for the Bromodecarboxylations. A weighed amount of the cinnamic acid (usually 250 mg) was placed in 20 mL of redistilled water. In early runs, two standards were used, *p*-toluic acid and hexamethylbenzene. Weighed quantities of each were placed in the reaction flask, along with a quantity of sodium carbonate equimolar to the two acids. A solution of 30 g of bromine in 100 mL of carbon tetrachloride was prepared, and 1 mL of this was added to the reaction flask. The flask was stirred vigorously until colorless and then worked up immediately. The aqueous solution was diluted to 100 mL and extracted twice with carbon tetrachloride. In early runs, this fraction was assayed separately. In later runs, the aqueous solution was acidified to pH 1 and extracted with methylene chloride and then with ether. The combined organic extracts were washed with water, dried ($MgSO_4$), evaporated, and assayed by NMR. Integration over the resonance in question vs. integration over the standard gave a molar ratio relative to the standard, from which a yield could be calculated using the known weight of the standard.

In runs using methanol, sufficient standard methoxide solution was added to neutralize the acids and the solution was made up to 20 mL with pure methanol. It was clear that the mass balances in methanol always were close to 100% so in later runs the standard was omitted, since its resonance interfered with other absorptions. Figure 1 shows the NMR spectrum of a typical reaction product and the assignment of peaks.

NMR assays of reaction products were run on A60-D and XL-100 instruments with product percentages determined from the average of 2–5 integrations over the characteristic resonances of the products.

Approximately 170 runs were made under various conditions, but only those using the procedure given earlier are reported. With X = *p*-CH_3O and CH_3, the mass balance was always very good (90% or above). With electron-withdrawing groups, the mass balance was poorer, but only those runs with a mass balance of 80% or greater are reported. The trends of the product yields in the runs not reported are quite similar to the ones reported.

Table VII. NMR Assignments (ppm) for the Products of Reaction[a]

compd	CH_3	CH
trans-**1a**	2.15	7.87
cis-**1a**	2.07	6.78
cis-**4a**	2.43	6.89
trans-**4a**[c]	2.47	6.62
cis-**5a**	1.49	5.80
trans-**5a**[c]	2.16	5.61
erythro-**6a**, OR′ = OCH_3	1.72	4.92
erythro-**6a**,[c] OR′ = OCH_3	1.67	
threo-**6a**,[c] OR′ = OCH_3	1.71	4.68
erythro-**6a**, OR′ = OH	1.73	5.36
erythro-**7a**	2.10	5.84
threo-**7a**[c]	1.88	5.83
8a	1.26	4.24
10a	2.68	5.38
11a	2.35	5.42
12a	1.37	5.23
13a	2.13	

compd	H	H′	$J_{HH'}$, Hz
1b	6.33	7.70	16
4b	6.62	6.97	14.5
trans-**5b**[b,d] (trans)	4.86	5.41	3.8
erythro-**6b**, OR′ = OCH_3	4.28	4.61	9.5
erythro-**6b**, OR′ = OH	4.44	5.04	variable
8b	3.52	4.13	1.7
9	3.67		
10b[e]	5.25	5.98	7
11b,[d] OR′ = OCH_3	5.03	5.81	5.5
11b, OR′ = OH[e]	4.96	5.72	5.5

[a] $COCl_3$ as solvent, unless otherwise specified. [b] CCl_4 as solvent. [c] CH_3OH as solvent. [d] X = H. [e] X = CH_3.

Product Identification. Products were identified by isolation and study by spectroscopic means, by synthesis by known methods, and in certain cases by study of the response of the material in question to reactions known to be characteristic of a certain structure. The NMR assignments are listed in Table VII, for X = *p*-Cl substituted substrates and products, in the solvents indicated.[41] Other substituents will give slightly different shifts.

Compound 4 appeared in the "neutral" extraction fraction during workup. For **4a**, the distinctive NMR doublet for methyl and multiplet for vinyl H were unmistakable. In one case (X = *p*-NO_2), the trans isomer was isolated: mp 85.5–86.5 °C; NMR (CCl_4) δ 2.52 (d, 3, J = 1.5 Hz, CH_3), 6.78 (m, 1, CH=C), 7.66 (d, 2, J = 9 Hz, Ar), and 8.14 (d, 2, J = 9 Hz, Ar).

Anal. Calcd for $C_9H_8BrNO_2$: C, 44.19; H, 3.42. Found: C, 44.19; H, 3.23.

The cis isomer (X = *p*-NO_2) showed the following NMR parameters: δ 2.46 (d, 3, J = 1.6 Hz, CH_3), 6.63 (m, 1, CHC), 7.07 (d, 2, J = 8 Hz, Ar), and 7.39 (d, 2, J = 8 Hz, Ar).

For **4b**, the NMR coupling constants were quite distinctive and clearly showed the state of isomerism.

The lactone **5a** also appeared in the neutral extraction fraction. This material was quite sensitive to acid, and especially to base, giving hydrolysis products. If stirred in water, 4 was also formed. The isolation of the lactone was attempted from the silver acetate catalyzed reaction, which formed a high level of lactone. A material of mp 76–78 °C was indeed obtained, but it was difficult to purify. The coupling constants for **5b** clearly indicate the state of isomerism (Table VII). The mode of formation of **5a** (both isomers) from the diastereomers of **7a** provides a strong indication of the state of isomerism.

The bromo ethers **6** appeared in the acid extraction fraction. The presence of CH_3, CH_3O, and CH was unmistakable from the NMR spectrum. In the case of **6b**, authentic materials (both diastereomers) were available from another study for comparison purposes. The bromohydrins **6a** and **6b** on treatment with base formed the epoxide

8, which was very sensitive to acid, in turn forming **9** and other materials.

Products **10** and **11** appeared in the neutral extraction fraction. These were also formed by the addition of bromine to **4** studied as a separate reaction. In the case of chlorination of **1b**, which is similar to bromination, the chloride analogues of **4** (7%), **11** (5%), and **10** (88%) were analyzed by VPC (Carbowax 20M, 0.1% on glass beads; flow 50 cm^3/min; column temperature 175 °C) with retention times of 1.7, 9.8, and 4.7 min, respectively. The first and third peaks were collected: NMR of **10** (CCl_4) δ 5.97 (d, 1, J = 6 Hz, PhC**H**Cl), 5.24 (d, 1, $CHCl_2$), and 7.4 (s, 5, Ph).

The structure of **12** appeared evident in the case of the reaction of **7a** (X = *p*-NO_2), where this was the predominant product in reactions run in Me_2SO–CH_3OH. This material was isolated for X = *p*-Cl for the reaction of **1a** with silver acetate. The structure of **13** was assigned as indicated in earlier discussion.

Acknowledgment. The funds for purchase of Varian XL-100 were partially supplied by NSF Grant GP-10293, which is gratefully acknowledged.

Registry No.—*cis*-**1a** (X = *p*-CH_3O), 66482-31-3; *trans*-**1a** (X = *p*-CH_3O), 66482-32-4; *cis*-**1a** (X = *p*-CH_3O) acid, 13048-81-2; *trans*-**1a** (X = *p*-CH_3O) acid, 13048-80-1; *cis*-**1a** (X = *p*-CH_3), 66482-33-5; *trans*-**1a** (X = *p*-CH_3), 66482-34-6; *cis*-**1a** (X = *p*-CH_3) acid, 66482-35-7; *trans*-**1a** (X = *p*-CH_3) acid, 32655-80-4; *cis*-**1a** (X = H), 66482-36-8; *trans*-**1a** (X = H), 66482-37-9; *cis*-**1a** (X = H) acid, 15250-29-0; *trans*-**1a** (X = H) acid, 1895-97-2; *cis*-**1a** (X = *p*-Cl), 66482-38-0; *trans*-**1a** (X = *p*-Cl), 66482-39-1; *cis*-**1a** (X = *p*-Cl) acid, 66482-40-4; *trans*-**1a** (X = *p*-Cl) acid, 14328-88-2; *cis*-**1a** (X = o-Cl), 66482-41-5; *trans*-**1a** (X = *o*-Cl), 66482-42-6; *cis*-**1a** (X = *o*-Cl) acid, 66482-43-7; *trans*-**1a** (X = *o*-Cl) acid, 66482-44-8; *cis*-1a (X = *p*-NO_2), 66482-45-9; *trans*-**1a** (X = *p*-NO_2), 66482-46-0; *cis*-**1a** (X = *p*-NO_2) acid, 13048-76-5; *trans*-**1a** (X = *p*-NO_2) acid, 13048-77-6; *cis*-**1b** (X = *p*-CH_3O), 66482-12-0; *trans*-**1b** (X = *p*-CH_3O), 66482-13-1; *cis*-**1b** (X = *p*-CH_3O) acid, 5676-64-2; *trans*-**1b** (X = *p*-CH_3O) acid, 943-89-5; *cis*-**1b** (X = *o*-CH_3O), 66482-14-2; *trans*-**1b** (X = *o*-CH_3O), 66482-15-3; *cis*-**1b** (X = *o*-CH_3O) acid, 14737-91-8; *trans*-**1b** (X = *o*-CH_3O) acid, 1011-54-7; *cis*-**1b** (X = H), 66482-16-4; *trans*-**1b** (X = H), 17263-38-6; *cis*-**1b** (X = H) acid, 102-94-3; *trans*-**1b** (X = H) acid, 140-10-3; *cis*-**1b** (X = p-CH_3), 66482-17-5; *trans*-**1b** (X = *p*-CH_3), 66482-18-6; *cis*-**1b** (X = *p*-CH_3) acid, 14290-88-1; *trans*-**1b** (X = *p*-CH_3) acid, 940-61-4; *cis*-**1b** (X = o-Cl), 66482-19-7; *trans*-**1b** (X = *o*-Cl), 66482-20-0; *cis*-**1b** (X = o-Cl) acid, 704-96-1; *trans*-**1b** (X = *o*-Cl) acid, 939-58-2; *cis*-**1b** (X = *m*-NO_2), 66482-21-1; *trans*-**1b** (X = *m*-NO_2), 66482-22-2; *cis*-**1b** (X = *m*-NO_2) acid, 5676-61-9; *trans*-**1b** (X = *m*-NO_2) acid, 1772-76-5; *cis*-**1b** (X = *p*-NO_2), 66482-23-3; *trans*-**1b** (X = *p*-NO_2), 66482-24-4; *cis*-**1b** (X = *p*-NO_2) acid, 14290-91-6; *trans*-**1b** (X = *p*-NO_2) acid, 882-06-4; *cis*-**1b** (X = *p*-Cl), 66482-25-5; *trans*-**1b** (X = *p*-Cl), 66482-26-6; *cis*-**1b** (X = *p*-Cl) acid, 5676-62-0; *trans*-**1b** (X = *p*-Cl) acid, 940-62-5; *cis*-**4a** (X = *p*-Cl), 66482-27-7; *trans*-**4a** (X = *p*-Cl), 66482-28-8; *cis*-**4b** (X = *p*-Cl), 66482-29-9; *trans*-**4b** (X = *p*-Cl), 66482-30-2; *cis*-**4a** (X = *p*-NO_2), 38319-07-2; *trans*-**4a** (X = *p*-NO_2), 38319-08-3; *cis*-**5a** (X = *p*-Cl), 66481-94-5; *trans*-**5a** (X = *p*-Cl), 66481-95-6; *trans*-**5b** (X = H), 66481-96-7; *erythro*-**6a** (X = *p*-Cl; R′ = CH_3), 66481-97-8; *threo*-**6a** (X = *p*-Cl; R′ = CH_3), 66481-98-9; *erythro*-**6a** (X = *p*-Cl; R′ = H), 66481-99-0; *erythro*-**6b** (X = *p*-Cl; R′ = CH_3), 66482-00-6; *erythro*-**6b** (X = *p*-Cl; R′ = H), 66482-01-7; *threo*-**7a** (X = *p*-Cl), 66482-06-2; *erythro*-**7a** (X = 4MeO,3-Br) acid, 66482-08-4; *erythro*-**7a** (X = *p*-CH_3) acid, 66482-09-5; *erythro*-**7a** (X = H) acid, 66482-10-8; *erythro*-**7a** (X = *p*-Cl) acid, 66482-11-9; *erythro*-**7a** (X = *p*-NO_2) acid, 66481-86-5; **8a** (X = *p*-Cl), 66481-87-6; **8b** (X = *p*-Cl), 66481-88-7; **9** (X = *p*-Cl), 4251-65-4; **10a** (X = *p*-Cl), 66481-89-8; **10b** (X = *p*-CH_3), 66481-90-1; **11b** (R′ = CH_3; X = H), 52809-81-1; **11b** (R′ = H; X = *p*-CH_3), 66481-91-2; **12a** (X = *p*-Cl), 66481-92-3; **13a** (X = *p*-Cl), 66481-93-4.

References and Notes

(1) (a) J. March, "Advanced Organic Chemistry, Reactions, Mechanism and Structure", 2nd ed, McGraw-Hill, New York, N.Y., 1977, p 672, 680, and references cited herein; (b) p 253.
(2) G. A. Olah and P. Schleyer, "Carbonium Ions", Vol. II, Wiley-Interscience, New York, N.Y., 1970.
(3) (a) N. Hanson and T. James, *J. Chem. Soc.*, 1955, 2979 (1928); (b) H. Robinson and T. James, *ibid.*, 1454 (1933); (c) S. DeYoung, S. Ehrlich, and E. Berliner, *J. Am. Chem. Soc.*, **99**, 290 (1977).
(4) D. S. Tarbell and P. D. Bartlett, *J. Am. Chem. Soc.*, **59**, 407 (1937).
(5) J. D. Berman and C. C. Price, *J. Am. Chem. Soc.*, **79**, 5974 (1957).
(6) (a) M. C. Cabaleiro and M. D. Johnson, *Chem. Commun.*, 454 (1965); (b) M. C. Cabaleiro, M. D. Johnson, and N. Swedlund, *J. Chem. Soc. B*, 1022 (1967); (c) M. D. Johnson and E. N. Trachtenberg, *ibid.*, 1018 (1968); (d) see also J. Read and A. Andrews, *ibid.*, **119**, 1774 (1921); (e) J. Agoff and M. C. Cabaleiro, *Tetrahedron Lett.*, 3535 (1975).
(7) In our hands, β-lactone can be observed by IR upon treatment of the anions of α-phenylcinnamate and *trans*-cinnamate acid with bromine and chlorine, respectively.
(8) C. A. Kingsbury, *J. Org. Chem.*, **33**, 3247 (1968).
(9) (a) H. T. Liang and P. D. Bartlett, *J. Am. Chem. Soc.*, **80**, 3585 (1958); (b) D. S. Noyce and E. H. Banitt, *J. Org. Chem.*, **31**, 4043 (1966); (c) W. Barnett and J. C. McKenna, *Chem. Commun.*, 551 (1971); (d) W. Adam, J. Baeza, and J.-C. Liu, *J. Am. Chem. Soc.*, **94**, 2000 (1972); (e) H. E. Zaugg, *Org. React.*, **8**, 305 (1954), reviews the reactions of β-lactones; (f) G. Blackburn and H. Dodds, *J. Chem. Soc., Perkin Trans. 2*, 377 (1972).
(10) (a) C. K. Ingold, "Structure and Mechanism in Organic Chemistry", Cornell University Press, Ithaca, N.Y., 1953, p 328; (b) W. R. Vaughan, R. Cayle, J. Csapilla, and P. Scheiner, *J. Am. Chem. Soc.*, **87**, 2204 (1965).
(11) The elusive α-lactone has now been characterized: O. L. Chapman, P. Wojtkowski, W. Adam, O. Rodriguez, and R. Fuckstand, *J. Am. Chem. Soc.*, **94**, 1365 (1972). It was stated that the zwitterionic and covalent forms were in equilibrium.
(12) (a) In addition, bromide converts bromine partially to tribromide and may alter the nature of the brominating agent, F. R. Jensen and D. D. David, *J. Am. Chem. Soc.*, **93**, 4049 (1971). (b) J. H. Ralston and K. Yates, *ibid.*, **94**, 1403 (1972), showed that Br_3^- additions are characterized by lower Hammett ρ values than molecular bromine additions.
(13) G. A. Russell and H. C. Brown, *J. Am. Chem. Soc.*, **77**, 4025 (1955).
(14) For a different possible route to epoxide see S. J. Cristol and W. Norris, *J. Am. Chem. Soc.*, **75**, 632, 2645 (1953).
(15) (a) P. I. Abell, *J. Am. Chem. Soc.*, **88**, 1346 (1966); (b) D. S. Noyce, P. King, F. Kirby, and W. Reed, *ibid.*, **84**, 1632 (1962).
(16) (a) R. C. Fahey and H.-J. Schneider, *J. Am. Chem. Soc.*, **90**, 4429 (1968), believe that addition of bromine to 1-phenylpropenes essentially involves open benzylic ions, although the tendency for bridged ions is greater than in the case of chlorination (M. L. Poutsma, *ibid.*, **87**, 4285 (1965)). (b) K. Yates and W. Wright, *Can. J. Chem.*, **45**, 167 (1967), show that Hammet's ρ for addition is rather small and conclude the intermediate is probably bridged. (c) J. Dubois and G. Barbier, *Tetrahedron Lett.*, 1217 (1965), favor a bridged ion where electron-withdrawing aromatic substituents are present but an open ion where electron donating substituents are present. (d) J. Ralston and K. Yates, *J. Am. Chem. Soc.*, **91**, 469 (1969) present evidence for an open ion; K. Yates and R. S. McDonald, *ibid.*, **93**, 6297 (1971). (e) M. F. Ruasse and J. Dubois, *ibid.*, **97**, 1977 (1975), again prefer an interpretation involving bridged bromonium ions. (f) G. Olah and T. Hockswender, *ibid.*, **96**, 3574 (1974), emphasize the importance of a π complex between olefin and bromine (cf. also ref 16a). See also: C. G. Gebelin and G. D. Frederick, *J. Org. Chem.*, **37**, 2211 (1972). (g) See also: V. Seth and A. Bose, *J. Indian Chem. Soc.*, **48**, 575 (1971), and A. Gzoszkowski and J. Sienkiewicz, *Rocz. Chem.*, **45**, 1779 (1971).
(17) For a related complex scheme for halogenation, see H. Kwart and F. Scalzi, *J. Am. Chem. Soc.*, **86**, 5496 (1964).
(18) L. A. Singer and N. Kong, *J. Am. Chem. Soc.*, **89**, 6805 (1967).
(19) (a) J. Hine, *J. Am. Chem. Soc.*, **88**, 5525 (1966), and related papers; (b) O. S. Tee, *ibid.*, **91**, 7144 (1969); O. S. Tee and K. Yates, *ibid.*, **94**, 3072 (1972); (c) S. Ehrenson, *ibid.*, **96**, 3778 (1974); **96**, 3784 (1974); (d) M. J. S. Dewar, "The Electronic Theory of Organic Chemistry", Oxford University Press, London, 1949, pp 104 and 114.
(20) The possibility exists that the system possesses enough energy at the first transition state to carry it over the second, without collisional deactivation and subsequent reactivation. Thus, product formation could occur within a very few vibrations, and thus be operationally concerted. This is essentially a "hot ion" explanation which, in general, is not well regarded by the scientific community. For most recent criticism, see R. Huisgen, *J. Org. Chem.*, **41**, 403 (1976). However, P. Beak, *Acc. Chem. Res.*, **9**, 230 (1976), favorably considers similar highly reactive intermediates. C. J. Collins and B. M. Benjamin, *J. Am. Chem. Soc.*, **85**, 2519 (1963), have shown that highly energetic ions may react in a stereospecific manner.
(21) Carbonium ions resulting from additions to alkenes generally show slightly different reactions compared to carbonium ions generated by solvolysis: H. C. Brown and K. T. Liu, *J. Am. Chem. Soc.*, **66**, 466, 3898, 3900 (1964). Subtle differences of a "memory" nature remain to be explained.
(22) E. Trumbull, T. Finn, K. Ibne-Rasa, and C. Sauers, *J. Org. Chem.*, **27**, 2339 (1962).
(23) (a) E. Grovenstein and D. Lee, *J. Am. Chem. Soc.*, **75**, 2639 (1953); (b) K. Ibne-Rasa and A. Ahmad, *J. Sci. Res. (Lahore)*, **3**, 1 (1968).
(24) F. G. Bordwell and A. C. Knipe, *J. Org. Chem.*, **35**, 295 (1970); **35**, 299 (1970).
(25) The stereochemical data given in ref 22 are regarded in ref 24 as inconclusive due to the fact that known reactions proceeding through zwitterions are stereospecific, namely the cleavage of β-lactones (possibly also a least motion process). However, Noyce and Brauman report that zwitterions derived from unstrained open chain substrates, namely hydroxy carboxylates, rather similar to **7**, react to give the most stable olefin after various types of internal rotation (cf. D. S. Noyce and S. Brauman, *J. Am. Chem. Soc.*, **90**, 5218 (1968)). See, however, ref 9b.
(26) A. J. Parker, *Q. Rev., Chem. Soc.*, **16**, 163 (1962); also ref 27, pp 81 and 93.
(27) W. H. Saunders and A. F. Cockerill, "Mechanisms of Elimination Reactions", Wiley-Interscience, New York, N.Y., 1973, pp 71–89.
(28) M. H. O'Leary, D. Richards, and D. Hendrickson, *J. Am. Chem. Soc.*, **92**, 4435 (1970).
(29) A. I. Vogel, "Practical Organic Chemistry", 3rd ed, Longmans, Green and Co., New York, N.Y., 1956, pp 708 and 711.
(30) W. H. Perkin, *J. Chem. Soc.*, **31**, 412 (1877).
(31) K. von Auwers, *Justus Liebigs Ann. Chem.*, **227**, 485 (1885).
(32) H. Erdman, *Justus Liebigs Ann. Chem.*, **227**, 247 (1885).
(33) W. J. Gensler and E. Berman, *J. Am. Chem. Soc.*, **80**, 4949 (1958).
(34) J. van der Lee, *Recl. Trav. Chim. Pays-Bas*, **45**, 674 (1926).

(35) T. Posner, *J. Prakt. Chem.*, **82**, 425 (1910).
(36) T. Posner and G. Schreiber, *Chem. Ber.*, **57**, 1127 (1924).
(37) K. von Auwers, *Justus Liebigs Ann. Chem.*, **422**, 133 (1920).
(38) F. Tiemann and J. Oppermann, *Chem. Ber.*, **13**, 2059 (1880).
(39) J. J. Sudborough, *J. Chem. Soc.*, 666 (1903).
(40) R. Stoermer and P. Heymann, *Chem. Ber.*, **44**, 637 (1911).
(41) T. Wittstruck and G. N. Trachtenberg, *J. Am. Chem. Soc.*, **89**, 3802 (1967).

Comparison of the Addition of Bromine Chloride to 1-Hexene and 1-Hexyne in Carbon Tetrachloride and Methanol

Victor L. Heasley,* Dale F. Shellhamer, John A. Iskikian, and David L. Street

Department of Chemistry, Point Loma College, San Diego, California 92106

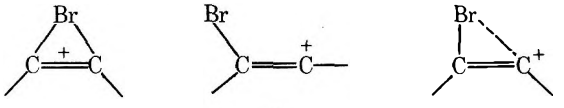
Gene E. Heasley

Department of Chemistry, Bethany Nazarene College, Bethany, Oklahoma 73008

Received January 26, 1978

Addition of bromine chloride (BrCl) to 1-hexene in CCl_4 gives a 61:39 ratio of Markownikoff to anti-Markownikoff products (1-bromo-2-chlorohexane to 1-chloro-2-bromohexane), suggesting a symmetrically bridged bromonium ion intermediate in this reaction. 1-Hexyne reacts with BrCl to give Markownikoff and anti-Markownikoff products in the ratio of 90:10 (*trans*-1-bromo-2-chloro-1-hexene/*trans*-1-chloro-2-bromo-1-hexene). These data, together with the fact that the alkene products have trans stereochemistry, implicate a weakly bridged bromonium in the addition of BrCl to 1-hexyne. The bromochlorohexanes were analyzed by mass specrometry, and ^{13}C NMR analyses distinguished between the bromochlorohexenes. In CH_3OH, 1-hexyne and BrCl give only Markownikoff bromochloride (trans isomer) and 1,1-dibromo-2-hexanone. (The result of two additions of Br, OCH_3, followed by hydrolysis of the intermediate ketal.) Markownikoff and trans additions suggest that a weakly bridged bromonium ion, rather than a vinyl cation, is involved. Addition of BrCl to 1-hexene in CH_3OH gives the following ratios of Markownikoff to anti-Markownikoff bromochlorides and methoxy bromides: 25:24 and 34:17.

A few years ago, Pincock and Yates[1] suggested that the intermediate involved in the bromination of some alkylacetylenes in acetic acid is a bridged bromonium ion (**1a**) and not an open vinyl cation (**1b**). They based their conclusion on the assumption that an unbridged vinyl cation should give some *cis*-1,2-dibromide; only *trans*-1,2-dibromide was reported.[2] More recently, Olah and Hochswender[3] drew the same conclusion from their studies of the bromination of 1-hexyne in 1,1,2-trichlorotrifluoroethane. Neither study, however, permitted a conclusion to be drawn concerning the symmetry of the bridging in the bromonium ion. Conceivably a weakly bridged ion such as **1c** is involved, but with sufficient bridging to prevent syn addition.

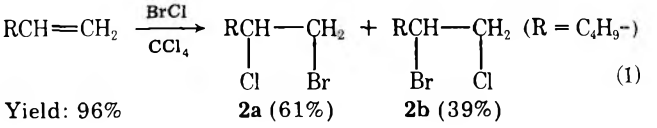


1a **1b** **1c**

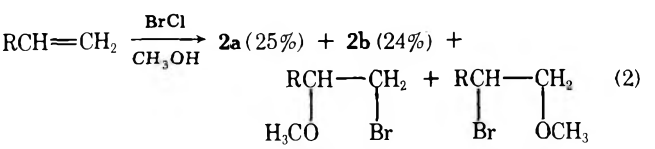
We proposed to study the addition of bromine chloride (BrCl) to both 1-hexene and 1-hexyne in a nonpolar solvent (CCl_4) and a polar solvent (CH_3OH). Our initial assumption was that the extent of anti-Markownikoff ring opening of either the saturated bromonium ion from 1-hexene or the unsaturated ion from 1-hexyne should be significant if the bridging is symmetrical and decrease to zero with a carbocation. Although Pincock and Yates[1] did not observe solvent incorporation when 1-hexyne was brominated in acetic acid, we suspected that ring opening of the intermediate bromonium ions would occur in the more nucleophilic solvent methanol. Solvent incorporation is a predominant reaction in the bromination of 1-hexene in methanol.[4,5]

Results

Products from the addition of BrCl to 1-hexene in CCl_4 and CH_3OH under ionic conditions are shown in eq 1 and 2.

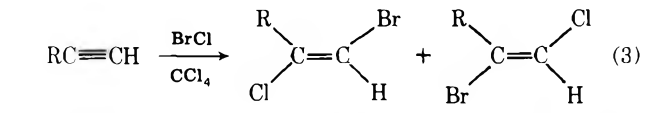


Yield: 96% **2a** (61%) **2b** (39%) (1)

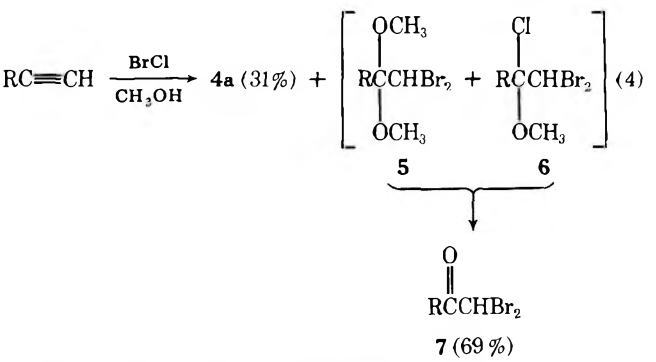


Yield: 84% **3a** (34%) **3b** (17%) (2)

1-Hexyne and BrCl under ionic conditions gave the products shown in eq 3 and 4. We postulate that **5** and **6** are involved and that they result from addition to **8**, because **8** is more reactive than the starting 1-hexyne (eq 5). 2,2-Dibromohexanal (**9**) was not detected, indicating that anti-Markownikoff addition of Br, OCH_3 did not occur (eq 6).

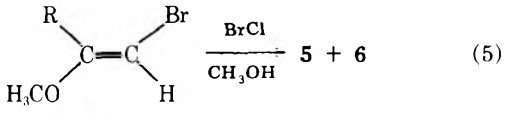


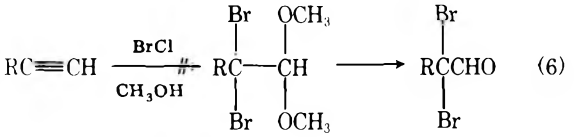
Yield: 79% **4a** (90%) **4b** (10%) (3)



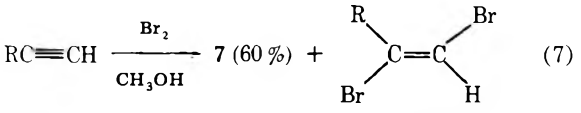
7 (69%) (4)

0022-3263/78/1943-3139$01.00/0



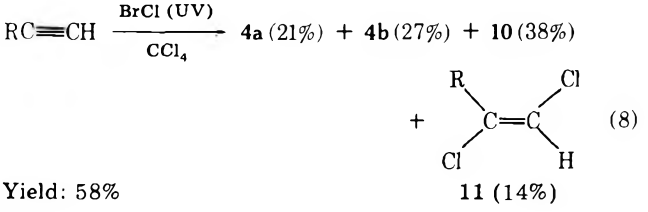


We also examined the bromination of 1-hexyne in methanol (eq 7).



Yield: 86% **10** (40%)

Radical addition (ultraviolet irradiation) of BrCl to 1-hexyne in CCl_4 gave a much different product composition than ionic addition (eq 8).



Yield: 58% **11** (14%)

The structures of bromochlorides **2a,b** from 1-hexene were established by their mass spectra. Both isomers (**2a,b**) have the same isotope cluster at *m/e* 169, 171, and 173, which corresponds to five-membered halonium ions **12a,b** (see Scheme I).[6] Loss of halogen Y and hydrogen halide HY gives isotope clusters which we assigned structures **13a** and **14a** or **13b**, and **14b**. Apparently, mass spectral analysis is a general diagnostic procedure for the structural determination of vicinal dihalides.[7]

The structures of the dihaloalkenes (**4a,b**) from 1-hexyne were determined by carbon-13 magnetic resonance. Chemical shifts of the vinyl carbons are reported in Table I. When bromine is on carbon-2, resonance is ca. 127 ppm, whereas the chemical shift is ca. 137 ppm when chlorine is on the same carbon. Resonances with bromine and chlorine on carbon-1 are about 102 and 114 ppm, respectively.[8] The coupling constant between carbon-1 and the vinyl hydrogen of carbon-1 was determined to be 244 Hz for **4a**.

Scheme I

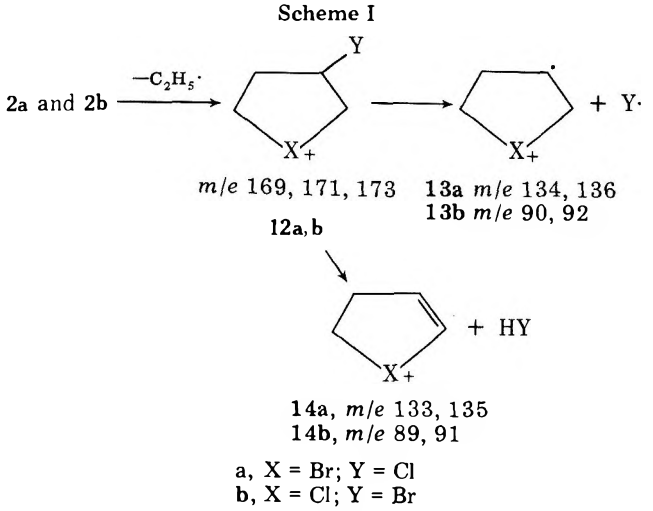
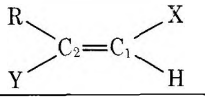


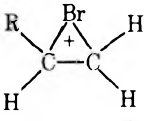
Table I. ^{13}C Chemical Shifts for *trans*-1,2-Dihalohexenes in $CDCl_3$



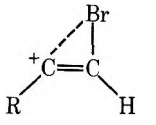
haloalkene	registry no.	X	Y	C_2	C_1
4a	66538-70-3	Br	Cl	137.8	101.6
4b	66538-71-4	Cl	Br	127.2	115.6
10	49677-13-6	Br	Br	127.8	102.7
11	59697-51-7	Cl	Cl	137.5	114.3

Discussion

The results show that anti-Markownikoff attack by chloride ion on bromonium ion **15** from 1-hexene to give **2b** is a significant pathway in CCl_4 and CH_3OH, indicating a symmetrically bridged intermediate in this reaction.[9] Attack by CH_3OH on the terminal carbon of **15** to give **3b** is also important. On the other hand, formation of only minor amounts of anti-Markownikoff product **4b** for BrCl and 1-hexyne in CCl_4 implicates an intermediate bromonium ion with very weak bridging (**16**).

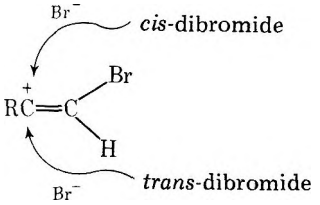


15

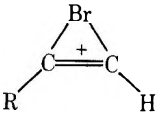


16

Although no *anti*-Markownikoff addition (**4b** or **9**) occurs in CH_3OH, we believe that a weakly bridged ion (like **16**), rather than an open vinyl cation, also is involved in this solvent, since an open ion should lead to some cis product.[10]



Suppose that a symmetrically bridged bromonium ion (**17**) were involved in the additions to 1-hexyne: How should it be opened? Since the bromonium ion from 1-hexene is opened to a significant extent at carbon-1, we can see no reason why attack should not occur just as readily at carbon-1 in **17**.



17

Furthermore, Schmid and co-workers[11] have shown that anti-Markownikoff addition is the main pathway in the reaction of 4-chlorobenzenesulfenyl chloride with 1-hexyne. These authors point out that an alkyl group should cause greater steric hindrance toward Markownikoff ring opening in a particular alkyne than in the corresponding alkene. Therefore, we conclude that the intermediate bromonium ion in the addition of BrCl to 1-hexyne is weakly bridged.

Another interesting aspect of this research concerns the

change in regiospecificity of ring opening of the intermediate bromonium ion (**15**) from 1-hexene by chloride in CCl_4 and CH_3OH. The results show that the ratio of Markownikoff to anti-Markownikoff attack (**2a/2b**) by chloride ion on **15** is ~60:40 in CCl_4 and ~50:50 in CH_3OH. Since the bridging in **15** should be weaker in the polar solvent CH_3OH, we anticipated an increase in Markownikoff addition (**2a**). An explanation of this unexpected result is that the chloride ion in CCl_4 is "naked" and experiences little steric hindrance from the alkyl group during ring opening at carbon-2. In CH_3OH, however, the chloride ion is solvated, $Cl(CH_3OH)_n^-$, and much larger, and prefers to attack the less hindered position (carbon-2) in bromonium ion **15**.

The greater ratio (2:1) of Markownikoff to anti-Markownikoff methoxy bromides (**3a/3b**) compared to the ratio (1:1) of bromo chlorides (**2a/2b**) for 1-hexene in CH_3OH probably results from the fact that methanol is less nucleophilic and prefers to react at carbon-2 which has greater carbocation character.

Under radical conditions, **4a,b** could result from photoaddition of either BrCl or a mixture of Br_2 and Cl_2 to 1-hexyne, since BrCl solution is known to contain a mixture of Br_2 and Cl_2.

Experimental Section

Materials. All solvents were obtained commercially in high purity and were used without further purification. 1-Hexene and 1-hexyne were distilled prior to use.

General Reaction Conditions. All ionic reactions of 1-hexene and 1-hexyne in CCl_4 and CH_3OH with BrCl were carried out in the dark to approximately 20% completion at room temperature; the concentration of the solutions was 0.04 mol fraction in alkene or alkyne.

Reaction of Bromine Chloride with 1-Hexene in Carbon Tetrachloride. To 1.00 g (0.012 mol) of 1-hexene in 27.5 mL of CCl_4 was added 1.9 mL of a 1.26 M bromine chloride–CCl_4 solution. The reaction mixture was stirred in the dark for 5 min and the solvent was then removed at reduced pressure. The yield of **2a,b** was obtained by NMR analysis of the crude mixture with benzene as an internal standard. The relative amounts of **2a,b** were determined by VPC analysis on a 10% DEGS column (19 ft × 0.25 in.) at 70 °C; retention times (min) are: **2b,** 16.3; **2a,** 17.2; 1,2-dichlorohexane, 11.2; and 1,2-dibromohexane, 23.4. The accuracy of the VPC analyses probably does not exceed ±(percentage of compound) × 0.025.

Compounds **2a,b** were separated by preparative VPC, and the following NMR data (CCl_4) were obtained: **2a** δ 0.97 (t, J = 5.0 Hz, 3 H), 1.1–2.5 (m, 6 H), 3.60 (d, J = 4.0 Hz, superimposed on multiplet), 3.2–4.3 (3 H). **2b** δ 0.97 (t, J = 5.0 Hz, 3 H), 1.1–2.5 (m, 6 H), 3.83 (d, J = 4.0 Hz, superimposed on multiplet) 3.3–4.3 (3 H).

The structures of **2a,b** were deduced from their mass spectra (70 eV). **2a** gave an isotope cluster at m/e 169, 171, and 173, which we assigned to the five-membered cyclic halonium ion **12a** (Scheme I). Loss of chlorine and hydrogen chloride from **12a** gave two sets of isotope clusters at m/e 134 and 136 and m/e 133 and 135 for **13a** and **14a,** respectively. Mass spectral analysis of **2b** gave isotope clusters at m/e 169, 171, and 173 for the cyclic halonium ion **12b.** Loss of bromine and hydrogen bromine from **12b** gave two sets of isotope clusters at m/e 90 and 92 and m/e 89 and 91, for **13b** and **14b,** respectively.

Reaction of Bromine Chloride with 1-Hexyne in Carbon Tetrachloride. Ionic Conditions. To 1.00 g (0.012 mol) of 1-hexyne in 28.3 mL of carbon tetrachloride was added 1.9 mL of a 1.26 M bromine chloride–CCl_4 solution. The reaction mixture was stirred in the dark for ca. 12 h, and the solvent was removed at reduced pressure. Crude reaction mixtures of **4a,b** were analyzed by NMR using benzene as an internal standard. All attempts to separate **4a,b** by VPC failed.

A mixture of **4a,b** was isolated by preparative VPC: 2.5% SE-30 column (8 ft × 0.15 in.) at 60 °C; retention times (min): **4a,b,** 4.8; **10,** 8.1; and **11,** 2.8. NMR spectra were made of the collected material: ^1H NMR (CCl_4) δ 0.97 (t, J = 6.2 Hz, 3 H), 1.1–1.9 (m, 4 H), 2.53 and 2.60 (2t, J = 6.0 Hz, 2 H), 6.16 and 6.23 (for **4a** and **4b,** respectively, s, 1 H). ^{13}C NMR ($CHCl_3$) **4a** δ 101.6 and 137.8 for the vinyl carbons C_1 and C_2, respectively; **4b** δ 115.6 and 127.2 for the vinyl carbons C_1 and C_2, respectively.

NMR data for *trans*-1,2-dibromo-1-hexene (**10**):[1] ^1H NMR (CCl_4) δ 0.98 (t, J = 6.8 Hz, 3 H), 1.1–1.9 (m, 4 H), 2.63 (t, J = 6.8 Hz, 2 H), 6.38 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 102.7 and 127.8 for the vinyl carbons C_1 and C_2, respectively.

NMR data for *trans*-1,2-dichloro-1-hexene (**11**): ^1H NMR (CCl_4) δ 1.00 (t, J = 6.5 Hz, 3 H), 1.50 (m, 4 H), 2.5 (t, J = 6.8 Hz, 2 H), 6.10 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 114.3 and 137.5 for the vinyl carbons C_1 and C_2, respectively.

Reaction of Bromine Chloride with 1-Hexene in Methanol. To 1.00 g (0.012 mol) of 1-hexene in 11.5 mL of CH_3OH was added 2 mL of a 1.26 M bromine chloride–CCl_4 solution. The reaction mixture was stirred for 5 min and added to water. The organic products were extracted into CCl_4.

The bromo chlorides and methoxy bromides[12] were analyzed by VPC using chlorobenzene as an internal standard: 2–5% FFAP column (14 ft × 0.125 in.) at 70 °C; retention times (min) are: **2b,** 17.9; **2a,** 19.3; **3b,** 14.0; and **3a,** 16.3.

Reaction of Bromine Chloride with 1-Hexyne in Methanol. To 1.0 g (0.012 mol) of 1-hexyne in 12.1 mL of CH_3OH was added 1.7 mL of a 1.45 M bromine chloride–CCl_4 solution. The reaction mixture was stirred for a short time and then was added to water containing a few drops of concentrated HBr to assure hydrolysis of the ketal. The organic products were extracted into CCl_4. After removal of the solvent, the crude mixture was analyzed by NMR using benzene as an internal standard.

1,1-Dibromo-2-hexanone (**7**) was isolated from the reaction mixture by preparative VPC: 2.5% SE-30 column (11 ft × 0.125 in.) at 100 °C; retention times (min): **7,** 12.8; **4a,b,** 4.9; and **10,** 7.6. The ketone was identified by its IR spectrum (CCl_4, C=O, 1725 cm^{-1}) and NMR spectrum (CCl_4): δ 0.97 (t, J = 6.2 Hz, 3 H), 1.2–1.8 (m, 4 H), 2.93 (t, J = 6.6 Hz, 2 H), 5.67 (s, 1 H).

Attempts were made to detect the aldehyde proton of 2,2-dibromohexanal (**9**) by NMR, but without success. A trace (ca. 2%) would have been detected had it been present. The oxidation product of the aldehyde, the carboxylic acid, was not observed by NMR.

Reaction of Bromine with 1-Hexyne in Methanol. To 1.0 g (0.012 mol) of 1-hexyne in 12.1 mL of CH_3OH was added 0.39 g of Br_2 dissolved in 2.73 mL of CCl_4. The reaction mixture, composed of dibromo ketone (**7**) and *trans*-dibromide (**10**), was isolated and analyzed by NMR as reported for the product from BrCl addition. Both **10** and **7** were isolated by preparative VPC (the SE-30 column). NMR and IR analyses established that the dibromo ketones from Br_2 and BrCl additions were identical. The NMR spectra of the dibromide and authentic **10** from bromination of 1-hexyne were identical.

Stability of Bromo Chlorides 4a,b in Methanol, Water, and Acid. A known amount of bromo chlorides **4a,b** with an internal standard was stirred in CH_3OH for a short time and then added to water and several drops of concentrated HBr to simulate reaction conditions. NMR and VPC analyses established that no dibromo ketone **7** was formed, nor did the amount of **4a,b** decrease.

Radical Reaction of Bromine Chloride with 1-Hexyne. To 1.0 g (0.012 mol) of 1-hexyne in 28.8 mL of CCl_4 was added 1.9 mL of a 1.28 M bromine chloride–CCl_4 solution. The solution was irradiated with a sunlamp, and the reaction was completed in approximately 2 min. The solvent was removed under pressure, and the mixture was analyzed by NMR using benzene as an internal standard.

Proof that Bromine Chloride Adds to 1-Hexyne by an Ionic Mechanism in the Dark. The reaction of BrCl with 1-hexyne in the dark was carried out using isoamyl nitrite as a radical inhibitor. Lower concentrations of isoamyl nitrite (4 equiv with respect to Br_2) appeared to induce a radical reaction, since the ratio of **4a/4b** increased from 90:10 (no inhibitor) to 70:30. Larger amounts of inhibitor (up to 8 equiv) reduced the ratio of **4a/4b** to a constant level of 90:10.

Acknowledgment. Support for this work was provided by the Research Corporation, the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Research Associates of Point Loma College. We thank Mr. Joe Earls (University of Oklahoma) and Dr. John Wright (University of California, San Diego) for the carbon-13 NMR spectra, Mr. Richard Dill (Oklahoma Bureau of Investigation) for the mass spectral analyses, and Dr. Francis Schmidt (Department of Chemistry, University of Oklahoma) for helpful suggestions and interpretation of the mass spectral data.

Registry No.—**2a,** 66538-72-5; **2b,** 66538-73-6; **3a,** 24618-32-4; **3b,** 24618-33-5; **7,** 54899-26-2; **12a,** 66538-74-7; **12b,** 66538-75-8; **13a,** 66538-76-9; **13b,** 66538-77-0; **14a,** 66538-78-1; **14b,** 66538-79-2; 1-hexene, 592-41-6; bromine chloride, 13863-41-7; 1-hexyne, 693-02-7.

References and Notes

(1) J. A. Pincock and K. Yates, *Can. J. Chem.*, **48**, 3332 (1970).
(2) Although Pincock and Yates state in the Results and Discussion section of their paper (ref 1) that only *trans*-dibromide is formed, the Experimental Section indicates that a mixture of *trans*- and *cis*-1,2-dibromide (72:28%) is formed when bromine in acetic acid is added to 1-hexyne in acetic acid. Therefore, we reinvestigated the bromination of 1-hexyne in acetic acid and found that *cis* dibromide is formed in concentrated solutions (13:87% cis to trans at a mole fraction of 0.8 in 1-hexyne), but that only *trans*-dibromide is formed in dilute solutions. We interpret these data as suggesting that *cis*-dibromide is a product of a molecule-induced radical reaction at higher concentrations, whereas ionic addition occurs in dilute solution.
(3) G. A. Olah and T. R. Hochswender, Jr., *J. Am. Chem. Soc.*, **96**, 3574 (1974).
(4) W. Puterbaugh and M. Newman, *J. Am. Chem. Soc.*, **79**, 3469 (1957).
(5) V. L. Heasley, C. L. Frye, G. E. Heasley, K. A. Martin, D. A. Redfield, and P. S. Wilday, *Tetrahedron Lett.*, **18**, 1573 (1970).
(6) The formation and stability of five-membered cyclic halonium ions in the mass spectrometer is well established. See H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds", Holden-Day, San Francisco, Calif., 1964, chapter 7.
(7) We found analogous isotope cluster patterns for the 1,2-dichloro- and 1,2-dibromohexanes.
(8) The ^{13}C chemical shifts for *trans*-dibromoethylene and *trans*-dichloroethylene are 109 and 119.4 ppm, respectively. See G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972, p 64.
(9) P. B. D. De La Mare and S. Galandauer, *J. Chem. Soc.*, 36 (1958), obtained a Markownikoff to anti-Markownikoff ratio of 54:46 in the addition of BrCl to 1-propene in the polar solvent water.
(10) Two alkynes which apparently involve open vinyl cations give both *trans*- and *cis*-dibromides: phenylacetylene[1] and cyclopropylacetylene (D. F. Shellhamer and M. L. Oakes, *J. Org. Chem.*, in press).
(11) G. J. Schmid, A. Modro, F. Lenz, D. G. Garratt, and K. Yates, *J. Org. Chem.*, **41**, 2331 (1976).
(12) A mixture of the methoxy bromides (**3a,b**) was prepared unambiguously by addition of *N*-bromosuccinimide to 1-hexene in methanol. The structures of **3a,b** have been established previously.[4,5]

Heterogeneous Catalysis by Solid Superacids. 4.[1] Methylation of Phenols with Methyl Alcohol and the Rearrangement of Anisole and Methylanisoles over a Perfluorinated Resinsulfonic Acid (Nafion-H) Catalyst

Joseph Kaspi[2] and George A. Olah*

Institute of Hydrocarbon Chemistry, Department of Chemistry, University of Southern California, Los Angeles, California, 90007

Received October 28, 1977

Anisole and methylanisoles are rearranged when passed in the gas phase over highly acidic solid perfluorinated resinsulfonic acid (Nafion-H) catalyst at 205 °C and atmospheric pressure. A mixture of anisole, mono- and dimethylanisoles, phenol, cresols, and xylenols was obtained. Methyl alcohol and phenol (for cresols) reacted under the same conditions to give a mixture of O- and C-methylated products. The latter reaction was shown to proceed via fast initial O-methylation of the phenol followed by an intermolecular rearrangement of the aryl methyl ether to methylphenols. Rearrangement of anisole and methylation of phenol gave *o*- and *p*-cresol. Methylanisoles or a mixture of cresol and methyl alcohol yielded mixtures of mono- and dimethylated ring products. When the directing effects of the methyl, methoxyl, or hydroxyl groups oppose each other, as is the case with *o*- and *p*-methylanisoles or cresols, 6–14% of products methylated meta to the methoxyl or hydroxyl group was obtained. Isomerization and ring transmethylation were negligible under the experimental conditions. Nafion-H was also compared to other solid catalysts. Its lack of selectivity toward ortho methylation is attributed to the absence of basic sites on the catalyst.

Alkylation of phenols by alcohols is well known.[3] Gas-phase methylation of phenol by methyl alcohol was reported by Ipatieff as early as 1925.[4] Liquid phase, acid catalyzed methylation gave ortho and para substitution with low selectivity. Meta alkylation was reported in some cases,[5] but forcing conditions were required and the meta isomer was obtained via secondary isomerization. Lately, solid catalysts of the mixed oxides type containing basic sites, or acidic and basic sites, were found to catalyze efficiently the methylation of phenols with methyl alcohol with high selectivity for ortho methylation.

Recently we reported the use of highly acidic perfluorinated resin sulfonic acid catalysts, such as Nafion-H,[6] for the alkylation of benzene and alkylbenzenes.[7] In continuation of our studies we felt it of particular interest to study the methylation of phenols with methyl alcohol using mild reaction conditions (ca. 200 °C and atmospheric pressure) and to compare the activity of Nafion-H with other solid catalysts. The behavior of anisoles and methylanisoles was also studied under the same conditions.

Experimental Section

Materials. Methyl alcohol, phenols, and anisoles used were of highest commercially available purity, higher than 99%. Dimethylanisoles and xylenols used for comparison in identifying products in the GLC analyses were also commercially available. The activation of the Nafion-H catalyst was as mentioned.[7]

Experimental Procedure. The catalytic flow reactor and the general procedures used were described previously.[8] All the reactions were carried out at 205 °C in a N_2 flow of 5 mL/min, using 2 g of the catalyst. Phenols, anisoles, or their mixtures with methyl alcohol (1:1 molar ratio) were introduced at a liquid rate of 0.02 mL/min. The contact time of the reagents over the catalyst under these conditions is 6–7 s.

Analysis. Product compositions were determined by gas liquid chromatography using a Perkin-Elmer Model 226 gas chromatograph equipped with a flame ionization detector. A capillary column of 150 ft × 0.01 in. coated with *m*-bis(*m*-phenoxyphenoxy)benzene + Apiezon L was used to separate the products. Anisoles were separated as such. Phenols were first silylated by hexamethyldisilazane or trimethylchlorosilane and identified as the trimethylsilyl ethers. Some of the dimethylanisole peaks overlapped with those of aryl trimethylsilyl ethers. Therefore, each fraction was analyzed twice. One portion was dissolved in ether and extracted with aqueous NaOH and the ethereal solution was analyzed for anisoles. Another portion was silylated and analyzed for phenols and anisoles. In cases where peak overlap occurred, corrections were made on the basis of the known composition of the anisoles. *m*- and *p*-methylanisole were not separated under these conditions. They were, however, separated by using a 20 ft × 0.125 in. column packed with 15% *p*-azoxyanisole on Chromosorb W at 125 °C (a liquid crystal column[9]), using a Perkin-Elmer Model 900 gas chromatograph. Peak areas were measured by an electronic integrator, using corrections for differences in detector sensitivities. The accuracy of the determination of the product com-

0022-3263/78/1943-3142$01.00/0

Table I. Products from Rearrangement of Anisole and Methylanisoles over Nafion-H Catalyst

starting reactant	registry no.	% product composition: starting material	anisole[a]	methylanisoles[a]	dimethylanisoles	phenol	cresols	xylenols
anisole	100-66-3	44.4		9.3	1.8	30.3	9.5	4.7
o-methylanisole	578-58-5	39.2	0.2	0.2	7.8	0.3	33.9	18.4
m-methylanisole	100-84-5	28.9	0.1	tr	10.1	0.2	37.5	23.2
p-methylanisole	104-93-8	35.1	3.4	1.1	8.3	4.6	34.7	12.8

[a] Excluding starting material

Table II. Methylation of Phenol, Cresols, and Anisole with Methyl Alcohol over Nafion-H Catalyst

	% product composition: unreacted starting material	anisole[a]	methylanisoles	dimethylanisoles	phenol[a]	cresols[a]	xylenols
phenol	37.3	37.2	9.7	1.0		10.4	4.4
anisole	58.6		13.9	3.0	18.1	4.7	1.7
o-cresol	51.4	0.1	23.4	4.7	0.4	0.6	19.4
m-cresol	48.1	tr	26.0	5.8	0.2	1.0	18.9
p-cresol	39.2	3.3	23.4	6.4	8.4	4.6	14.8

[a] Excluding starting material.

Table III. Composition of Methylanisoles and Cresols Obtained in the Nafion-H Catalyzed Transformation Reactions

starting reactant(s)	% methylanisoles: ortho	meta	para	% cresols: ortho	meta	para
anisole	45	1	54	58	1	41
phenol + methanol	54	tr	46	61	6	33
anisole + methanol	48	1	51	45	2	53

positions is considered, based on comparison with mixtures of known composition, ±0.5%.

Results

When anisole, or any of the isomeric methylanisoles, was passed over Nafion-H in the gas phase at 205 °C and atmospheric pressure (in N_2 atmosphere) mixtures of phenols and ring-methylated anisoles were obtained. About 60–70% of the starting materials were converted giving anisole, methylanisoles, dimethylanisoles, phenol, cresols, and xylenols. The product compositions obtained (in mole percent) are given in Table I. The relative amounts of methylanisoles and cresols obtained in the rearrangement of anisole are given in Table III. The isomeric compositions of obtained dimethylanisoles and xylenols are listed in Table IV. Equimolar mixtures of phenol, or an isomeric cresol with methyl alcohol, were passed over Nafion-H catalyst using the same experimental conditions. Both O- and C-methylation occurred giving anisoles and higher ring methylated phenols and anisoles. Similar results were obtained from the reaction of anisole and methyl alcohol. The amount of products obtained, the relative amounts of methylanisoles and cresols, as well as the isomeric compositions of dimethylanisoles and xylenols are given in Tables II, III, and IV, respectively. Usually about 40–50% of the starting phenol was methylated. Methyl alcohol was hardly detected in the products.

When neat methyl alcohol was passed over Nafion-H catalyst at 190 °C with a contact time of 4 s, the liquid product obtained contained 19% methyl alcohol and 81% water (by ^1H NMR), while in a subsequent cold trap at −78 °C dimethyl ether was condensed in the corresponding amount. The gaseous effluent contained only the carrier N_2 gas. Dehydration of methyl alcohol to form dimethyl ether thus competes with the methylation process. Indeed, small amounts of dissolved dimethyl ether could always be detected in the products obtained from the phenol–methyl alcohol reaction mixtures.

We also studied the activity of the catalyst as a consequence of onstream time. Figure 1 shows the product composition obtained as a function of onstream time in the reaction of anisole with methyl alcohol. After 3 h the catalytic activity was stabilized and did not change between 3 to 6 h of reaction time.

Table IV. Isomeric Dimethylanisoles and Xylenols Formed in Transmethylation and Methylation Reactions

starting reactant(s)	% dimethylanisoles: 2,3[a]	2,4[b]	2,5[c]	2,6[d]	3,4[e]	% xylenols: 2,3[f]	2,4[g]	2,5[h]	2,6[i]	3,4[j]
anisole	6	76	6	6	6	4	41	2	51	2
o-methylanisole	10	76	4	10		6	44	5	45	
m-methylanisole	24		34		42	28		42		30
p-methylanisole		87			13		94			6
phenol + methanol		100					55		45	
anisole + methanol	7	83	3	tr	7	12	64	12	6	6
o-cresol + methanol	7	70	7	16		14	43	2	41	
m-cresol + methanol	25		30		45	34		41		25
p-cresol + methanol		89			11		96			4

[a] Registry no. 2944-49-2, [b] Registry no. 6738-23-4. [c] Registry no. 1706-11-2. [d] Registry no. 1004-66-6. [e] Registry no. 4685-47-6. [f] Registry no. 526-75-0. [g] Registry no. 105-67-9. [h] Registry no. 95-87-4. [i] Registry no. 576-26-1. [j] Registry no. 95-65-8.

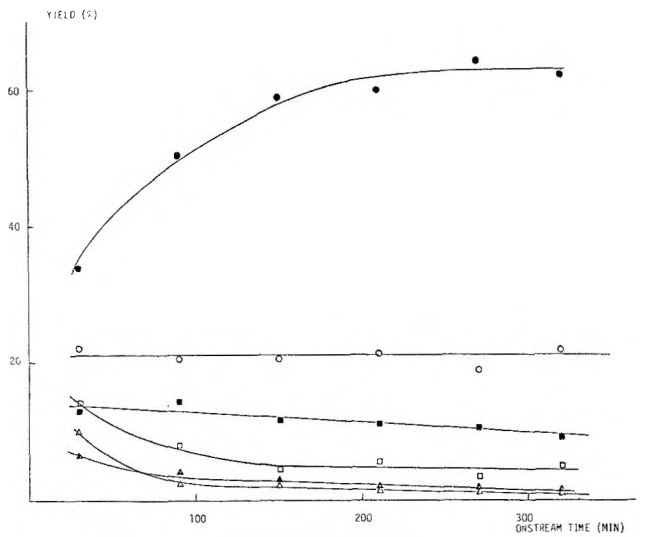


Figure 1. Reaction of anisole with methyl alcohol over Nafion-H. Yields vs. onstream time: (●) anisole; (■) methylanisoles; (▲) dimethylanisoles; (○) phenol; (□) cresols; (△) xylenols.

Discussion

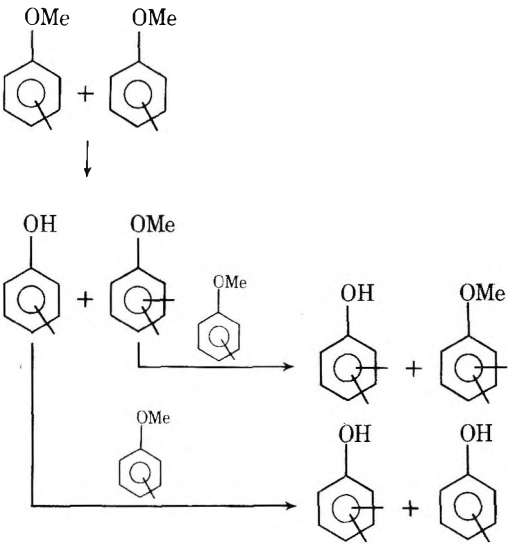
As seen from the results in Tables I and II, under the experimental conditions Nafion-H readily catalyzes both the rearrangement of anisoles and the methylation of phenols with methyl alcohol. Anisoles rearranged to an extent of 60–70% in the flow system. Phenol was methylated in 65% yield and cresols in 40–50% yield. The consumption of methyl alcohol was somewhat higher.

Methylation of phenols with methyl alcohol in the gas phase over solid catalysts is well known. Reports in the literature (including the patent literature) are numerous and thus only representative ones can be cited. Recently the selective ortho methylation of phenols was reported. Catalysts such as Al_2O_3,[10] TiO_2,[11] $ZnO{\cdot}Fe_2O_3$,[12] ZnO·MO (M = Cu, Ba, Ca, Co, Mn, Mg, Ni),[13] MgO alone,[14] or mixed with oxides of Mn,[14] Cu,[15] Sn,[15] Bi,[15] Pb,[15] or Cr,[15] as well many other oxides showed good to excellent selectivity toward ortho methylation. Temperatures employed were in the range of 250–400 °C and were typically around 350 °C. However, it is questionable whether acid catalysis is involved in these cases.[12a] Rearrangement of anisole in the gas phase over alumina[16] and zeolite catalyst[17] was also reported.

C- vs. O-Methylation. The intermediacy of anisole in the ring methylation of phenols is a question of still unresolved controversy. It was reported[18] that alkoxybenzenes are intermediates in the alkylation of phenols over alumina. Other authors,[10a] however, reported that over the same catalyst O- and C-alkylation are parallel reactions and suggested different mechanisms for each. Kotanigawa[12a] found anisole and its mixtures with methyl alcohol to be unreactive over $ZnO{\cdot}Fe_2O_3$ catalyst, thus excluding anisole as a possible C-alkylation intermediate. Using Nafion-H as the catalyst the situation is more complicated. Methylation of phenols always gives also significant amounts of the appropriate anisole. In the reaction of phenol and methyl alcohol 48% anisole and isomeric methylanisoles were obtained. Cresols and methyl alcohol gave ca. 30% anisoles. Further, anisole and methylanisoles were found to rearrange when passed over Nafion-H (Table I).

We suggest that under the experimental conditions initial O-methylation forming aryl methyl ether takes place followed by intermolecular O → C methyl transfer leading to ring methylated products. It is significant to point out that when anisole and methyl alcohol were passed over Nafion-H, only 5% of the methyl alcohol methylated any aromatic compound.

Scheme I



With phenol 79% of the methyl alcohol was consumed in methylation and with cresols 40–55%. Thus, competition from the transmethylation by anisole minimized alkylation by methyl alcohol. The small amount of methyl alcohol used can be due to secondary O-methylation of the phenols formed and maybe to some direct C-methylation.

If O-methylation occurs first, the reaction of phenols (such as *m*-cresol) and methyl alcohol should give similar product composition (excluding unreacted starting material) as would be obtained from the intermolecular rearrangement of the appropriate anisole (i.e., *m*-methylanisole). In order to test this assumption we should consider, first, the suggested reaction paths. Transmethylation from anisoles is depicted in Scheme I. In the first step one molecule of methylanisole transmethylates another molecule of methylanisole giving cresol and dimethylanisole. The formed cresol can be further methylated by a second molecule of the starting anisole (present in large excess) to give the related xylenol and cresol. The dimethylanisole obtained in the first step can also methylate another molecule of the starting material to give xylenol and dimethylanisole. The other possibility, i.e., methylation of the dimethylanisole by methylanisole, is less likely as the former has better methylating ability. We assume only intermolecular transfer of O-methyl groups, as cresols were found hardly to isomerize or transfer ring methyl groups (vide infra) and the amount of ring isomerization of methylanisoles is also negligible (Table I). Further, in preceding studies it was shown that methyl migration in phenyl alkyl oxonium ions is an exclusively intermolecular process.[19]

The reaction of cresol and methyl alcohol is schematically depicted in Scheme II. The first step is the fast formation of methylanisole, which then methyl transfers. The relative high amount of the appropriate methylanisole (no isomerization has appeared under the experimental conditions) present shows that methyl transfer is slower than its formation in the O-methylation by methyl alcohol. Phenols formed by the transmethylation can be further O-methylated by methyl alcohol to give anisoles, which subsequently can continue the transmethylation process. The extent of the second transmethylation is limited due to the short contact time of the feed over the catalyst. In fact, the observed conversions of methyl alcohol were always higher than the conversion of the starting phenol, in accord with the suggested reaction path.

If the reaction mechanisms are those outlined in Schemes I and II, and the assumption is correct that O-methylation by methyl alcohol is faster than the subsequent O → C transmethylation, then the combined fraction of xylenols and

dimethylanisoles should be obtained in comparable yield and should have similar composition whether we start with a methylanisole (e.g., *o*-methylanisole) or a mixture of methyl alcohol and the appropriate cresol (*o*-cresol). One cannot, however, compare the composition of the dimethylanisoles or xylenols, as secondary O-methylation is possible only in the presence of methyl alcohol (the lack of C → O transmethylation is shown by the absence of any detectable anisoles when a neat cresol was passed over Nafion-H catalyst). We consequently calculated the combined isomeric compositions of xylenols and dimethylanisoles. The results obtained, shown in Table V, support our assumption. *o*-Methylanisole gave 26% of dimethylated ring products, while *o*-cresol and methyl alcohol gave these products in 24% yield. The isomeric compositions are also very similar. Similar results were obtained for the meta and para methyl compounds too (Table V).

Dimethyl ether, which was formed in the dehydration of methyl alcohol over Nafion-H, is also a possible methylating agent. It was observed that dimethyl ether methylates benzene over Nafion-H[20] and methylates phenol over alumina.[21] We, however, did not establish whether dimethyl ether is involved in the present reaction as a reactant.

Isomerization and Transmethylation. Alkylbenzenes are known to isomerize and disproportionate (transalkylate) by acid catalysis.[22] We have shown that Nafion-H catalyzes the isomerization and transalkylation of methyl,[1] ethyl, propyl, and isopropylbenzenes.[3] We expected a higher degree of isomerization and transmethylation from methylanisoles and methylphenols due to their high reactivity in electrophilic aromatic substitution. Methylbenzenes show higher reactivity both for electrophilic substitution and methyl transformations when the number of the methyl groups increases. However, this is not the case with the studied methylanisoles and phenols. Under the present experimental conditions ring methyl groups remain inert. Neither methyl transfer nor isomerization occurs to any significant extent. When *o*- and *m*-methylanisoles were reacted over Nafion-H, or when *o*- or *m*-cresol were methylated with methyl alcohol over the same catalyst, ring methyl isomerization was limited to the extent of 0.5% or less. Disproportionation was also minimal, as seen from the minute amounts of anisole and phenol formed. *p*-Cresol and *p*-methylanisole were an exception. They showed 3–4% isomerization and 8–10% disproportionation (combined yield of phenol and anisole). Ethylphenols showed similar behavior. *p*-Ethylphenol disproportionated in the gas phase over an aluminum fluoride–alumina catalyst twice as much as the other isomers.[23] Under reducing conditions (Ni on alumina catalyst, H_2 atmosphere) para-alkylphenols disproportionated almost exclusively rather than hydrodealkylated, in contrast with other isomers.[24] Enhancement of disproportionation of the para isomer was also reported for xylenes.[1,25]

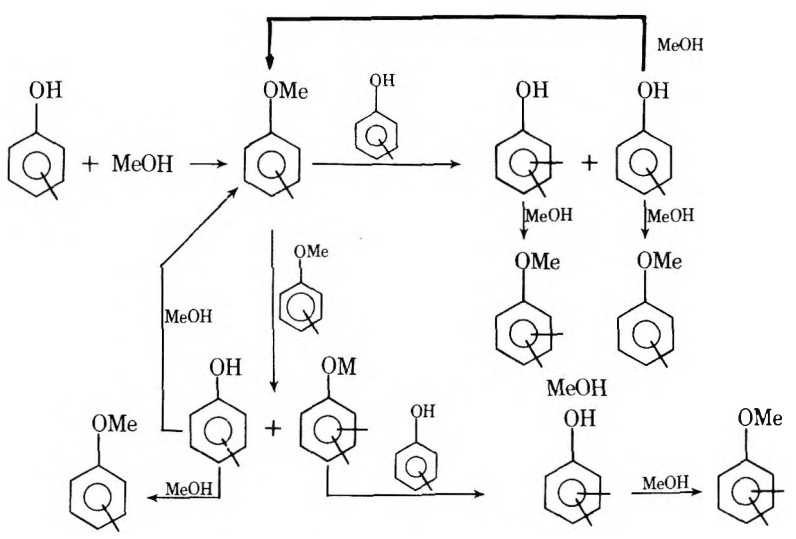
Table V. Isomer Composition of Ring Dimethylated Products Obtained in Methylation Reactions

reactants	% ring dimethylated products composition 2,3	2,4	2,5	2,6	3,4
o-methylanisole	8	53	5	34	
o-cresol + methanol	12	50	2	36	
m-methylanisole	26		40		34
m-cresol + methanol	32		38		30
p-methylanisole		91			9
p-cresol + methanol		94			6

We did not check the possibility of methyl transfer from dimethylanisoles and xylenols. It was shown[26] in gas-phase reactions that the migratory ability of the ethyl group in ethylphenols decreased by the introduction of a methyl group into the ring. Thus, we do not anticipate dimethylanisoles and xylenols to show a higher tendency toward methyl transfer than is the case with cresols and methylanisoles. In addition, the dimethylated species obtained were always structurally related to the monomethyl precursors, indicating that methylation is the sole process to take place. When dimethylanisoles were isomerized over silica–alumina,[27] 3,5-xylenol was always formed in sizable amounts. With excess of the stronger $AlCl_3$–HCl catalyst 3,5-xylenol was the major product (>90%) and probably the only isomer formed (if reaction was carried out to completion).[28] Both 3,5-xylenol and 3,5-dimethylanisole were totally absent in the products of our experiments, showing that isomerization does not take place.

Isomeric Dimethylanisoles and Xylenols. Cresols or methylanisoles have two different functional groups, i.e., methyl and hydroxyl (methoxyl), which exert activating and directing effects on the aromatic ring. As already mentioned[10–15] many solid acid catalysts direct the alkylation selectively ortho to the hydroxyl group, regardless of other substituents. o-Cresol and 2,6-xylenol were obtained from phenol and methyl alcohol. Ortho substitution was also found to predominate in the methylation of cresol. Thus, *p*-cresol and methyl alcohol gave over alumina 2,4-xylenol and 2,4,6-trimethylphenol[29] and over MgO 2,4,6-trimethylphenol.[30] *m*-Cresol and methyl alcohol gave 2,3,6-trimethylphenol over MgO[30] or PBO–MgO[15] while *o*-cresol gave 2,6-xylenol

Scheme II



over alumina,[10c] MgO,[30] or PbO–MnO_2.[15] Nafion-H, on the other hand, did not show any special tendency toward ortho methylation and the isomer distributions reflect kinetic control, i.e., the activation of ring positions for methylation.

Rearrangement of anisole or methylation of phenol by methyl alcohol showed (Table III) that methylation occurred at the ortho and para positions to the same extent (calculated for the sum of cresols and methylanisoles). The para position is thus preferred by a factor of 2. Meta methylated products comprised only 1% of this fraction. The observed regioselectivity thus is para > ortho ≫ meta.

A different reactivity pattern is observed when the starting material is a cresol or a methylanisole. The methyl and the hydroxyl (or methoxyl) group can either augment each others directing effect (for the *m*-methyl compounds) or oppose it (for the ortho and para isomers).

Starting with a *m*-methyl compound three out of the four available positions are activated toward methylation. The 5 position being meta to both hydroxyl and methyl groups is not activated, and, indeed, 3,5-xylenol (or dimethylanisole) was not observed as product. Methylation of the 2, 4, or 6 position leading to the 2,3-, 3,4-, or 2,5-dimethyl products occurs almost to the same extent (Tables IV and V).

When the directing effects oppose each other, the effect of the methyl group is expected to be minor in comparison with that of a hydroxyl or methoxyl group, in view of the large difference of the σ^+ values of these substituents and the high ρ values characteristic of electrophilic aromatic substitution.[31] However, we found that with Nafion-H catalysis in the gas phase, the directing effects of the methyl groups are small, but not negligible. Starting with *p*-cresol or *p*-methylanisole we obtained 6–9% of the "abnormal" 3,4-dimethyl product. Four xylenols and four dimethylanisoles were obtained from *o*-methylanisole or *o*-cresol, respectively (Table IV). The composition of the isomeric dimethylanisoles is different from that of the isomeric xylenols. The reason may be the sluggishness of the ortho methylation of 2,6-xylenol by methyl alcohol due to the obvious steric hinderance by the two methyl groups in the 2 and 6 positions. When the xylenol and dimethylanisole fractions are combined (Table V) one can see that methylation directed by hydroxyl and methoxyl groups (2,4 and 2,6 isomers) comprises 86% of the dimethylated products, while the directing effect of the methyl group (2,3 and 2,5 isomers) accounts for 14% of the products. From these results it seems that hydroxyl (or methoxyl) groups are 10–15 times more effective in directing the intermolecular O → C methyl transfer than a *p*-ethyl group and only 6 times more so than an *o*-methyl group. These ratios of the competing directing effects are surprisingly low, as usually no substitution directed by methyl group while being opposed by that of a hydroxyl group was found. An exception is the reported acetylation of 2,4-xylenol which gave 9% of the "abnormal" 5-acetyl-2,4-dimethylphenol, but it probably involved 2,4-dimethylphenyl acetate as an intermediate which can account for this result.[32] But, in this case two methyl groups give a combined directing effect against the hydroxyl.

A possible reason for the diminished directing effect of the hydroxyl and methoxyl groups is the partial protonation (or strong protosolvation) of the oxygen atoms by the acidic sites of Nafion-H. This will weaken the ortho–para directing effect and will permit methylation at positions meta to the hydroxyl or methoxyl groups when these positions are activated by methyl groups. Phenols and anisoles were found to be ring protonated by superacids in the liquid phase,[33] rather than O-protonated. With somewhat weaker acids and at low temperatures, however, oxygen protonation also takes place, with both C- and O-protonated species being observed simultaneously.

Conclusions

Products obtained in the Nafion-H catalyzed methylation of phenols with methyl alcohol or from the intermolecular rearrangement of anisoles are derived from substitution of all the activated positions. These results are quite different from those obtained with a wide range of solid catalysts which show high selectivity for ortho methylation. Kotanigawa studied the mechanism of phenol methylation over ZnO–Fe_2O_3.[12a] He found that phenol is dissociated upon adsorbtion on the catalyst to give the phenoxide anion. Methyl alcohol is then adsorbed onto the proton to form an adsorbed methyl cation. This intermediate dictates the location of the methylating agent close to the ortho position explaining the selectivity in the reaction. Similar intermediates were suggested for the specific ortho alkylation in homogeneous solution catalyzed by aluminum phenoxide.[34] Such a mechanism raises the question whether this reaction is catalyzed by basic sites[12a] or some sort of dual acid–base catalysis. Kotanigawa found[12b] that methylation of phenol by methyl alcohol over ZnO–Fe_2O_3 is not the major reaction path. About 80% of the methyl alcohol decomposed, giving H_2, CH_4, CO, and CO_2 as products. Similar reactions were obtained by substituting ZnO with other metal oxides.[13] The primary reaction is the dehydrogenation of methyl alcohol to give hydrogen and CO. Alkylation with higher alcohols over ZnO–Fe_2O_3 was also accompanied by dehydrogenation to give aldehydes or ketones.[35] The reaction of 2-propanol was studied over a zeolite catalyst.[36] By selective poisoning, dehydration was found to be acid catalyzed, while dehydrogenation was base catalyzed. Thus, it seems that selective ortho alkylation is connected with the basicity of the catalyst, which is absent in the case of Nafion-H. We checked the reaction of methyl alcohol over Nafion-H for possible dehydrogenation. Only water and dimethyl ether were formed. We were unable to detect any CO in the gaseous affluent. Higher alcohols were also found to only dehydrate, when passed over Nafion-H.[7]

Acknowledgment. Support of our work by the National Science Foundation and the University of Southern California is gratefully acknowledged.

Registry No.—Nafion-H, 63937-00-8; phenol, 108-95-2; *o*-cresol, 95-48-7; *m*-cresol, 108-39-4; *p*-cresol, 106-44-5; methyl alcohol, 67-56-1.

References and Notes

(1) Part 3: G. A. Olah, J. Kaspi and J. Bukala, *J. Org. Chem.*, **42**, 4187 (1977).
(2) Postdoctoral Research Associate 1975–1977. Research was carried out in part at the Department of Chemistry, Case Western Reserve University, Cleveland, Ohio.
(3) A. Schriesheim in "Friedel Crafts and Related Reactions", Vol. II, Part 1, G. A. Olah, Ed., Interscience, New York, N.Y., 1964, Chapter 18.
(4) (a) V. N. Ipatieff, N. Orloff, and G. Razuvaeff, *Bull. Soc. Chim. Fr.*, **37**, 1576 (1925); (b) V. N. Ipatieff, N. Orloff, and A. Petrov, *Ber.*, **60**, 1006 (1927).
(5) (a) M. Inoue and S. Enomoto, *Chem. Pharm. Bull.*, **19**, 2518 (1971); **20**, 232 (1972); (b) J. F. Olim, U. S. Patent 3 014 079 (1961); *Chem. Abstr.*, **57**, 12385 (1962).
(6) Nafion is a registered trademark of the DuPont Co. whom we thank for samples of the potassium salt of Nafion 501.
(7) The active H form was generated from the commercial potassium salt by treatment with nitric acid, washing with water, and drying at 105 °C.
(8) G. A. Olah, J. Kaspi and J. Bukala, *J. Org. Chem.*, **42**, 4191 (1977).
(9) M. J. S. Dewar and J. P. Schroeder, *J. Am. Chem. Soc.*, **86**, 5235 (1964); *J. Org. Chem.*, **30**, 3485 (1965).
(10) (a) S. V. Kannan and C. N. Pillai, *Indian J. Chem.*, **8**, 1144 (1970); (b) Y. Ogata, K. Sakanishi, and H. Hosoi, *Kogyo Kagaku Zasshi*, **72**, 1102 (1969); *Chem. Abstr.*, **71**, 80842 (1969); (c) H. L. Schlichting, A. D. Barbopoulos, and W. H. Prahl, U.S. Patent 3 426 358 (1969); (d) J. Jonas, Czech. Patent 132 353 (1967); *Chem. Abstr.* **73**, 35039 (1970); *Chem. Abstr.*, **71**, 12809 (1969); (e) Y. V. Churkin, L. A. Rusanova, and R. M. Masagutov, Tr., Nauchno-Issled. *Inst. Neftekhim. Proizvod.*, 13 (2) (1970); *Chem. Abstr.* **74**, 76120 (1971).
(11) J. A. Sharp and R. E. Dean, British Patent 1 125 087 (1968) *Chem. Abstr.*, **70**, 37452 (1969).
(12) (a) T. Kotanigawa, *Bull. Chem. Soc. Jpn.* **47**, 950 (1974); (b) *ibid.*, **47**, 2466 (1974); (c) T. Wada, Japan Kokai 75 76 033 (1975); *Chem. Abstr.*, **83**, 178557 (1975).
(13) T. Kotanigawa, M. Yamamoto, K. Shimokawa, and Y. Yoshida, *Bull. Chem.*

Soc. Jpn. **44**, 1961 (1971).
(14) Y. Ichikawa, Y. Yamanaka, and O. Kobayashi, Japan Kokai 73 99129 (1973); *Chem. Abstr.*, **80**, 95477 (1974); Japan Kokai 73 96529 (1973); *Chem. Abstr.*, **80**, 95481 (1974); Japan Kokai 73 99128 (1973); *Chem. Abstr.*, **80**, 95486 (1974).
(15) W. Funakoshi, T. Urasaki, I. Oka, and T. Shima, Japan Kokai 73 97825 (1973); *Chem. Abstr.*, 80, 59675 (1974); Japan Kokai 74 07235 (1974); *Chem. Abstr.*, **80**, 120534 (1974); Japan Kokai 74 13128 (1974); *Chem. Abstr.*, **80**, 120532 (1974); Japan Kokai 74 14432 (1974); *Chem. Abstr.*, **80**, 120527 (1974); Japan Kokai 74 18834 (1974); *Chem. Abstr.*, **81**, 3586 (1974).
(16) V. N. Vinogradova and G. D. Kharlampovich, *Izv. Vyssh, Uchebn. Zaved., Khim. Khim. Tekhnol.*, **18**, 71 (1975); *Chem. Abstr.*, **82**, 124966 (1975).
(17) (a) S. Kawakami and S. Fujii, *Kogyo Kagaku Zasshi*, **73**, 2180 (1970); *Chem. Abstr.*, **74**, 80220 (1971); (b) S. Kawakami, S. Takanashi, and S. Fujii, *Kogyo Kagaku Zasshi*, **74**, 899 (1971); *Chem. Abstr.*, **75**, 48168 (1971).
(18) Reference 6 in ref 12a.
(19) G. A. Olah and E. G. Melby, *J. Am. Chem. Soc.*, **95**, 4971 (1973).
(20) J. Kaspi and G. A. Olah, unpublished results.
(21) P. Mueting and J. Zimmerman, German Offen. 2 237 591 (1974); *Chem. Abstr.*, **80**, 133026 (1974).
(22) D. A. McCaulay in "Friedel Crafts and Related Reactions", Vol. II, Part 1, G. A. Olah, Ed., Interscience, New York, N.Y. 1964, Chapter 24.
(23) P. Schneider, M. Kraus, and V. Bazant, *Collect. Czech. Chem. Commun.*, **26**, 1636 (1961).
(24) L. Beranek, M. Kraus, and V. Bazant, *Collect. Czech. Chem. Commun.*, **29**, 239 (1964).
(25) (a) M. A. Lanewala and A. P. Bolton, *J. Org. Chem.*, **34**, 3107 (1969); (b) R. H. Allen and L. D. Yats, *J. Am. Chem. Soc.*, **81**, 5289 (1959).
(26) M. Kraus and V. Bazant, *Collect. Czech. Chem. Commun.*, **28**, 1,877 (1963).
(27) M. B. Nevworth, British Patent 748 269 (1956); *Chem. Abstr.*, **51**, 471 (1957).
(28) L. A. Fury, Jr., and D. E. Pearson, *J. Org. Chem.*, **30**, 2301 (1965).
(29) Y. V. Churkin, A. G. Lebekhov, and R. M. Masagutov, *Neftekhimiya*, **12**, 87 (1972); *Chem. Abstr.*, **77**, 61432 (1972).
(30) General Electric, Netherlands Appl. 6 506 830 (1965); *Chem. Abstr.*, **65**, 2173 (1966).
(31) D. A. R. Happer and J. Vaughan in "The Chemistry of the OH Group", Part 1, S. Patai, Ed., Interscience, London, 1971, Chapter 8.
(32) N. M. Cullinane and B. F. R. Edwards, *J. Appl. Chem.*, **9**, 133 (1959).
(33) G. A. Olah and Y. K. Mo, *J. Org. Chem.*, **38**, 353 (1973), and references given therein.
(34) A. J. Kolka, J. P. Napolitano, A. H. Filbey, and G. G. Ecke, *J. Org. Chem.*, **22**, 642 (1957).
(35) T. Kotanigawa and K. Shimokawa, *Bull. Chem. Soc. Jpn.*, **47**, 1535 (1974).
(36) T. Yashima, H. Suzuki, and N. Hara, *J. Catal.*, **33**, 486 (1974).

Heterogeneous Catalysis by Solid Superacids. 5.[1] Methylation of Benzene and Methylbenzenes with Methyl Alcohol over a Perfluorinated Resinsulfonic Acid (Nafion-H) Catalyst

Joseph Kaspi,[2] Donald D. Montgomery,[3] and George A. Olah*

Institute of Hydrocarbon Chemistry, Department of Chemistry University of Southern California, Los Angeles, California 90007

Received October 28, 1977

Nafion-H,[4] a perfluorinated resinsulfonic acid, catalyzes the gas-phase methylation of benzene and methylbenzenes with methyl alcohol under relatively mild experimental conditions (185 °C and atmospheric pressure). Reactions are clean, and water formed as byproduct does not deactivate the catalyst. Dimethyl ether is also formed in the competitive dehydration of methyl alcohol when the extent of methylation is low. Generally, low substrate selectivity is observed, indicating that a highly energetic methylating species is participating in the reaction. Dimethyl ether was also found to be an effective methylating agent, but weaker than methyl alcohol. The catalytic activity was found to drop quickly with onstream time when using dimethyl ether, probably due to esterification of the acidic sites. The catalytic activity can be, however, regenerated by steam treatment of the catalyst. Mechanistic aspects of the reactions are also discussed.

Nafion-H,[4] a perfluorinated resinsulfonic acid, activated in its H form, was found to be an efficient alkylating catalyst for heterogeneous gas-phase reactions.[5] Ethene and propene alkylate benzene to give ethylbenzene and cumene, respectively. Alkylations with ethyl and isopropyl alcohol are also catalyzed by Nafion-H. The observations that propylation of benzene with *n*-propyl alcohol gave only cumene as the alkylation product and that the alcohols dehydrate to the corresponding alkenes almost quantitatively when passed over Nafion-H raise the question whether the alcohols are merely precursors to the corresponding alkenes (or their protonated form, i.e., the corresponding carbenium ions). In the case of methylations with methyl alcohol no alkene formation is possible, and under the experimental conditions carbene formation is improbable. The high energy of the methyl cation makes its formation in the reactions also questionable.

In recent work[1] we found that gas-phase methylation of phenol and cresols with methyl alcohol over Nafion-H catalyst proceeds readily. The reaction involves fast initial O-methylation of the phenol followed by intermolecular rearrangement to ring-methylated phenols. In continuation of our work, we would like to report that the methylation of less activated aromatic hydrocarbons, such as benzene and methylbenzenes, also takes place with methyl alcohol in the gas phase over Nafion-H as catalyst.

Experimental Section

The catalytic reactor and the experimental procedures were previously described.[5c] Dry nitrogen was passed at the rate of 5 mL/min. The liquid feed rate was 0.02 mL/min. Contact time of the catalyst with the gaseous feed was 5–7 s. The temperature was kept at 185 ± 2 °C, except when temperature effects were studied. All compounds used were of commercially available high purity, generally higher than 99.5%. Products were analyzed by gas liquid chromatography using a Perkin-Elmer Model 226 gas chromatograph, equipped with a flame ionization detector. Separation was obtained with a 150 ft × 0.01 in. capillary column coated with *m*-bis(*m*-phenoxyphenoxy)benzene + Apiezon L. Peak areas were measured with an electronic integrator and were corrected for differences in detector sensitivity. The accuracy of the determination of the product compositions is considered, based on comparison with mixtures of known composition, as ±0.5%.

Results

Benzene, toluene, and the three isomeric xylenes were methylated with methyl alcohol over Nafion-H catalyst. Polymethylation hardly occurred in the case of reaction of ben-

$$ArH + CH_3OH \xrightarrow[185\ ^\circ C]{\text{Nafion-H}} ArCH_3 + H_2O$$

zene and toluene. The increased reactivity of xylenes and trimethylbenzenes toward methylation is reflected in the

0022-3263/78/1943-3147$01.00/0

Table I. Products of Methylation of Benzene, Toluene, and Xylenes with Methyl Alcohol over Nafion-H Catalyst

aromatic substrate[a]	registry no.	benzene	toluene	dimethylbenzene 1,2	1,3	1,4	trimethylbenzene 1,2,3[e]	1,2,4[f]	1,3,5[g]	tetramethylbenzene 1,2,3,4[h]	1,2,3,5[i]	1,2,4,5[j]
benzene[b]		95.9	4.1									
benzene[c]		95.5	4.5									
benzene[d]	71-43-2	99.0	1.0									
toluene[b]	108-88-3		90.8	4.5	1.6	2.5	0.2	0.4				
toluene		0.2	89.3	4.7	1.7	2.3	0.4	0.8				
o-xylene	95-47-6	1.0	57.2	6.2	0.3	7.6	17.9	0.8	2.5	3.5	3.0	
m-xylene	108-38-3		0.6	1.1	68.2	2.5	2.8	14.4	2.3		4.1	4.0
p-xylene	106-42-3		3.4	1.3	2.5	59.5	0.8	18.0	1.1	0.7	5.3	7.4

[a] Methanol:aromatic = 1:2 unless otherwise stated. [b] Methanol:aromatic = 1:5. [c] Methanol:aromatic = 1:1. [d] Methanol:aromatic = 5:1. [e] Registry no. 526-73-8. [f] Registry no. 95-63-6. [g] Registry no. 108-67-8. [h] Registry no. 488-23-3. [i] Registry no. 527-53-7. [j] Registry no. 95-93-2.

Table II. Methylation of Toluene with Methyl Alcohol over Nafion-H Catalyst at Different Temperatures

temp, °C	% xylene yield	% o:m:p ratio
145	0.82	56:18:26
155	2.21	56:18:26
171	6.26	55:17:28
185	11.7	53:18:29
209	14.3	32:29:39

appearance of tri- and tetramethylbenzenes, respectively, in the products. The product compositions obtained at 185 °C are summarized in Table I. The reaction of toluene with methyl alcohol was studied at several temperatures. The results are given in Table II.

Dimethyl ether was also studied as a methylating agent with Nafion-H catalysis. When a mixture of dimethyl ether and benzene (molar ratio 1:2.7) was passed over the catalyst at 185 °C, a 1.2% yield of toluene was obtained during the first 30 min of onstream time. The reactivity of the catalyst thereafter quickly diminished and after 90 min only traces of toluene were observed. No alkylating activity was found after 120 min. Steam was then passed through the catalyst at 185 °C for 1 h and the reaction continued. Catalytic reactivity was found to be regenerated to its initial value. The use of moist benzene (saturated with water) slowed the deactivation of the catalyst considerably.

Several competitive methylations of aromatics with methyl alcohol were also conducted. Benzene with an isomeric xylene and methyl alcohol (in 1:1:1 molar ratio) gave the products listed in Table III. The isomeric composition of the tri- and tetramethylbenzenes obtained is similar, but not identical with those observed in the noncompetitive methylation of xylenes. The reason is probably that secondary processes, especially isomerization, are more suppressed in the competition experiments with benzene present (vide infra). Results of competitive methylation of phenol and benzene, aromatics of significantly different reactivity, and competitive alkylation of toluene with methyl and ethyl alcohol are also listed in Table III.

Discussion

The results summarized show that methylation of benzene and methylbenzenes with methyl alcohol is readily accomplished over Nafion-H catalyst in the gas phase. The yields differ markedly and depend upon the aromatic compound being methylated. Methylation is enhanced going from benzene to toluene to xylenes. An equimolar mixture of benzene and methyl alcohol gave 4% of toluene at 185 °C. The use of a fivefold excess of benzene hardly changed the toluene/benzene ratio in the products, but the conversion of methyl alcohol increased to 23%. From the data in Table II, activation energy for the Nafion-H catalyzed methylation of toluene can be calculated as 28 kcal mol, assuming that the rate constants are proportional to the xylene yield, as at low conversions secondary processes are negligible, and using these values in the Arrhenius equation.

Methylbenzenes gave a higher utilization of methyl alcohol in their methylation than is the case with benzene. With a 2:1 molar toluene to methyl alcohol ratio 21% of the latter was used in the methylation process. Venuto et al.,[6] using a rare earth exchanged zeolite X catalyst, obtained, with a molar feed composition of benzene:methyl alcohol of 3:1, a 17.3% conversion to toluene, based on methyl alcohol, at 200 °C. Yashima et al.[7] found about 18% methyl alcohol conversion over the H form of a zeolite Y catalyst at 185 °C. Ni- and Co-exchanged catalysts were as effective as the H form, while Ce- and La-exchanged catalysts were ca. 50% more active. It is apparent that Nafion-H due to its enhanced acidity is comparable or somewhat superior to zeolite type catalysts. The special geometric arrangement of the zeolite catalysts increases markedly their catalytic activity. The lack of three-dimensional lattice in Nafion-H is compensated by its high

Table III. Competitive Alkylation Experiments over Nafion-H Catalyst

arenes	alcohols	reagents ratio	% product composition: toluene	xylenes	ethyl toluenes	trimethyl-benzenes[a]	tetra-methyl-benzenes[a]	cresols	dimethyl-phenols
o-xylene + benzene	methyl	1:1:1	14.7			59.7	25.6		
m-xylene + benzene	methyl	1:1:1	17.6			54.4	28.0		
p-xylene + benzene	methyl	1:1:1	15.0			61.5	23.5		
phenol + benzene	methyl	2:6:1	2.3					75.2[b]	22.5[c]
toluene	methyl + ethyl	4:1:1		20.3	79.7[d]				

[a] Isomeric composition similar to that obtained with xylenes alone. [b] Isomer ratio o:m:p = 47:10:43. [c] Isomer composition: 2,3 7%, 2,4 27%, 2,5 20%, 2,6 32%, 3,4 7%, 3,5 7%. [d] Isomer ratio o:m:p = 39:36:25.

acidity. Xylenes are methylated more easily than toluene. *m*-Xylene under similar conditions to toluene gave 43% methyl alcohol conversion, while the ortho and para isomers gave 86 and 84% conversions, respectively.

As discussed, an activation energy of 28 kcal/mol was estimated for the methylation of toluene. As the same composition of xylenes was obtained in the temperature range of 145–185 °C, they seem to be formed in the methylation process and do not undergo further isomerization. Indeed, xylenes were found to isomerize and transfer methyl groups only to a limited extent when reacted over Nafion-H at 193 °C.[8] Their isomerizing ability increased at higher temperatures and more prolonged contact time. At 209 °C, methylation of toluene gave a xylene fraction much richer in the meta isomer indicating substantial isomerization of the formed xylenes.[8,9] The overall yield at 209 °C is, however, lower than that expected from extrapolation and data obtained at lower temperatures. This may be due to the increasing thermal instability of Nafion-H above 200 °C reducing its activity.

Methylation of toluene under the regular reaction conditions gave an isomeric xylene composition of about 54% *o*-, 19% *m*-, and 27% *p*-xylene. The high ortho–para ratio of 2 is characteristic of an electrophilic substitution with a reactive alkylating agent. Such cases are usually accompanied by low substrate selectivity, generally measured by the toluene/benzene rate ratio.[10,11] Since the competitive methylation of toluene and benzene could be followed only with the use of labeled compounds, instead, in the present study we carried out the competitive methylation of an equimolar mixture of benzene and an isomeric xylene. According to the data in Table III, *m*-xylene is 4.7 times more reactive in methylation than benzene, and the corresponding value for the other isomeric xylenes is 5.6. We did not consider toluene formation by transmethylation of benzene with xylene, as this reaction is insignificant under the reaction conditions.[5] Methyl transfer from trimethylbenzenes is more significant, but such a process can occur only after methylation and the limited contact time of the reagents over the catalyst in the flow system will minimize this process.

Another way to estimate the reactivity of the different methylbenzenes is to compare the methyl alcohol conversion under the same conditions. From the values of Table I, toluene seems to be 2.5 times more reactive than benzene, while xylenes react 5–10 times faster. The differences found between the results obtained from comparative conversions and competitive methylations may be due to competing dehydration of methyl alcohol and to some differences in the surface activity of the catalytic resin. Such changes are known to change the reactivities in solid acid catalysis.[12]

The lack of regioselectivity and of steric restraints of the methylating agent is again seen in the methylation products of xylenes. Analysis of the products in this case is more complex. The enhanced reactivity of trimethylbenzenes toward methylation gives tetramethylbenzenes in considerable yield. In addition, isomerization of higher methylbenzenes is not insignificant, although the much slower transmethylation is still negligible.[8] The trimethylbenzene composition gives a fair estimate of the positional selectivity in xylenes. Methylation of *p*-xylene should, of course, give only one product, i.e., pseudocumene. In fact this isomer was observed as 90% of the trimethylbenzene fraction, showing that the secondary isomerization process is only of limited importance (10%). Methylation of *o*-xylene gives a trimethylbenzene fraction comprised of 29% hemimellitene, 68% pseudocumene, and 3% mesitylene. The high amount of 1,2,3-isomer again reflects the lack of steric hinderance toward methylation of the activated ortho position. Due to possible isomerization the initial amount of this isomer is probably higher, as being the least stable isomer[9] it isomerizes faster than the other trimethylbenzenes.[8] Indeed, in competitive methylation where individual compounds experience shorter contact times, a somewhat higher (37%) amount of hemimellitene was found.

All three possible isomeric trimethylbenzenes were found in the methylation of *m*-xylene, including 12% mesitylene. This amount is much higher than those obtained from secondary isomerization of trimethylbenzenes in the course of the methylation of other xylenes. Direct methylation of the 5 position meta to both methyl groups may be questionable, but formation of 1,3,5-trialkylbenzene from the 1,3-dialkyl precursor has precedents in transmethylation[13] and transethylation[5,14] reactions. The high amount of hemimellitene obtained shows lack of steric hinderance even in a position ortho to two methyl groups.

The methylating agent clearly has electrophilic character. However, it is not considered to be a free methyl cation, an unfavorable, highly energetic species, but a polarized methyl alcohol entity which methylates the aromatic rings. We suggest that methyl alcohol is preferentially adsorbed on the acidic sites of Nafion-H. Its high polarization occurs upon adsorption. The partially positively charged methyl group then reacts with an aromatic hydrocarbon absorbed on an adjacent site. Desorption of the products, water and the methylated arene, completes the reaction.

It is further reasonable to assume that methyl alcohol, being a stronger nucleophile than benzene or toluene, will be more easily adsorbed. In addition, we found that the same percentage of benzene was methylated with methyl alcohol when their mole ratio was 5:1 or 1:1. The same observation was made with toluene (5:1 and 2:1 molar ratios). Higher excess of the aromatics causes a proportional increase in acidic sites containing adsorbed arene (which represents, however, only a small fraction of all the sites) adjacent to sites with adsorbed methyl alcohol, the essential condition for the methylation process. The higher yields in the methylation of toluene are the result of the higher susceptibility of toluene toward methylation and not of increased adsorption. Once a toluene molecule is adsorbed on a site adjacent to one containing an adsorbed methyl alcohol molecule, the chance of methylation to take place is higher in comparison with an adsorbed benzene molecule. *m*-Xylene, which has a much higher basicity than all the other compounds investigated, does compete efficiently with methyl alcohol for adsorption. As a result less methyl alcohol is adsorbed. The decrease in the amount of available methylating agent is reflected in the lower yields of methylation of *m*-xylene in comparison with other xylenes. This suggested reaction path is, however, speculative and detailed kinetic studies[15] would be required in order to verify it.

When methyl alcohol is in excess to benzene, the toluene yield drops appreciably. Polarized methyl alcohol molecules adsorbed on the catalyst can also readily methylate a second molecule of methyl alcohol. Dimethyl ether and water are the products of this reaction, which always take place to some extent. As a result, less toluene and more dimethyl ether are formed. The dehydration of methyl alcohol probably involves an electrophilic attack of the partially positively charged methyl group, rather than the nucleophilic attack of methoxide ion on a second molecule of methyl alcohol, as suggested for the dehydration of alcohols over alumina.[16] The latter mechanism requires the existence of both acidic and basic sites on the catalysis which is not the case with Nafion-H. The perfluorinated ether oxygen atoms seem to lack significant nucleophilicity.

Dimethyl ether itself is a known methylating agent. Using methyl alcohol and benzene over alumina[17] dehydration to dimethyl ether took place first, followed by methylation of benzene by the ether. With Nafion-H catalysis dimethyl ether was found to be an inferior methylating agent relative to

methyl alcohol, thus ruling out the intermediacy of the former in methylation reactions with methyl alcohol. Apart from its reduced methylating ability, dimethyl ether deactivates the catalyst by esterifying the sulfonic acid groups of Nafion-H, thus reducing its acidity. Water vapor hydrolyzes the ester and regenerates the catalytic activity. Using moist benzene and dimethyl ether, the deactivation was slowed down appreciably, but the low concentration of water due to its limited solubility did not supress the esterification completely. When methyl alcohol is the methylating agent, water formed in the methylation process as the by-product is present in high enough concentration to prevent esterification.

Methyl alcohol and phenol, as reported, react smoothly over Nafion-H to give a mixture of anisoles and methylphenols.[1] Competitive methylation between phenol and benzene showed methylation of phenol to be preferred by a factor of ca. 250. Comparison of the yields in noncompetitive direct methylation of phenol and benzene gives a reactivity ratio of 15–20. Gas-phase ethylation of phenol and benzene with ethene using a rare earth exchanged zeolite X catalyst gave a selectivity value of 7 in favor of phenol.[18] Homogeneous gas-phase *tert*-butylation showed phenol to be only 4–5 times more active than toluene.[19] The tenfold difference in the selectivity obtained in the present work compared with the literature values indicates a marked difference in the adsorption over Nafion-H in the competition experiment. The presence of phenol prevents adsorption of benzene as they compete for the same sites. Similar phenomenon in liquid phase catalysis was reported.[12b]

We also found ethyl alcohol to be a better alkylating agent than methyl alcohol. An equimolar mixture of these alcohols reacted with toluene gave four times more ethyltoluenes than xylenes. As these alcohols do not differ much in the basicity, we assume simlar adsorption ability for both on Nafion-H. The higher amounts of ethyltoluenes formed are due to the easier formation of the ethylating agent (ethyl cation or protonated ethyl alcohol) than the methylating species, i.e., easier polarization of the alcohol upon adsorption.

Acknowledgment. Support of our work by the National Science Foundation and the University of Southern California is greatly acknowledged.

Registry No.—Methyl alcohol, 67-56-1; Nafion-H, 63937-00-8; dimethyl ether, 115-10-6; ethyl alcohol, 64-17-5; o-cresol, 95-48-7; *m*-cresol, 108-39-4; *p*-cresol, 106-44-5; 2,3-dimethylphenol, 526-75-0; 2,4-dimethylphenol, 105-67-9; 2,5-dimethylphenol, 95-87-4; 2,6-dimethylphenol, 576-26-1; 3,4-dimethylphenol, 95-65-8; 3,5-dimethylphenol, 108-68-9; *o*-ethyltoluene, 611-14-3; *m*-ethyltoluene, 620-14-4; *p*-ethyltoluene, 622-96-8.

References and Notes

(1) Part 4: J. Kaspi and G. A. Olah, *J. Org. Chem.*, preceding paper in this issue.
(2) Postdoctoral Research Associate. Work was carried out in part at Case Western Reserve University, Cleveland, Ohio.
(3) Undergraduate Research Student, Case Western Reserve University.
(4) Nafion is a registered trademark of the DuPont Co. whom we thank for samples of the potassium salt of Nafion 501 resin.
(5) G. A. Olah, G. Messina, J. Bukala, J. A. Olah, and G. D. Matesscu, Abstract of papers PHSC 153, 1st North American Chemical Conference, Mexico City, December 1975. (b) J. Kaspi, J. Bukala, J. A. Olah, and G. A. Olah, Abstracts, 173rd National Meeting of the American Chemical Society, New Orleans, La., March 1977, No ORGN-186. (c) G. A. Olah, J. Kaspi, and J. Burala, *J. Org. Chem.*, **42**, 4187 (1977).
(6) P. B. Venuto, L. A. Hamilton, P. S. Landis, and J. J. Wise, *J. Catal.*, **5**, 81 (1966).
(7) T. Yashima, H. Ahmad, K. Yamazaki, M. Katsuta, and N. Hara, *J. Catal.*, **16**, 273 (1970).
(8) J. Kaspi and G. A. Olah, submitted.
(9) S. H. Hastings and D. E. Nicholson, *J. Chem. Eng. Data*, **6**, 1 (1961).
(10) G. A. Olah, *Acc. Chem. Res.*, **4**, 240 (1971).
(11) M. Attina, F. Cacace, G. Ciranni, and P. Giacomello, *J. Am. Chem. Soc.*, **99**, 2611 (1977).
(12) (a) R. B. Wesley and B. C. Gates, *J. Catal.*, **34**, 288 (1974); (b) F. Ancillotti, M. M. Mauri, and E. Pescarollo, *ibid.*, **46**, 49 (1977).
(13) M. A. Lanewala and A. P. Bolton, *J. Org. Chem.*, **34**, 3107 (1969).
(14) A. P. Bolton, M. A. Lanewala, and P. E. Pickert, *J. Org. Chem.*, **33**, 1513 (1968).
(15) K. H. Yang and O. A. Hougen, *Chem. Eng. Prog.*, **46**, 146 (1950).
(16) V. R. Padmanabhan and F. J. Eastburn, *J. Catal.*, **24**, 88 (1972).
(17) P. H. Given and D. L. Hammick, *J. Chem. Soc.*, 928 (1947).
(18) P. B. Venuto, L. A. Hamilton, and P. S. Landis, *J. Catal.*, **5**, 484 (1966).
(19) M. Attina, F. Cacace, G. Ciranni, and P. Giacomello, *Chem. Commun.*, 466 (1976).

Functionalization of Polystyrene. 1. Alkylation with Substituted Benzyl Halide and Benzyl Alcohol Compounds

A. Warshawsky,* R. Kalir, and A. Patchornik

Organic Chemistry Department, The Weizmann Institute of Science, Rehovot, Israel

Received February 3, 1978

The alkylation of several macroreticular type polystyrenes with substituted benzyl chloride (**2a–e**, **4c**, **5**, and **7b**) and benzyl alcohol compounds (**4a** and **7a**) was investigated under various reaction conditions in order to obtain functionalized polymers. In parallel, the alkylation of toluene as a model compound was studied. It was found that the alkylation depends on the following factors: (1) catalyst concentration—higher than 0.18 M concentrations of $AlCl_3$ in nitrobenzene are enough to secure high conversion yields; (2) the molar ratio between catalyst and alkylating agent, which is dependent on the metal-binding ability of the substituents on the alkylating compound. With weak ligands, such as phenols, only catalytic amounts of catalysts were used. With strong ligands, hydroxycarbonyls, amines, and hydroxyamines, excess over equimolar amounts had to be applied. With benzyl alcohol derivatives, equimolar ratios were applied to convert the alcohol into the chloride. Of the polymers studied, XE-305, a 4% divinylbenzene–styrene copolymer, could be functionalized under controlled conditions to any desired degree of functionality, by the right choice of the ratio polymer–alkylating agent–catalyst. Exhaustive alkylations were achieved by an impregnation method which employed high local concentration under the reaction conditions. Highly cross-linked polymers, XAD-2 and XAD-4, were harder to alkylate, and only a limited degree of functionalization was achieved.

Introduction

Insoluble polymers are drawing attention in all fields of research where recycle of reagent, catalyst, or ligand is essential and where facile separation between reactants and products is required. Major advances in applying polymeric reagents have been made in peptide synthesis,[1] organic synthesis,[2,3,4] catalysis,[5] and metal ion coordination.[6–8] Generally, success relied on the right choice of both functional group and polymeric matrix.

Polystyrene, because of its commercial availability in gel, macroreticular,[9] expanded,[10] or isoporous[11] form, is the polymer of choice for most applications. However, the number of synthetic reactions used in the functionalization of this polymer is restricted to chlorosulfonation, chloromethylation, halogenation, acylation, lithiation, nitration, and a few others.[12] Recently, we have shown that highly efficient acyltransfer agents for peptide synthesis could be prepared by alkylation of polystyrene with chloromethylaryl compounds. 4-Hydroxy-3-nitrobenzylated polystyrene (**2b**)[13] and polystyrene-bound 1-hydroxybenztriazole[14] are now routinely used in this department; 4-hydroxy-3-nitrobenzylated polystyrene and poly(triphenylmethyllithium) prepared by this method were used in various interpolymeric reactions.[15–17]

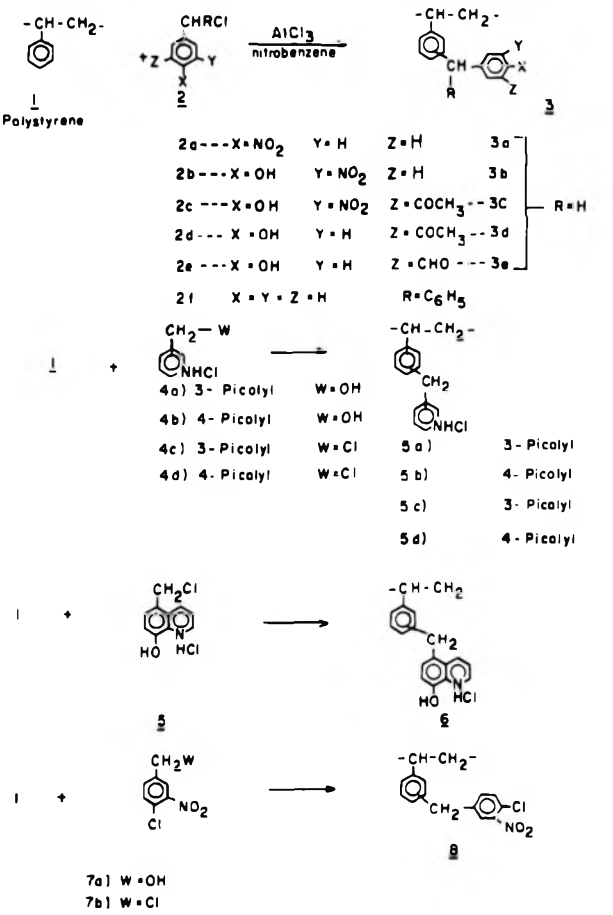
In this paper we have made a systematic study of the alkylation of polystyrene and of a model compound, toluene, under a variety of reaction conditions, with the intention of learning about the factors which might allow the facile preparation of desired functionalized polystyrenes.

Results and Discussion

The alkylation[18] of polystyrene of the macroreticular type, XE-305, with chloromethylaryl derivatives (**2**) was investigated in nitrobenzene (N) using aluminum chloride (A) as catalyst (see Scheme I).

First the generation of the benzylcarbonium ions derived from several chloromethylphenol derivatives (**2b–e**) and 5-chloromethyl-8-hydroxyquinoline (**5**) was investigated using three catalysts, aluminum chloride, boron trifluoride, and zinc chloride, as 1 M solutions in nitrobenzene at 25 °C. The ratio of the benzylic hydrogens assigned to the benzylcarbonium ions at 4.0–4.3 ppm and benzylic hydrogens assigned to starting materials at 4.6–5.25 ppm was measured in the reaction mixture after 24 h (see Table I); this ratio served to determine the degree of formation of carbonium ions.

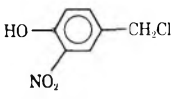
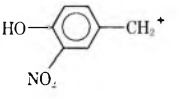
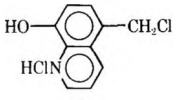
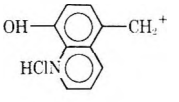
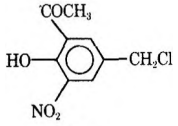
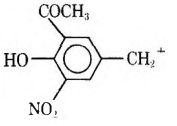
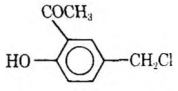
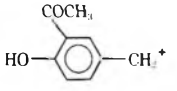
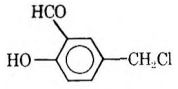
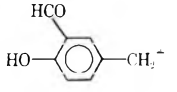
Scheme I. Alkylation of Polystyrene with Substituted Benzyl Chloride and Benzyl Alcohol Compounds



The reaction mixture was then poured on concentrated HCl, to regenerate the starting halide, and again the ratio of the benzylic hydrogens assigned to the self-alkylation products (having same chemical shift as the benzyl carbonium ion signals) and the starting material was measured. This ratio gives the degree of self-alkylation and oligomerization reactions (see Table I). In the case of 2-acetyl-4-chloromethylphenol (**2d**) and 4-chloromethyl-2-formylphenol (**2e**), polymeric products precipitated out of solution, and the degree of self-alkylation could not be measured.

0022-3263/78/1943-3151$01.00/0

Table I. Control Experiments for Autoalkylation and Polymerization

compd	$ArCH_2Cl$, ppm	Catalyst (1 M)	reaction mixture[a] $ArCH_2^+$ carbonium ion	$ArCH_2^+$, ppm[b]	intensity ratio $ArCH_2Cl$/$ArCH_2^+$	conditions temp, °C	time, h	product[c]
 **2b**	4.60	$AlCl_3$		4.2	0.1	25	24	starting compound
 **5**	5.25	$AlCl_3$		4.3	0.1	25	24	starting compound
		BF_3		4.5	0	70	24	90% self-alkylated product
		$ZnCl_2$			0			starting compound
 **2c**	4.90	$AlCl_3$		4.3	0.1			
		BF_3		4.3	0.05	70	24	starting compound
		$ZnCl_2$		4.3	0.2			
 **2d**	4.60	$AlCl_3$			>100	25	24	insoluble polymer
		BF_3		3.98	2.4	70	24	50% self-alkylated product (no reaction at 25 °C)
		$ZnCl_2$		4	>100	70	24	100% condensation[d]
 **2e**	4.65	$AlCl_3$			100	25	24	insoluble polymer
		BF_3		4.0	0.5	70	24	40% self-alkylated (no reaction at 25 °C)
		$ZnCl_2$		4.0	1.43	70	24	70% self-alkylated (no reaction at 25 °C)

[a] 24 h at 25 °C in nitrobenzene. [b] The carbonium ions are characterized by a broad absorption band of 30–60 Hz. [c] Condensation products have the same chemical shifts as carbonium ions. [d] Condensation products are soluble in reaction media.

Table II. Alkylation of Toluene[a]

compd	$ArCH_2Cl$, ppm	catalyst[b]	$ArCH_2C_6H_4CH_3$ ppm	$ArCH_2C_6H_4CH_3$ % yield	$ArCH_2Ar$ ppm	$ArCH_2Ar$ % yield	$ArCH_2Cl$ unreacted %
2b	4.6	$AlCl_3$	4.2	100	4.2	0	0
5	5.25	$AlCl_3$	4.3	90	4.3	0	10
		BF_3		40		0	60
		$ZnCl_2$		0		0	100
2c	4.90	$AlCl_3$	4.3	100	4.3	0	0
		BF_3		20		0	80
		$ZnCl_2$		75		0	25
2d	4.6	$AlCl_3$	4.0	85	4.0	15	0
		BF_3		70		10	10
		$ZnCl_2$		80		20	0
2e	4.65	$AlCl_3$	4.0	90	4.0	10	0
		BF_3		90		10	0
		$ZnCl_2$		80		20	0

[a] 1 M concentration of all the components in nitrobenzene. [b] $AlCl_3$, 24 h at 25 °C; BF_3 and $ZnCl_2$, 24 h at 70 °C.

Examining Table I it is clear that 4-chloromethyl-2-nitrophenol (**2b**), 5-chloromethyl-8-hydroxyquinoline (**5**), and 2-acetyl-4-chloromethyl-6-nitrophenol (**2c**) are perfectly stable, but form, with aluminum chloride as catalyst, sufficient amount of reactive carbonium ions. 2-Acetyl-4-chloromethylphenol (**2d**) and 4-chloromethyl-2-formylphenol (**2e**) are turned completely into the corresponding carbonium ions in the presence of aluminum chloride and produce unwanted side products. However, their activity can be moderated by the use of boron trifluoride or zinc chloride.

Next, the alkylation of toluene, representing a polystyrene analogue, was studied with compounds **2b**, **2c**, **2d**, **2e**, and **5** in nitrobenzene (see Table II) containing 1 M concentration of aluminum chloride, boron trifluoride, or zinc chloride.

Aluminum chloride was found to be an effective catalyst with all the phenols studied, and quantitative alkylations were achieved at 25 °C. For the other two catalysts 70 °C was needed for efficient conversions. From the percent of unreacted chloromethyl compound, the order of reactivity of the various chloromethylphenols is as follows: 4-chloromethyl-2-formylphenol > 2-acetyl-4-chloromethylphenol > 4-chloromethyl-2-nitrophenol > 2-acetyl-4-chloromethyl-6-nitrophenol > 5-chloromethyl-8-hydroxyquinoline.

The amount of self-alkylation products, determined by the ratio of the intensities of the CH_3 to CH_2 protons in the NMR spectra, before and after workup (see Experimental Section), is low. Only in the case of **2d** and **2e** were 10–20% amounts detected independent of the catalyst used.

Table III. Alkylation of XE-305[a] with 4-Chloromethylnitrobenzene

$ArCH_2Cl$, mmol	A/N, mL[b]	N, mL[c]	temp, °C	time, h	product wt, g	product $ArCH_2$ incorporation mmol[e]	product mmol/g of polymer e	product mmol/g of polymer f	% conversion[d,e] $ArCH_2Cl \rightarrow ArCH_2$–Ⓟ	D.F.	obsd
5	10	0	70	72	2.61	4.47	1.71	1.67	89.6	0.23	all solvent absorbed
8	10	0	70	72	2.98	7.26	2.42	2.28	90.1	0.38	all solvent absorbed
16	10	0	70	72	3.77	13.00	3.4	3.08	81.3	0.6	all solvent absorbed
3	30	0	70	72	2.31	2.30	1.0		76.0	0.12	
8	30	0	70	72	2.87	6.40	2.23		80.0	0.33	
8	1	9	70	72	2.83	6.10	2.15	1.9	76.2	0.32	all solvent absorbed
8	1	19	70	72	2.28	2.05	0.90	1.04	25.6	0.11	
8	1	29	70	72	2.10	0.73	0.35	0.49	9.1	0.04	
8	1	39	70	72	2.00	0	0	0	0	0	
16	30	0	70	72	3.41	10.36	3.04	2.55	64.7	0.54	
8	1	9	70	24	2.60	4.41	1.69	2.68	55.1	0.23	g

[a] 2 g of XE-305. [b] A/N = 1.8 M aluminum chloride in nitrobenzene. [c] N = nitrobenzene. [d] Equivalent weight of XE-305 = 104 (uncorr). [e] By weight increase. [f] From nitrogen analysis. [g] Impregnation, method B.

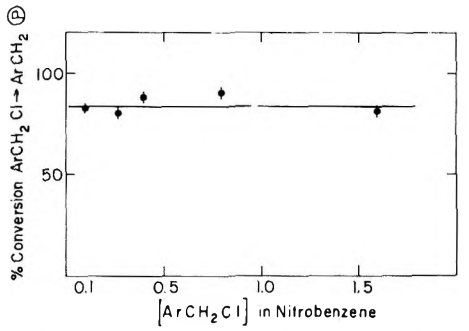


Figure 1. Percent conversion dependency on 4-chloromethylnitrobenzene concentration in 1.8 M $AlCl_3$ in nitrobenzene.

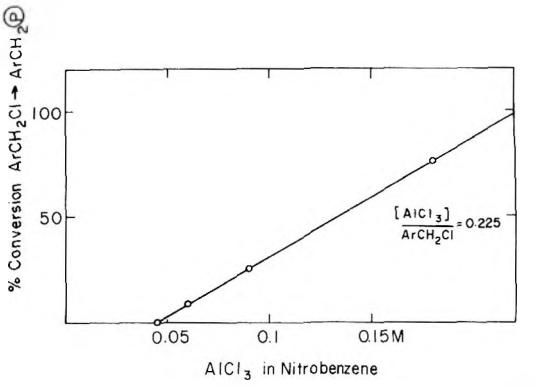


Figure 2. Percent conversion dependency of 4-chloromethylnitrobenzene on $AlCl_3$ concentration.

The alkylation[18] of macroreticular polystyrene XE-305[19,20] was investigated under various reaction conditions, with substituted benzyl halides of the following types: (I) not incorporating any metal-chelating ligands (**2a, 2f, 7b**); (II) incorporating only weak metal-chelating ligand, such as phenolic OH groups (**2b**); and (III) incorporating strong metal-chelating ligands such as carbonyl (**2c, 2d,** and **2e**) or amine (**4c** and **5**).

Although preparative alkylations (see Experimental Section) were carried out successfully even at 25 °C for shorter periods, comparative alkylations were conducted mostly at 60–70 °C for 72 h for the purpose of obtaining comparative results of conversion degrees at equilibrium conditions.

Alkylation with Nonchelating Ligands. 4-Chloromethylnitrobenzene seemed an appropriate model to study the dependency of product formation on both substrate and catalyst concentration, since this compound forms a stable carbonium ion, free from side reactions or ion association effects throughout the range of concentration studied.

The dependence of $ArCH_2Cl$ conversion to $ArCH_2$–Ⓟ (Ⓟ representing the polystyrene matrix, Ar the substituted aryl moiety) on $ArCH_2Cl$ concentration is shown in Figure 1. With 0.18–1.8 M aluminum chloride the conversion factor is independent of the $ArCH_2Cl$ concentration. The same degree of conversion is achieved throughout the range of 0.1–1.8 M $ArCH_2Cl$ concentration. In <0.18 M aluminum chloride solutions, the conversion is directly proportional to the catalyst concentration (Figure 2), implying that for maximum conversions higher than 0.18 M concentration of catalyst must be used.

Alkylation with Weak Metal-Chelating Ligands. Similarly to 4-chloromethylnitrobenzene (**2a**), which needs only a catalytic amount of aluminum chloride, 4-chloromethylnitrophenol (**2b**) and 4-chloromethyl-2-nitrochlorobenzene (**7b**) complex with aluminum chloride very weakly and require only a catalytic amount of aluminum chloride (see Table IV).

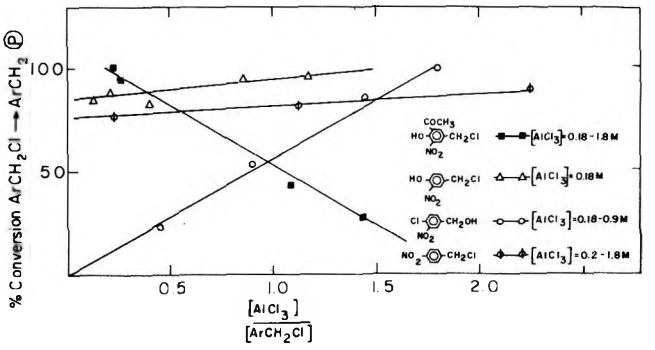
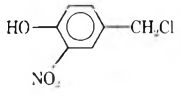
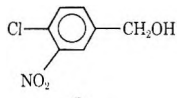
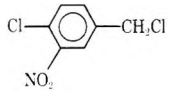


Figure 3. Percent conversion dependency on the ratio $AlCl_3/ArCH_2Cl$.

The conversion factor (see Figure 3) for **2a** and **2b** is practically independent of the ratio $AlCl_3/ArCH_2Cl$ and this is expected for other monovalent-type ligands as **7b**.

The Alkylation with Strong Metal-Chelating Ligands. Type III substrates, incorporating strong metal-chelating ligands as hydroxy or carbonyl (**2c, 2d,** or **2e,** see Table V) or amine (**4a, 4b,** or **5,** see Table VI) bind an equivalent amount of $AlCl_3$ by chelation, and therefore reduce the effective catalyst concentration, leading to lower conversion figures. As demonstrated in Figure 3, 4-chloromethylnitrobenzene (**2a**)

Table IV. Alkylation of XE-305 with Weak Metal-Chelating Ligands[a]

compd	mmol	$AlCl_3$, mmol	N, mL	wt, g	$ArCH_2$ incorporation mmol[b]	mmol/g of polymer b	mmol/g of polymer c	% conversion $ArCH_2Cl$ → $ArCH_2$–Ⓟ	D.F.	notes
 2b	1.54	1.8	10	2.23	1.51	0.68	0.7	98.05	0.08	
	2.10	1.8	10	2.30	1.97	0.85	0.9	93.8	0.10	
	4.20	0.72	10	2.47	3.09	1.25	1.1	73.5	0.16	
	4.20	1.8	10	2.53	3.48	1.38	1.17	83.1	0.18	
	4.20	3.6	10	2.58	3.81	1.49	1.27	90.7	0.20	
	4.20	1.8	10	2.55	3.60	1.42	1.33	85.9	0.19	
	8.4	1.8	10	3.14	7.50	2.39	2.14	89.3	0.39	
	12.6	1.8	10	3.60	10.5	2.92	2.70	83.3	0.55	
	12.6	1.8	10	2.06	0.39	0.19	0.23	3.1	0.02	at 25 °C
	20.0	10.8	10	4.80	18.42	3.85	3.2	92.1	0.965	after procedure B
 7a	4	1.8	10	2.15	0.88	0.41	0.25[d]	22.0	0.05	
	4	3.6	10	2.36	2.11	0.89	0.81[d]	52.7	0.11	
	4	5.8	10	2.60	3.52	1.36	1.33[d]	88.0	0.18	
	4	9.0	10	2.60	3.52	1.36	1.32[d]	88.0	0.18	
	2	3.6	10	2.36	2.11	0.90	0.67[d]	105.5	0.11	
	4	7.2	10	2.70	4.10	1.53	1.33[d]	102.5	0.21	
	6	10.8	10	2.96	5.63	1.90	1.70[d]	94.7	0.29	
	8	14.4	10	3.26	7.39	2.28	2.18[d]	93.8	0.39	
	6	14.4	10	3.00	5.9	1.97	1.77[d]	98.3	0.31	
 7b	20	1.6	13.4	4.23	13.08	3.09		65.4	0.68	

[a] 2 g of XE-305 at 70 °C for 72 h. [b] By weight increase. [c] By %N analysis. [d] By %Cl analysis.

Table V. Alkylation of XE-305 with Strong Metal-Chelating Ligands[a]

compd	mmol	A/N,[b] mL	N,[c] mL	temp, °C	time, h	wt, g	$ArCH_2$ incorporation mmol[d]	mmol/g of polymer d	mmol/g of polymer e	% conversion[d] $ArCH_2Cl$ → $ArCH_2$–Ⓟ	D.F.	Oxime mmol/g	notes
2c	10	8	12	25	24	2.5	2.57	1.03		25.7	0.13		
	13	12	8	60	48	3.2	6.18	1.93		47.5	0.32		
	20	12	0	60	72	3.7	8.76	2.37		43.8	0.46	1.07	
	7	1	9	70	72	3.3	6.70	2.03	1.36	95.6	0.35		16 mL $SnCl_4$
	8	1	9	70	72	3.6	8.25	2.29	1.67	100	0.43		0.5 mL $SnCl_4$
	8	0	5	70	72	3.2	6.18	1.93	1.59	77.2	0.32		0.5 mL $SnCl_4$ B method
2d	20	0.03	10	60	72	2.1	0.67	0.32		3.3	0.03		
	10	7.5	92.5	60	24	2.4	2.68	1.12	1.15	26.8	0.14		$ArCH_2Cl$ added dropwise for 24 h
	8.6	6	0	25	72	2.62	4.16	1.59		48.3	0.22	1.32	
	8	5	0	70	24	2.4	2.68	1.12		33.5	0.14	1.01	B method
2e	8	6	0	70	3	2.9	6.66	2.30		83.2	0.34	1.56	B method

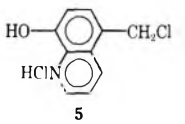
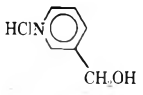
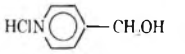
[a] 2 g of polymer. [b] 1.8 M aluminum chloride in nitrobenzene. [c] Nitrobenzene. [d] From weight increase. [e] From nitrogen analysis.

and 4-chloromethyl-2-nitrophenol (**2b**) [type I substrates] bind to XE-305 independently of the $AlCl_3$ to $ArCH_2Cl$ ratio. 2-Acetyl-4-chloromethyl-6-nitrophenol (**2c**) is strongly dependent on this ratio. High conversion of type III ligands are obtained only when an equivalent amount of a strong complexing agent, such as $SnCl_4$, is added and the $AlCl_3$ is then able to catalyze. The fact that conversion yields are even lower at $AlCl_3/ArCH_2$ ratios of higher than unity is due to the deactivation of the partially-substituted polymer by the complexation of its functional hydroxycarbonyl groups with the excess aluminum chloride (see Tables V and VI).

The Alkylation with Benzyl Alcohols. In the alkylations with 4-chloro-3-nitrobenzyl alcohol (**7a**) and 3-picolyl alcohol (**4a**) (see Table VI) aluminum chloride is consumed to convert the alcohol to the chloride, and a linear relationship is obtained (see Figure 3). For **7a**, a ratio of $AlCl_3/ArCH_2OH = 1.5$ is required to obtain the ordinary conversion factors (>80%) for monovalent ligands **2a** and **2b**, in comparison to 4-chloro-3-nitrobenzyl chloride (**7b**) where a ratio of $AlCl_3/ArCH_2Cl = 0.18$ is enough (see Table IV). Practically, benzyl alcohol compounds can be used for alkylation, but excess $AlCl_3$ is to be supplied.

Alkylation of Other Polymers. Besides low cross-linked XE-305 polymer and 2% divinylbenzene–styrene copolymer,[13] highly cross-linked polystyrenes of the polymeric adsorbant type, XAD-2 and XAD-4,[21] were alkylated (see Table VII). Figure 4 shows distinctly the effect of high cross-linkage on polymer reactivity. Whereas macroreticular XE-305 (containing approximately 4% divinylbenzene) and gel-type 2% divinylbenzene copolymer alkylate to high conversions

Table VI. Alkylation of XE-305 with Nitrogen Ligands[a]

compd	mmol	A/N, mL	N, mL	temp, °C	time, h	wt, g	$ArCH_2$ incorporation mmol/g of polymer mmol[d]	d	e	% conversion[e] $ArCH_2Cl$ → $ArCH_2$-Ⓟ	D.F.	notes
 5	1	1	0	70	48	2.1	0.52	0.25	0.17	51	0.03	
	2	2	0	70	48	2.15	0.77	0.36	0.49	38.5	0.04	
	4	4	0	70	48	2.4	2.11	0.88	0.96	52.7	0.11	
	6	6	0	70	48	2.5	2.57	1.03	1.08	42.8	0.13	
	6	6	0	70	72	3.1	5.65	1.82	1.28	94.2	0.30	B method
	8	5	20	25	72	2.8	4.11	1.47		51.3	0.22	
 4a	11	30	0	80	72	2.6	4.70	1.80		42.7	0.24	*f*
 4b	22	30	0	80	72	2.0	0	0		0		*f*

[a] 2 g of XE-305. [b] 1.8 M aluminum chloride in nitrobenzene. [c] Nitrobenzene. [d] From weight increase. [e] From nitrogen analysis.

Table VII. Alkylations of Various Macroreticular Polymers with 4-Chloromethyl-2-nitrophenol (2b)[a]

Ⓟ	2b, mmol	A/N,[b] mL	N, mL	temp, °C	time, h	wt, g	$ArCH_2$ incorporation mmol/g of polymer mmol[d]	d	e	% conversion[d] $ArCH_2Cl$ → $ArCH_2$-Ⓟ	D.F.
XAD-2	2	1	11	65	48	2.18	1.18	0.54	0.41	59	0.06
	4	1	11	65	48	2.18	1.18	0.54	0.48	29.5	0.06
	8	1	11	65	48	2.25	1.64	0.73	0.48	20.5	0.09
	20	1	11	65	48	2.30	1.97	0.86	0.53	9.8	0.10
XAD-4	2	1	11	65	48	2.18	1.18	0.54	0.69	59	0.06
	4	1	11	65	48	2.22	1.44	0.65	0.88	36	0.08
	8	1	11	65	48	2.26	1.71	0.75	0.92	21.4	0.10
XE-305	2.1	1	10	70	72	2.30	1.97	0.85	0.9	93.8	0.10
	4.2	1	10	70	72	2.53	3.49	1.38	1.17	83.1	0.18
	8.4	1	10	70	72	3.14	7.50	2.39	2.14	89.3	0.39

[a] 2 g of polymer. [b] 1.8 M aluminum chloride in nitrobenzene. [c] Nitrobenzene. [d] From weight increase. [e] From nitrogen analysis.

(80–90%) independently of the $AlCl_2/ArCH_2Cl$ ratio at $AlCl_3$ concentration of higher than 0.18 M, the highly cross-linked XAD-2 and XAD-4, containing apparently 25–40% of divinylbenzene,[21] are linearly dependent on this ratio.

Finally, out of the two experimental methods applied, the impregnation method usually offered higher conversion degrees and yields. This is simply because of the high local concentration of both aryl chloride and catalyst achieved under reaction conditions. However, special proximity effects were observed and are under further investigation.

In conclusion, we have shown that polystyrene may be functionalized by alkylation under typical Friedel–Crafts conditions with a variety of substituted halomethyl- or hydroxymethylphenol derivatives. The alkylation may be carried out under controlled conditions to yield various functional polymers containing calculated and varying concentrations of functional groups. But under exhaustive conditions, using a stoichiometric excess of alkylating compound and under high local concentrations (impregnation method B), high binding of up to 4 mmol of functional group per gram of polymer are obtained.

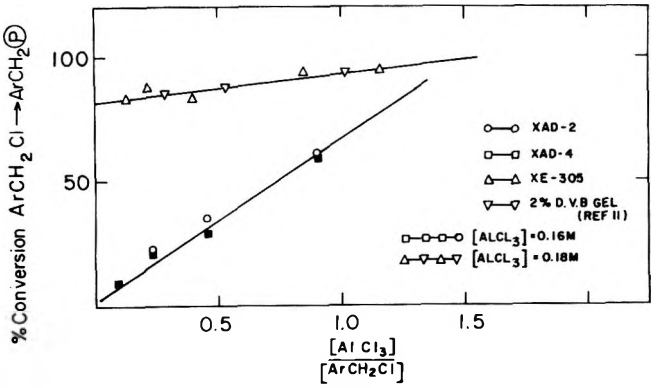


Figure 4. Alkylation of various polymers with 4-chloromethyl-2-nitrophenol.

Experimental Section

Polymers. Amberlites XE-305, XAD-1, XAD-2, and XAD-4 were obtained by courtesy of Rohm and Haas, U.S.A. The polymers were washed with 1 N HCl, H_2O, 1 N NaOH, DMF, methanol, and finally with ether, then dried at 80 °C for 24 h. No nitrogen or chlorine could be detected in polymer samples after this washing procedure.

Substituted 4-chloromethylphenols: 4-nitrobenzyl chloride (Puris) (**2a**), Fluka, mp 71–72.5 °C; 4-chloromethyl-2-nitrophenol[22] (**2b**), mp 72–74 °C; 2-acetyl-4-chloromethyl-6-nitrophenol (**2c**), mp 142–144 °C; 2-acetyl-4-chloromethylphenol[22] (**2d**), mp 73–75 °C; 4-chloromethyl-2-formylphenol[22] (**2e**), mp 84–85 °C; 3-picolyl chloride hydrochloride (**4c**), Aldrich, mp 147–150 °C; 4-picolyl chloride hydrochloride (**4d**), Aldrich, mp 160–163 °C; 5-chloromethyl-8-hydroxyquinoline hydrochloride[23] (**5**), mp 225 °C dec; 4-chloro-3-nitrobenzyl alcohol (**7a**), 98%, Aldrich, mp 62–64 °C.

Aluminum Chloride in Nitrobenzene (1.8 M) (A/N Solution). Aluminum chloride (243 g) from a freshly opened ampule was dis-

solved in 1 L of nitrobenzene (A.R. grade) which was standing over calcium chloride in an Erlenmeyer flask fitted with a calcium chloride drying tube.

2-Acetyl-4-chloromethyl-6-nitrophenol (2c). (A) Nitric Acid Solution A. Nitric acid (65%, 3.2 mL) was added dropwise to 6.40 mL of acetic anhydride stirred magnetically and cooled to 0–4 °C.

(B) The nitric acid solution A was added dropwise during 1 h to a solution of 6 g of 2-acetyl-4-chloromethylphenol and 6 mL of acetic anhydride in 20 mL of chloroform, cooled to 0–4 °C. The reaction mixture was left to stand for 1 h and the yellow crystalline product was filtered and washed with hexane. The final product is colorless, weighing 7.2 g: mp 142–144 °C; NMR ($CDCl_3$) δ 8.28 (d, 1 H), 8.12 (d, 1 H), 4.61 (s, 2 H), 2.75 (s, 3 H). Anal. Calcd for $C_9H_8NO_4Cl$: N, 6.10; Cl, 15.46. Found: N, 6.30; Cl, 15.17.

Control Experiments and Catalyst Selection (Table I). 4-Chloromethyl-2-formylphenol (**2e**), 2-acetyl-4-chloromethylphenol (**2d**), 2-acetyl-4-chloromethyl-6-nitrophenol (**2c**), and 5-chloromethyl-8-hydroxyquinoline (**5**) (5 mmol of each) were placed in 5 mL of 1 M solutions of aluminum chloride, boron trifluoride, and zinc chloride in nitrobenzene for 24 h at 25 and 70 °C. NMR spectra of **2c, 2d, 2e,** and **5** in nitrobenzene, as well as of the reaction mixtures after 24 h, were taken. The reaction samples were poured on 10 mL of 32% HCl, extracted with 2 × 25 mL of $CHCl_3$, and dried over Na_2SO_4, and the $CHCl_3$ was removed by evaporation under vacuum. NMR spectra of the samples were taken again in the nitrobenzene solvent. The ratio between the carbonium ion and condensation product was then calculated from the corresponding NMR signals.

Alkylation of Toluene in Nitrobenzene with 2b, 2c, 2d, 2e, and 5 (Table II). Solutions of the compounds **2b, 2c, 2d, 2e,** and **5** (1 M) in nitrobenzene containing equimolar amounts of toluene were prepared. NMR spectra of these solutions were taken to assure a CH_3/CH_2 ratio of 3:2. Equimolar amounts of catalyst were added and the reaction was allowed to proceed at 25 (with $AlCl_3$ as catalyst) or 70 °C (BF_3, $ZnCl_2$) for 24 h. The reaction mixtures were poured on 32% HCl, extracted with 2 × 25 mL of $CHCl_3$, dried over Na_2SO_4, and filtered, and the $CHCl_3$ and any excess toluene were removed by distillation under vacuum. The NMR spectrum of the remaining nitrobenzene solution was taken. The ratio of the alkylation product to the self-condensation products was calculated from the equations:

$$Y_{AP} = \frac{2}{3}\frac{I_{CH_3}}{I_{CH_2}} \times 100$$

$$Y_{CP} = \frac{I_{CH_2} - \frac{2}{3}I_{CH_3}}{I_{CH_2}} \times 100$$

where Y_{AP} = yield of alkylation product on toluene, Y_{CP} = yield of self-condensation products, I_{CH_3} = CH_3 signal intensity, and I_{CH_2} = CH_2 signal intensity.

The Alkylation of 4-Chloromethylphenol Compounds. General Procedure A (Tables III–VII). Dry XE-305 (2 g) was added to a measured volume of 1.8 M aluminum chloride in nitrobenzene (A/N solution) in a Erlenmeyer flask with a $CaCl_2$ drying tube. When necessary, nitrobenzene was added to dilute the catalyst concentration. After the addition of the alkylating compound, which dissolved readily in this reaction mixture, the reaction was allowed to proceed in a temperature-controlled oil bath without stirring for the specified time. The mixture was then poured on methanol, filtered, and washed thoroughly with hot CH_3OH/HCl (1:1), and then with CH_3OH, $CHCl_3$, and finally with ether. It was then dried at 60–80 °C for 24 h and weighed. A sample was submitted for elementary analysis. This washing procedure was tested on blank samples containing polymer, aryl chloride compound, and nitrobenzene, or polymer, $AlCl_3$, and nitrobenzene, and reproducibility was found to be satisfactory (±1%). In comparison, nitrogen or chlorine analysis showed reproducibility of not better than ±3%, due to the difficulty of weighing accurately electrostatically charged finely crushed polymer particles.

General Procedure B (Impregnation Method) (Tables III–VII). The 4-chloromethylphenol compound was dissolved in 5 mL of $CHCl_3$ and 2 g of dry XE-305 was added. The mixture was allowed to stand until all the solvent was swallowed by the polymer, usually 0.5 h. The excess solvent was then evaporated under vacuum at 40–50 °C. If the solubility of the 4-chloromethylphenol compound in $CHCl_3$ was low, as in the case of 5-chloromethyl-8-hydroxyquinoline, a fresh 5-mL solution was added and this procedure repeated until the desired amount was introduced into the polymer. The impregnated polymer was now reacted in A/N solution and worked up as described in procedure A.

Preparative Alkylations of XE-305. 4-Hydroxy-3-nitrobenzylated Polystyrene (3b) (after Procedure A). XE-305 (70 g) and 42 g (220 mmol) of 4-chloromethyl-2-nitrophenol were added to 300 mL of nitrobenzene, followed by 20 mL of 1.8 M aluminum chloride in nitrobenzene solution. The mixture kept without stirring at 65–70 °C for 48 h, with exclusion of moisture. The polymer worked up as described in procedure A to yield 104 g of product, representing 2.15 mmol of nitrophenol groups per gram of polymer, or a functionalization degree (D.F.) of 0.33.[24] The acetate derivative was prepared and titrated with 0.1 N benzylamine,[25] yielding 2.2 mmol/g of CH_3CO groups.

4-Hydroxy-3-nitrobenzylated Polystyrene (3b) (after Procedure B). XE-305 (10 g) was added to 50 mL of a solution of 18.7 g (100 mmol) of 4-chloromethyl-2-nitrophenol in 50 mL of CH_2Cl_2. The mixture was allowed to stand for 30 min to allow maximum swelling of the polymer and then the solvent was evaporated slowly. CH_2Cl_2 (50 mL) was added and this procedure repeated until all the 4-chloromethyl-2-nitrophenol was absorbed by the polymer. After drying at 50 °C under high vacuum for 18 h, 30 mL of 1.8 M aluminum chloride in nitrobenzene was added with swirling and shaking of the vessel. The polymer beads were wetted homogeneously, but all the catalyst solution was completely adsorbed by the polymer. The reaction was allowed to proceed in this dry state for 48 h at 65–70 °C and worked up as described in procedure A to yield 24 g of product representing 3.8 mmol of nitrophenol groups per gram of polymer (D.F. = 0.96). The acetate derivative was prepared and titrated with benzylamine, yielding 3.6 mmol/g of $COCH_3$ groups.

4-Chloro-3-nitrobenzylated Polystyrene (8) (after Procedure A). XE-305 (10 g) was reacted with 10 g (53 mmol) of 4-chloro-3-nitrobenzyl alcohol in 50 mL of nitrobenzene containing 10 g (76 mmol) of aluminum chloride for 3 days at 70 °C. The polymer was isolated as described in procedure A: 14.3 g of colorless polymer (1.77 mmol of chloronitrobenzene groups per gram of polymer) by weight (D.F. = 0.26) and 1.69 mmol/g by nitrogen analysis. The hydrazide was prepared by reflux with N_2H_4 in diglyme, yielding 1.4 mmol/g of $-NH_2NH_2$ groups according to %N analysis.

4-Chloro-3-nitrobenzylated Polystyrene (8) (after Procedure B).[26] XE-305 (18 g) was impregnated with 37 g (180 mmol) of 4-chloro-3-nitrobenzyl chloride and then reacted at 70 °C for 3 days in a solution of 2 g (15.3 mmol) of $AlCl_3$ in 120 mol of nitrobenzene. The polymer was isolated as described in procedure A: 38.1 g of product (3.1 mmol/g) (D.F. = 0.68). The hydrazide derivative was prepared, yielding 2.8 mmol/g of N_2H_4 by nitrogen analysis.

3-Acetyl-4-hydroxy-5-nitrobenzylated Polystyrene (3c) (after Procedure A). XE-305 (10 g) was reacted with 20 g (87 mmol) of 2-acetyl-4-chloromethyl-6-nitrophenol and 14 g (105 mmol) of aluminum chloride in 100 mL of nitrobenzene at 60 °C for 2 days, according to procedure A: 16 g of product, containing 1.94 mmol/g of hydroxy groups (D.F. = 0.32). The product has (2 mg/100 mg of KBr) a broad absorption at 3600 (OH bonded) and at 1660 cm^{-1} (CO). The oxime was prepared (see oxime preparations) and contains 1.47 mmol/g of ketoxime groups by %N analysis, showing a capacity of 0.3 mmol of Cu^{2+} per gram of polymer at pH 4: IR (2 mg/100 mg of KBr) 1620 cm^{-1} (C=N).

3-Acetyl-4-hydroxybenzylated Polystyrene (3d) (after Procedure B). XE-305 (20 g) was impregnated with 15.8 g (86 mmol) of 2-acetyl-4-chloromethylphenol and reacted at 25 °C for 3 days in 60 mL of 1.8 M aluminum chloride in nitrobenzene according to procedure B to yield 26.2 g of product **3d**, containing 1.6 mmol/g of hydroxy groups (D.F. = 0.22). The product has the following adsorption in the IR (2 mg/100 mg of KBr): 3610 (OH, bonded), 1650 cm^{-1} (CO).

The oxime was prepared as usual, yielding 1.32 mmol/g of ketoxime groups by %N analysis, showing a capacity of 0.08 mmol of Cu^{2+} per gram of polymer at pH 9.

3-Formyl-4-hydroxybenzylated Polystyrene (2e) (after Procedure B). XE-305 (20 g) was impregnated with 14 g (82 mmol) of 4-chloromethylsalicylaldehyde and reacted in 60 mL of 1.8 M aluminum chloride in nitrobenzene, according to procedure B, for 3 days at 70 °C to yield 29 g of product, containing 2.3 mmol/g of hydroxyl groups (D.F. = 0.35). The product has the following absorptions in the IR (2 mg/100 mg of KBr): 3600 (OH bonded), 1670 cm^{-1} (HC=O).

The oxime was prepared as usual, containing 1.6 mmol/g of aldoxime groups by %N analysis. The oxime has a capacity of 0.19 mmol/g for Cu^{2+} at pH 9.

Oximation Procedure. The polymer samples **3c, 3d,** and **3e** (10 g) were refluxed in 50 mL of a solution of 1 M NH_2OH·HCl + 1 N NEt_3 in methanol for 20 h. The polymers were filtered, washed with methanol, water, and methanol, and dried at 60–80 °C for 20 h.

Metal Complexation Experiments. The polymeric oximes derived from **3c, 3d, 3e** and polymer **6** (10 g) were swollen in 100 mL of

CH_2Cl_2, filtered, washed with CH_3OH to replace the CH_2Cl_2 then with H_2O to replace the CH_3OH, and then placed in 1.0-cm diameter columns. $CuSO_4$ solutions (100 mL of 0.1 N) adjusted with 1 N H_2SO_4 to pH 4 or with NH_4OH to pH 9 were passed at a 1 mL/min rate, and then followed by pH 4 water. The effluents were combined and analyzed. The polymer was eluted using 3 N H_2SO_4, and this solution was analyzed also. Good agreement was obtained for results by both methods; Cu^{2+} was determined using a Varian A-1000 atomic absorption spectrophotometer.

Registry No.—**2a**, 100-14-1; **2b**, 6694-75-3; **2c**, 66358-54-1; **2d**, 30787-43-0; **2e**, 23731-06-8; **4a**, 52761-08-7; **4b**, 62302-28-7; **4c**, 6959-48-4; **4d**, 1822-51-1; **5**, 4053-45-6; **7a**, 55912-20-4; **7b**, 57403-35-7; toluene, 108-88-3; divinylbenzene–styrene copolymer, 9003-70-7; Amberlite XE-305, 39464-91-0; Amberlite XAD-2, 9060-05-3; Amberlite XAD-4, 37380-42-0.

References and Notes

(1) R. B. Merrifield, *J. Am. Chem. Soc.*, **85**, 2149 (1963).
(2) A. Patchornik and M. A. Kraus, *Pure Appl. Chem.*, **43**, 503 (1975); *Encycl. Polym. Sci. Tech. Suppl.*, **1**, 469 (1976).
(3) C. G. Overberger and K. N. Sannes, *Angew. Chem., Int. Ed. Engl.*, **13**, 99 (1974).
(4) C. C. Leznoff, *Chem. Soc. Rev.*, **3**, 65 (1974).
(5) R. H. Grubbs, C. Gibbson, L. C. Kroll, W. D. Bonds, and C. H. Brubaker, Jr., *J. Am. Chem. Soc.*, **95**, 2373 (1973).
(6) G. Nickless and G. R. Marshall, *Chromatogr. Rev.*, 154 (1964).
(7) V. G. Manecke and H. Heller, *Makromol. Chem.*, **55**, 51 (1962).
(8) A. Warshawsky, *Inst. Min. Metall., Trans., Sect. C*, **83**, 101 (1974).
(9) R. Kunin, E. F. Meitzner, and N. Bortnick, *J. Am. Chem. Soc.*, **84**, 305 (1962).
(10) J. A. Mikes in "Ion exchange in the Process Industries", SCI Conference, Imperial College, 1970, p 16.
(11) T. R. E. Kressman, ref 10, p 3.
(12) J. A. Petterson in "Biochemical Aspects of Reactions on Solid Supports", G. R. Stark, Ed., Academic Press, New York, N.Y., 1971, Chapter 5; J. M. J. Frechet and J. Farrall in "Chemistry and Properties of Crosslinked Polymers", Academic Press, New York, N.Y., 1977, p 59.
(13) R. Kalir, M. Fridkin, and A. Patchornik, *Eur. J. Biochem.*, **42**, 151 (1974).
(14) R. Kalir, A. Warshawsky, M. Fridkin, and A. Patchornik, *Eur. J. Biochem.*, **59**, 55 (1975).
(15) J. Rebek, D. Brown, and S. Zimmerman, *J. Am. Chem. Soc.*, **97**, 454 (1975); see also, *ibid.*, **96**, 7112 (1974).
(16) B. J. Cohen, M. A. Kraus, and A. Patchornik, *J. Am. Chem. Soc.*, **99**, 4165 (1977).
(17) A. Warshawsky, R. Kalir, and A. Patchornik, Israel Chemical Society, 43rd Meeting, Beer-Sheba, 1975, p 126.
(18) A. Patchornik, R. Kalir, M. Fridkin, and A. Warshawsky, Israeli Patent App. 43366 (1973); U.S. Patent 3 974 110 (1976).
(19) S. Sano, R. Tokunaga, and K. A. Kun, *Biochim. Biophys. Acta*, **244**, 201 (1971).
(20) G. Baum, *Biotech. Bioengin.* **17**, 253 (1975).
(21) Rohm and Haas products.
(22) S. J. Angyal, P. J. Morris, J. R. Tetaz, and J. G. Wilson, *J. Chem. Soc.*, 2141 (1950).
(23) H. Zinner and H. Fiedler, *Arch. Pharm.*, **291**, 493 (158).
(24) Degree of functionalization (D.F.) represents the conversion of Ⓟ–H to Ⓟ–CH_2Ar and calculated from D.F. = actual weight gain/weight gain for complete monofunctionalization.
(25) A. Patchornik, S. Ehrlich-Rogozinsky, and M. Fridkin in "Peptides", Proceedings of the 13th European Peptide Symposium, Hebrew University Press, Jerusalem, Israel, 1974, p 255.
(26) B. J. Cohen, unpublished results.

Electrochemical and Mercury-Promoted Reduction of α,α′-Dibromophenylacetones in Acetic Acid[1]

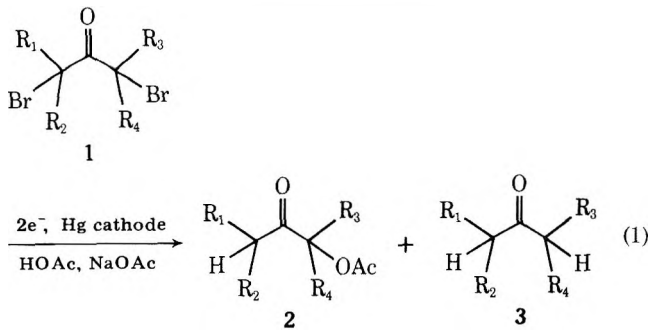
Albert J. Fry* and Jane P. Bujanauskas[2]

Hall-Atwater Laboratories of Chemistry, Wesleyan University, Middletown, Connecticut 06457

Received February 6, 1978

The factors governing the competition between formation of α-acetoxy ketones and the doubly dehalogenated ("parent") ketones in the electrochemical and chemical reduction of α,α′-dibromo ketones in acetic acid are explored in a series of dibromophenylacetones. The degree of substitution in the dibromo ketone has a major effect upon the competition. The mass spectra of starting ketones and product α-acetoxy ketones are discussed, and several characteristic features are observed.

We have previously described the conversion of a number of α,α′-dibromo ketones (**1**) to α-acetoxy ketones (**2**) by electrochemical reduction in acetic acid containing sodium acetate.[3] In general (neglecting small amounts of other products), the reaction generates a mixture of **2** and the corresponding "parent" ketone **3** (eq 1), with **2** predominating when at least



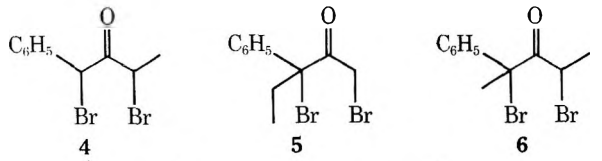
(1)

three of the substituents R_1–R_4 are alkyl and **3** predominating otherwise.[3] More recently, we have found that a very similar conversion to that shown in eq 1 can be effected by allowing the dibromo ketone **1** to react with ultrasonically dispersed mercury in acetic acid.[4] Although similar products are formed in this chemical reduction, acetoxy ketones **2** are formed in higher relative amounts than in the electrochemical reduction. In the interests of exploring further the differences between the chemical and electrochemical versions of eq 1, and to test the hypothesis that the competition between **2** and **3** depends upon the relative ease of formation of an intermediate 2-oxyallyl cation[3,4] (see Discussion), we decided to carry out a study of the reduction, by both methods, of a series of α,α′-dibromophenylacetones (**4**–**10**) with differing degrees of α substitution. We report herein the results of that study, which are consistent with our original mechanistic hypothesis.[3,4]

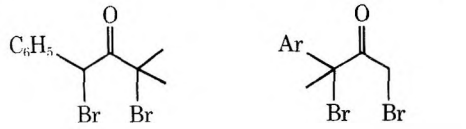
Results

Synthesis of Ketones and Dibromo Ketones. Ketone **11** was commercially available; **12** was prepared by a straightforward route (phenylacetaldehyde plus isopropyl Grignard, and chromic acid oxidation of the resulting alcohol). Ketones **13**–**16** were all prepared by phase-transfer alkylation of the corresponding benzyl ketone, using a two-phase system consisting of aqueous sodium hydroxide and dichloromethane containing ketone, alkyl iodide, and tetrabutylammonium iodide according to the method of Brandstrom and Junggren.[5]

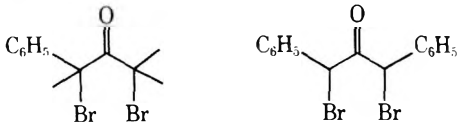
0022-3263/78/1943-3157$01.00/0



4 5 6

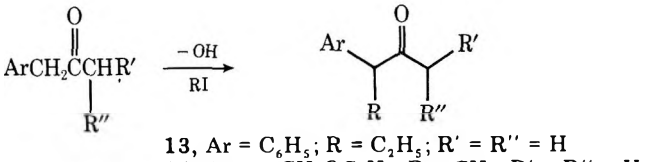


7 8, Ar = p-$CH_3OC_6H_4$



9 10

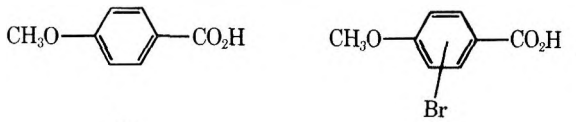
11 12



13, Ar = C_6H_5; R = C_2H_5; R′ = R″ = H
14, Ar = p-$CH_3OC_6H_4$; R = CH_3; R′ = R″ = H
15, Ar = C_6H_5; R = R′ = CH_3; R″ = H
16, Ar = C_6H_5; R = R′ = R″ = CH_3

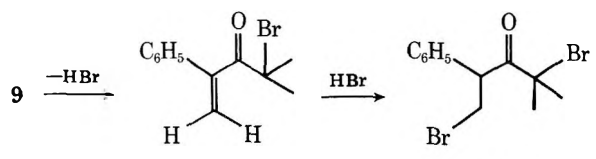
Yields were only moderate due to competing aldol condensation of the starting ketone.

Dibromides **4** and **7** could be prepared in good yield by the method of Claesson and Thalen.[6] This method was less satisfactory as a route to **5** and **6**, and to obtain these materials in a purer form the bromination of **13** and **15** was carried out in acetic acid. It was not possible to obtain dibromo ketones **8** and **9** in sufficiently pure form for further investigation. One small scale bromination of **14** in dichloromethane afforded fairly pure **8** (NMR), but when the reaction was scaled up a more complex mixture was obtained. Oxidative degradation of this mixture afforded a mixture of p-anisic acid (**17**) and a bromoanisic acid (**18**), demonstrating that bromination had occurred at least partially on the aromatic ring.



17 18

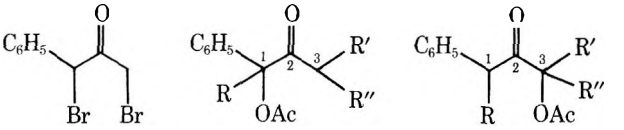
Although bromination of $\alpha,\alpha,\alpha',\alpha'$-tetraalkylacetones can be readily effected using the procedure (aqueous HBr, neat, 65 °C) of Claesson and Thalen,[6] we were unable to obtain **9** in this way. Under these vigorous bromination conditions **9** (or the corresponding monobromide, or both) apparently suffers dehydrohalogenation to **19** (NMR singlets at δ 5.84 and 5.99), and there is also some evidence for the subsequent conjugate addition of HBr to **19** to afford **20** (NMR δ 4–5).



19 20

Other bromination methods that were tried (acetic acid at room temperature, N-bromosuccinimide in refluxing carbon tetrachloride,[7] and photochemical bromination using molecular bromine)[8] either gave similar results under vigorous conditions or afforded mixtures of monobromides when carried out under mild conditions. Thus, the reduction experiments were carried out only on dibromo ketones **4–7**. Dibromide **10**[9] was reduced only by mercury.

Electrochemical and Chemical Reduction of Dibromo Ketones. The electrochemical reactions on **4–7** were carried out under previously established standard conditions[3] (acetic acid containing 1.0 M sodium acetate; mercury cathode, controlled potential). Reactions generally proceeded as in eq 1, though small amounts of other materials were also formed (usually in sufficiently small quantity to preclude isolation and characterization). All major products of the electrochemical reactions were isolated by preparative VPC and identified by NMR and mass spectroscopy. Mercury reductions on **4–7** and **10** were carried out by allowing the dibromo ketone and mercury to react at 25 °C in acetic acid containing 1.0 M sodium acetate with ultrasonic stirring.[4] Since the characterization of products had generally already been carried out on the products of the electrode reaction, the mixtures were generally simply analyzed for the relative ratios of acetoxy ketone to parent ketone. Some reductions afforded monobromo ketones; for mechanistic reasons (see Discussion), these were included with the parent ketone when calculating such ratios. The results of reduction of the various dibromo ketones under the two reduction methods are outlined in Table I. The previously reported[3] result of electrochemical reduction of dibromophenylacetone (**21**) is included for comparison. In general, two isomeric acetoxy ketones may be formed from each dibromo ketone, a 1-phenyl-1-acetoxy-2-propanone (**22**) or a 1-phenyl-3-acetoxy-2-propanone (**23**)



21 22 23

(numbering as shown). The total yields of products were generally good (≥80%) in both types of reduction, in keeping with our previous experience with the electrochemical reaction[3] but in contrast with the mercury reduction of aliphatic dibromo ketones.[4]

Several observations may be made concerning the data in Table I. First, it may be noted that the relative proportion of α-acetoxy ketone(s) in the product mixture (last column) increases as the degree of α-alkyl substitution in the dibromo ketone increases from **21** through **4** and **5** to **6** and **7**. Secondly, the relative proportions of **22** to **23** in the α-acetoxylated products are quite dependent upon the structure of the dibromo ketone; 1-acetoxy ketone **22** predominates from **5** and **6**, while 3-acetoxy ketone **23** predominates from **4** and **7**. Finally, the relative proportion of acetoxy ketone from a given dibromo ketone is usually greater in the mercury reaction than in the electrochemical reduction, though the relative amounts of **22** and **23** are the same in the two reactions for a given dibromo ketone.

Discussion

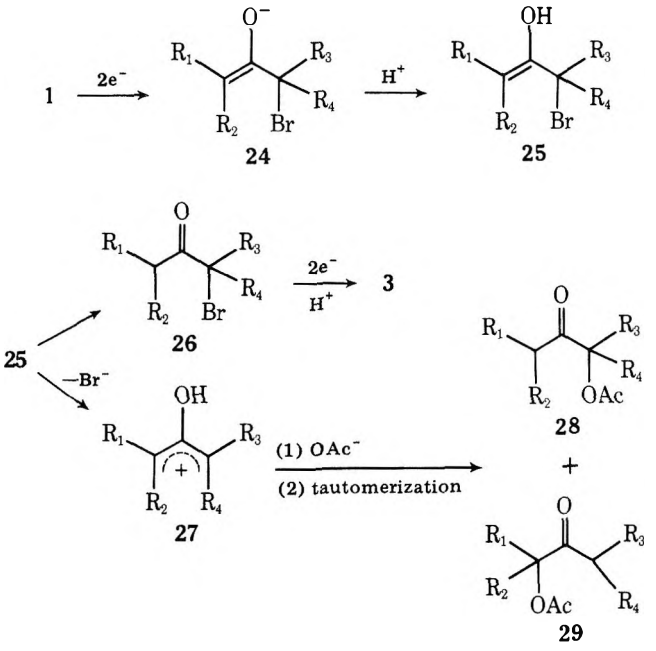
The results of this study are fully consistent with the mechanism previously proposed for the electrochemical reduction of dibromo ketones in acetic acid (Scheme I).[3,10] Prominent features of this mechanism include the following: (a) an enolate anion (**24**) is first formed but is quickly protonated in acid to form enol allylic bromide **25**; (b) this intermediate may tautomerize to bromo ketone **26**, which would

Table I. Reduction of Dibromo Ketones in Acetic Acid

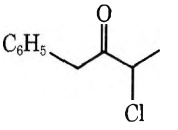
Dibromo ketone	Reduction method	22, %	23, %	Parent ketone, %	Monobromo ketone, %	Other, %	Acetoxylation efficiency[a]
21	Electrochemical[b,c]	0	0	100	0	0	0
4	Electrochemical[b,c]	8	21	66	0	5	0.4
4	Mercury[d,e]	12	66	16	0	6	4.9
4	Mercury[e,f]	7	59	16	15	3	2.1
4	Mercury[e,g]	11	48	21	9	11	2.8
5	Electrochemical[b,e]	43	11	38	0	8	2.0
5	Mercury[c-e]	29	8	20	33	10	0.7
6	Electrochemical[b,c,e]	64	15	14	0	7	5.6
6	Mercury[c-e]	62	17	12	0	9	6.6
7	Electrochemical[b,c,e]	3	83	8	0	6	10.8
7	Mercury[c-e]	6	88	0	0	6	∞[h]
10	Mercury[c-e]	100		0	0	0	∞[h]

[a] (% 22 + % 23)/(% 3 + % 26). [b] Mercury cathode, 25 °C, 1.0 M NaOAc in HOAc. [c] Analysis by VPC. [d] 1.0 M NaOAc in HOAc. [e] Analysis by NMR. [f] HOAc. [g] HOAc saturated with NaOAc. [h] No parent ketone was detectable by VPC or NMR.

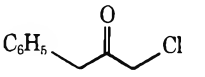
Scheme I



undergo subsequent reduction to parent ketone **3** by the same pathway, in known fashion; or (c) **25** may eject bromide ion to afford the 2-hydroxyallyl cation **27**. Subsequent nucleophilic attack on **27** by acetate and/or acetic acid would afford the isomeric acetoxy ketones **28** and **29**. We have argued[3] that the particular branch chosen by **25** depends mainly on the stability of cation **27** and that the path leading to acetoxy substitution will be chosen in acetic acid when at least three of the substituents (R_1, R_2, R_3, and R_4) are alkyl. (We do of course recognize the fact that highly substituted enols can be rather long-lived[11] and that therefore a high degree of alkyl substitution in **25** will probably retard the rate of conversion to **26**, as well as enhancing the rate of ionization to **27**.) We have supported our emphasis on the effect of substitution on the rate of ionization of **25** by reference to literature data which show that ionization of allylic chlorides is indeed very sensitive to the degree of alkyl substitution.[12] Since cinnamyl chloride ionizes at a rate slower than any of the dimethylallyl chlorides[12] and two alkyl groups in **25** do not apparently provide sufficient stabilization to **27** to render ionization competitive with tautomerization to **26**, we found it unsurprising that **21** should afford only the parent ketone, phenylacetone, upon reduction.[3] The mechanism in Scheme I suggests that increasing amounts of α-acetoxy substitution product should be formed as alkyl substituents are successively introduced into the two α positions of **21**. As the data in Table I indicate, this is indeed the case. Introduction of a single alkyl group into **21** (**4** and **5**) increases the yield of acetoxy ketones from 0% to 29 and 54%, and addition of a second methyl group (**6** and **7**) increases the yield of substituted materials to 79 and 86%. A second phenyl substituent (**10**) leads to clean formation of acetoxy ketone. This experiment cannot be compared directly with the electrochemical reduction of **21** because of the intrinsic tendency of the mercury reaction to favor substitution (vide infra), but a comparison of the mercury reductions of **4** and **10** clearly shows the superior carbonium ion stabilizing ability of phenyl over methyl. We had expected that **8** would give more α substitution than **5** because of the strong electron-releasing power of a p-OCH_3 substituent, but the difficulty we experienced in the preparation of this material prevented a test of this hypothesis. The effects of alkyl substituents found herein find close parallel in studies of the Favorskii rearrangement of α-halo ketones.[13,14] Chloride **30** reacts with methanolic methoxide 250 times faster than **31** and exhibits a k_{Br}/k_{Cl} ratio of 1 with only



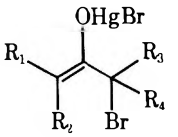
30



31

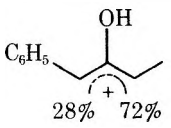
5% deuterium exchange as opposed to a k_{Br}/k_{Cl} ratio of 63 and 80% deuterium exchange for **31**.[13d] These results constitute clear evidence that the enolate from **30** ionizes considerably faster than that from **31** so that the rate-determining step changes from ionization of chloride from the enolate of **30** to proton removal as rate-determining in the case of **31**.

In almost every case the acetoxylation efficiency, i.e., the ratio of acetoxylated product to parent ketone [actually, the sum of parent ketone and monobromo ketone since the latter occurs after the mechanistic branch (Scheme I) and is believed to lie on the route to parent ketone], is higher in the mercury reaction than in the corresponding electrochemical reaction. This, the fact that the ratio of **22** to **23** is the same in both electrochemical and chemical reactions for a given dibromide, and the trend toward higher acetoxylation efficiency with increasing alkyl substitution are all consistent with our previous experience with the mercury reduction of aliphatic dibromo ketones.[4] All of these factors strongly suggest similar but nonidentical mechanisms for the two kinds of reduction. We have previously suggested that the mercury reaction involves intermediate **32** rather than **25** and that the increased acetoxylation efficiency in the mercury reaction is associated with a slower conversion of **32** to monobromo ketone **26** rather than with a greater tendency of **32** to ionize compared with **25**.[4]

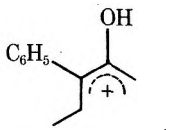


32

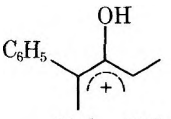
It is interesting to note that the 1-acetoxy ketone **22** predominates in the reduction of dibromo ketones **5** and **6**, while the 3-acetoxy ketone **23** is favored in the reduction of **4** and **7**. We believe that this feature of the results may be understood in terms of the competitive factors governing attack at the two possible sites of 1-phenylallyl cation **27** (or its mercury analogue). There are two principal factors to be considered: charge distribution in the cation and stability of the enol acetate resulting from nucleophilic attack on the 2-hydroxyallyl cation. We may consider the ions **33–36** derived from dibromo



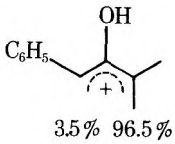
33



34



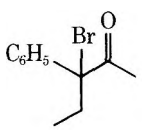
35



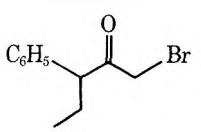
36

ketones **4–7**, respectively, and the relative amounts of attack at the two sites in each. Attack on **34, 35,** and **36** occurs principally at the tertiary site, presumably the locus of greatest charge in each case. It is interesting, however, that a substantial amount of attack does occur at the other site in **34** and **35.** This may be because a more stable enol (tetrasubstituted double bond and conjugated with the aromatic ring) is formed by attack at C-3 of **34** and **35.** Cation **33** is attacked at the site of lower charge (C-3); it may be that here the effect of obtaining preferentially that enol whose double bond is conjugated with the benzene ring is dominant when neither carbon is tertiary. (It is worth commenting here, incidentally, that we have been unable to obtain any evidence for equilibration of isomeric acetoxy ketones under our experimental conditions. The electrochemical reactions are run on a time scale of hours and the mercury reductions for days, yet the relative ratios of **22** and **23** are the same in the two reactions.) The ratios of **22** to **23** found in this work are consistent with previous studies by Bordwell et al. on positional selectivity in the reaction of halo ketones in dilute methanolic methoxide to afford α-methoxy ketones[13] and with the limited data in the literature on the products of nucleophilic attack on substituted cinnamyl cations.[15] The analogy to Bordwell's work is to be expected since intermediates **24, 25,** and **27** are also proposed by Bordwell as the precursors to α-methoxy ketones in that reaction.[13]

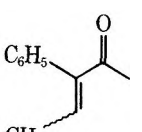
Monobromides have occasionally been observed by us in reductions of dibromo ketones by mercury. It was quite surprising, however, to find that the monobromide formed in the reduction of **5** is the benzylic bromide **37** (NMR) rather than its isomer **38** since reduction of the benzyl bromine of **5** ought



37

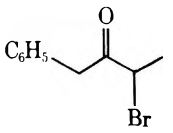


38



39

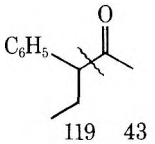
to be markedly easier.[16] It is possible that the initially formed bromide might actually have been **38** but that isomerization to **37** by known routes[17] then occurred on standing. This interpretation is supported by the observation that after 2 months the product mixture began to decompose rapidly to afford the new unsaturated ketone **39** (NMR) component(s). The monobromide formed in the reduction of **4** was the expected **40.**



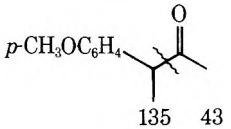
40

Mass Spectra. We previously found mass spectroscopy to be quite useful for assignment of structures to isomeric α-acetoxy ketones.[3] For that reason we paid careful attention to the mass spectral cracking patterns of the substituted phenylacetones prepared during this study in order to identify common features.

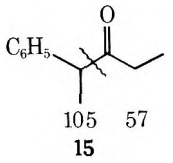
The ketones **13–16** fragmented, as previously observed[17]



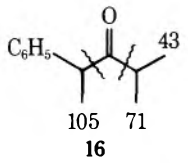
13



14



15



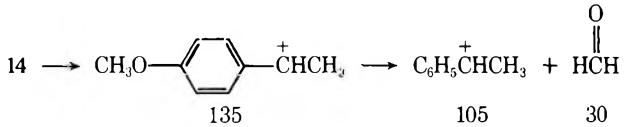
16

for benzyl alkyl ketones, predominantly between the benzyl and carbonyl carbons.

The benzylic fragments formed in this manner exhibited a variety of fragmentation pathways. Common fragments in all ketones were at *m/e* 43, 77, and 91. The origin of a number of such secondary ions was established by analysis of metastable ions[18] observed in the various spectra using a computer program written for this purpose.[19] For example, a metastable ion peak at *m/e* 69.6 in the spectrum of **13** was shown to be the conversion of an ion of mass 119 to one of 91 with extrusion of a fragment of mass 28 (eq 2).

$$\mathbf{13} \xrightarrow{-43} \underset{119}{C_6H_5C^+HCH_2CH_3} \rightarrow \underset{91}{C_7H_7^+} + \underset{28}{CH_2{=}CH_2} \quad (2)$$

On the other hand, a metastable ion peak at *m/e* 81.7 in the spectrum of **14** was shown to be associated with the process 135 → 105 + 30, probably as in eq 3



(3)

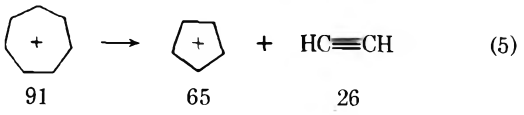
(anisole has previously been shown to expel formaldehyde in the mass spectrometer).[20]

A metastable peak at *m/e* 101 in the mass spectra of **14, 15,** and **16** was found to arise from the process 105 → 103 + 2, possibly via eq 4.

$$\underset{105}{C_6H_5C^+HCH_3} \rightarrow \underset{103}{C_6H_5{}^+C{=}CH_2} + \underset{2}{H_2} \quad (4)$$

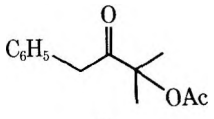
The fragment of mass 91 in all of the spectra is presumably the tropylium ion. Every spectrum showed a metastable peak

at *m/e* 46.4 due to the process 91 → 65 + 26, probably[21] as in eq 5.

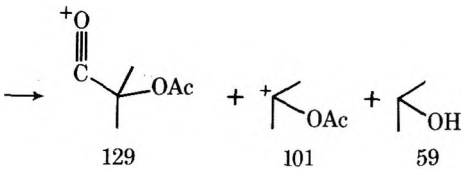


(5)

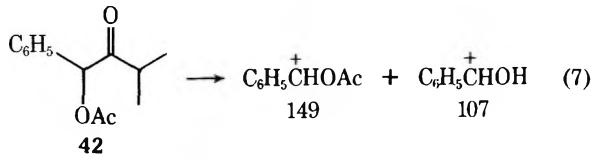
The mass spectra of the various acetoxy ketones exhibit the same major cleavage paths as the parent ketones. In every case there is at least one major fragment by which isomers can be distinguished. For example, acetate **41** exhibits fragments at *m/e* 129, 101, and 59 (eq 6) which distinguish it from its isomer **42**, which has fragments at *m/e* 149 and 107 (eq 7).



41



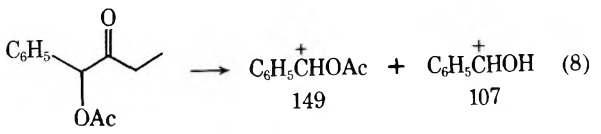
(6)



42

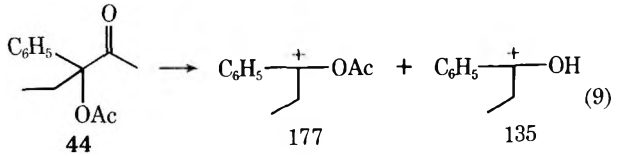
(7)

The mode of cleavage shown here is quite general and was also observed for acetoxy ketones **43**–**45** (eq 8–10).



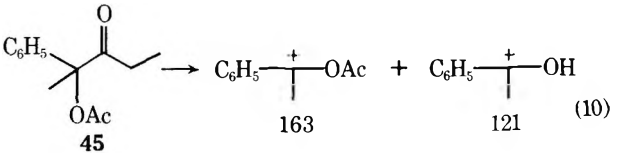
43

(8)



44

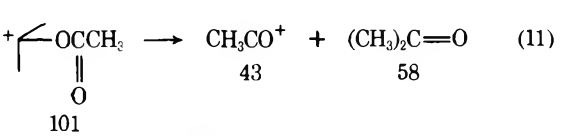
(9)



45

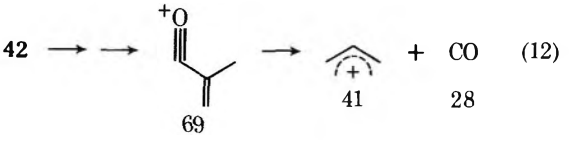
(10)

We obtained no evidence from metastable ion analysis concerning whether the second ion in each of these cases is derived from the first (by loss of the elements of ketene) or by an independent pathway. A metastable ion at *m/e* 18.3 in the mass spectrum of **41** demonstrated another decomposition path for the fragment of mass 101 observed in that spectrum (eq 11).



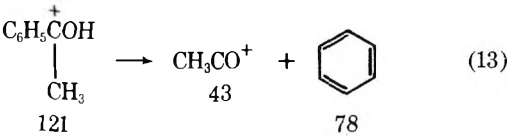
(11)

An interesting metastable peak at *m/e* 24.4 in the spectrum of acetate **42** arises from a fragment of *m/e* 69 decomposing to a daughter of *m/e* 41, perhaps by eq 12.



(12)

There is a metastable peak at *m/e* 15.3 in the spectrum of **48** corresponding to 121 → 43 + 78 (eq 13).



(13)

These types of processes may be common to all of the spectra, but of varying degrees of importance so that the appropriate metastable ions to establish their existence are not always of sufficient intensity to be observed.

Experimental Section

General. Melting points were determined on a Mel-Temp capillary apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian A60-A spectrometer in $CDCl_3$ containing internal tetramethylsilane (Me_4Si) unless otherwise noted. Mass spectra were recorded at 70 eV on a Perkin-Elmer Hitachi RMU-6L spectrometer and were calibrated against the spectrum of perfluorokerosene; relative intensities are indicated for new compounds. VPC separations were made using a Varian Model 1720 dual column thermal conductivity instrument, equipped with a temperature programmer, on a 0.25 × 8 ft column packed with 60% (sic) SE-30 on Chromosorb P. Electrochemical experiments were carried out using a Princeton Applied Research Model 170 electrochemistry system. Elemental analyses were performed by Chemalytics, Inc., Tempe, Ariz.

3-Methyl-1-phenyl-2-butanone (12). 3-Methyl-1-phenyl-2-butanol was prepared in 70% yield by the addition of phenylacetaldehyde (0.18 mol) to a solution of 0.21 mol of isopropylmagnesium bromide in ether. The crude alcohol was oxidized directly by chromium trioxide in acetic acid to afford the desired ketone in 58% yield. This route is more convenient than that employed by Bordwell.[13c]

3-Phenyl-2-pentanone (13) was prepared by the method of Brandstrom and Junggren.[5] Tetrabutylammonium iodide (44.32 g, 0.12 mol) was dissolved in 100 mL of dichloromethane. To this mixture was added phenylacetone (13.42 g, 0.1 mol) and 37.43 g (0.24 mol) of ethyl iodide. To the flask was added a solution of 9.6 g of sodium hydroxide (0.24 mol) in 120 mL of water. The two-phase mixture was stirred vigorously magnetically and heated to reflux. The reaction was terminated after 41 h, at which time VPC analysis showed that less than 10% of the starting phenylacetone remained. The aqueous layer was extracted twice with dichloromethane and combined with the original organic layer, and the combined organic extracts were washed with H_2O, 5% HCl, and H_2O. After evaporation of the dichloromethane, tetrabutylammonium iodide was precipitated by the addition of ether and removed by filtration for reuse. Evaporation of the ether and distillation afforded 12.5 g of 3-phenyl-2-pentanone (**13**) (77% yield; >95% pure by VPC): bp 55–56.5 °C (1.3 mm); NMR δ 0.75 (t, 3 H), 1.7 (m, 2 H), 1.95 (s, 3 H), 3.25 (t, 1 H), and 7.16 (s, 5 H); mass spectrum, *m/e* (relative intensity) 162 (15, M^+), 119 (49), 118 (7), 105 (6), 103 (6), 92 (8), 91 (100), 77 (12), 65 (6), 51 (9), 43 (38), and 41 (15).

The 2,4-dinitrophenylhydrazone, mp 130–131 °C, was purified by repeated recrystallization from ethanol.

Anal. Calcd for $C_{17}H_{18}N_4O_4$: C, 59.64; H, 5.30. Found: C, 59.66; H, 5.23.

3-(4-Methoxyphenyl)-2-butanone (14). Using the same procedure as described for the synthesis of 3-phenyl-2-pentanone, anisylacetone (16.4 g) (Research Organic Chemical Corp.) was allowed to react with methyl iodide for 125 h until the anisylacetone had completely disappeared (VPC). Distillation afforded 8.05 g (45% yield; >95% pure by VPC) of ketone **14**: bp 60–61 °C (0.03 mm) [lit.[23] bp 267 °C (755 mm)]; NMR δ 1.35 (d, 3 H), 1.98 (s, 3 H), 3.68 (q, 1 H), 3.73 (s, 3 H), and 6.83 and 7.08 (AB quartet, J = 8.5 Hz); mass spectrum, *m/e* 178 (M^+), 136, 135 (base), 123, 120, 105, 103, 91, 79, 77, 65, 51, and 43.

2-Phenyl-3-pentanone (15). Methylation of 12.3 g of 1-phenyl-2-butanone (Aldrich Chemical Co.) was carried out as in the synthesis of 3-phenyl-2-pentanone. The reaction was terminated after 148 h,

at which time the starting ketone had completely reacted (VPC). A 5.6-g amount of distilled ketone (42% yield; >95% pure by VPC) was obtained: bp 27–28 °C (0.025 mm) [lit.[22] bp 225–228 °C (760 mm)]; NMR δ 0.93 (t, 3 H), 1.48 (d, 3 H), 2.36 (q, 2 H), 3.75 (q, 1 H), and 7.22 (s, 5 H); mass spectrum, *m/e* 162 (M^+), 141, 133, 119, 106, 105 (base), 104, 103, 91, 79, 78, 77, 63, 57, 51, and 43.

2-Methyl-4-phenyl-3-pentanone (16). Methylation of ketone **12** (9 g) by the procedure used in the synthesis of 3-phenyl-2-pentanone was difficult to follow by VPC because the starting material and product had the same VPC retention time. The reaction was stopped after 316 h when the organic layer had become very dark yellow. Workup and distillation afforded ketone **16:** 3.7 g (38%; >95% pure by VPC); bp 34 °C (0.05 mm) [lit.[22] bp 256–257 °C (760 mm)]; NMR δ 0.91 (d, 3 H), 1.05 (d, 3 H), 1.37 (d, 3 H), 2.65 (m, 1 H), 3.92 (q, 1 H), and 7.26 (s, 5 H); mass spectrum, *m/e* 176 (M^+), 141, 106, 105, 104, 103, 91, 79, 78, 77, 71, 70, 51, and 43 (base).

1,3-Dibromo-1-phenyl-2-butanone (4). Bromination of ketone **11** was carried out according to the method of Claesson and Thalen. NMR spectroscopy showed the crude product to be an 87:13 mixture of dibromide **4** and a tribromide [δ 6.35 (1 H)]. The dibromide **4** was a mixture of diastereomers in the ratio 57:43. Repeated recrystallization from heptane afforded **4** as a white solid, mp 34–45 °C, still a mixture of diastereomers: NMR δ 1.7 (d, 3 H), 1.77 (d, 3 H), 4.47 (q, 1 H), 4.98 (q, 1 H), 5.88 (s, 1 H), 6.04 (s, 1 H), and 7.2–7.7 (m, 5 H).

Anal. Calcd for $C_{10}H_{10}Br_2O$: C, 39.25; H, 3.29. Found: C, 39.07; H, 3.31.

1,3-Dibromo-3-phenyl-2-pentanone (5). Bromination of ketone **13** in acetic acid at room temperature afforded a 90:10 mixture of dibromide **5** and a tribromide (NMR δ 5.98). This mixture was used as obtained because of its decomposition upon attempted vacuum distillation: NMR δ 0.83 (t, 3 H), 2.15–2.4 (m, 2 H), 3.99 and 4.34 (AB quartet, J = 14.0 Hz), and 7.3 (s, 5 H).

2,4-Dibromo-2-phenyl-3-pentanone (6). Bromination of ketone **15** in acetic acid afforded dibromide **6** in ≥96% purity (NMR) (90% yield) as a viscous liquid consisting of almost equal amounts of erythro and threo diastereomers: NMR δ 1.52 (d, 2 H), 1.85 (d, 2 H), 2.19 (s, 3 H), 2.23 (s, 3 H), 4.63 (q, 1 H), 4.82 (q, 1 H), and 7.3–7.7 (m, 5 H).

1,3-Dibromo-3-methyl-1-phenyl-2-butanone (7). Ketone **12** was brominated according to the method of Claesson and Thalen.[6] Two distillations at oil pump pressure and a final recrystallization from heptane afforded a white solid: mp 58.8–59.8 °C; NMR δ 1.8 (s, 3 H), 2.0 (s, 3 H), 6.1 (s, 1 H), and 7.2–7.8 (m, 5 H).

Anal. Calcd for $C_{11}H_{12}Br_2O$: C, 41.28; H, 3.78. Found: C, 41.57; H, 3.91.

Bromination of 3-(4-methoxyphenyl)-2-butanone in dichloromethane at 0 °C afforded a mixture containing some of the desired dibromide [NMR δ 2.34 (s), 3.82 (s), 4.12 (s), and 6.93 and 7.42 (AB pattern)] but also a considerable amount of other material. The material was suspended in water at 70 °C and vigorously stirred, and an aqueous solution of potassium permanganate was added over an hour interval with a second hour of stirring and heating. Manganese dioxide was removed by filtration, and the filtrate was acidified with 5% HCl. A white precipitate formed and was isolated by filtration. The NMR spectrum of this material indicated the presence of anisic acid and a bromoanisic acid in a ca. 2:1 ratio: δ 3.82 (s), 3.94 (s), 7.01 and 7.92 (AB quartet), and 7.1–8.2 (m); mass spectral peaks (inter alia) at *m/e* 230 and 232 ($C_8H_7BrC_3$) and 152 ($C_8H_8O_3$).

Electrochemical reductions were carried out as previously described.[3] Acetoxy ketones were isolated for spectral characterization by preparative VPC. Microanalyses were carried out on most acetoxy ketones, except when the substances were formed in very small amounts or were unstable (as noted below). When VPC conditions could not be found to separate a pair of isomeric acetoxy ketones, spectral characterization and microanalysis were carried out on the mixture. Mixtures were analyzed by VPC (cut and weigh) or NMR integration, or a combination of these, as appropriate.[25]

Reductions by ultrasonically dispersed mercury were carried out as previously described.[4] Workup and analysis were carried out as with the electrochemical reactions.

Acetoxy Ketones. Characterization data for the various acetoxy ketones are summarized below. Only the largest mass spectral lines are listed.

2-Acetoxy-2-methyl-4-phenyl-3-butanone (41): mp 41.5–42.5 °C from heptane; NMR δ 1.5 (s, 6 H), 2.09 (s, 3 H), 3.77 (s, 2 H), and 7.24 (s, 5 H); mass spectrum, *m/e* (relative intensity) 220 (1.5, M^+), 162 (4), 160 (3), 130 (2), 129 (34), 119 (8), 101 (32), 92 (8), 91 (60), 69 (5), 65 (16), 59 (54), and 43 (100).

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.88; H, 7.32. Found: C, 70.89; H, 7.46.

1-Acetoxy-1-phenyl-3-methyl-2-butanone (42): Mass spectrum, *m/e* (relative intensity) 220 (5, M^+), 160 (54), 149 (38), 107 (100), 91 (69), and 71 (22).

1-Acetoxy-1-phenyl-2-butanone (43) and **3-acetoxy-1-phenyl-2-butanone (46)** were inseparable by VPC and hence were collected as a single fraction by preparative VPC. The NMR spectrum of the mixture exhibited absorptions at δ 0.94 (t, J = 6.8 Hz),* 1.25 (d, J = 7 Hz), 1.99 (s), 2.09 (s),* 2.22 (q, J = 6.9 Hz),* 3.66 (s), 5.81 (s),* and 5.02 (q, J = 7 Hz), together with an aromatic multiplet from δ 7.1–8.0; the mass spectrum of the mixture exhibited prominent peaks at *m/e* (relative intensity) 206 (6, M^+),* 160 (8),* 149 (15),* 122 (20), 115 (24), 107 (30),* 105 (35), 103 (20), 91 (43), 87 (22), 77 (25), 57 (13),* 51 (13), and 43 (100)* (the peaks in the NMR and mass spectra attributable with certainty to isomer **43** are marked with an asterisk; the relative intensities of the NMR absorptions are consistent with the assignments given).

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 68.50; H, 6.73.

3-Acetoxy-3-phenyl-2-pentanone (44): NMR δ 0.6 (t, 3 H), 1.79 (s, 3 H), 2.19 (s, 3 H), 2.4 (m, 2 H), 7.13 (broad s, 2 H), and 7.22 (broad s, 3 H); mass spectrum, *m/e* (relative intensity) 220 (3, M^+), 177 (22), 160 (7), 136 (1), 135 (100), 119 (30), 117 (13), 115 (7), 105 (8), 91 (30), 77 (13), 57 (21), and 43 (53).

1-Acetoxy-3-phenyl-2-pentanone (47): NMR δ 1.00 (t, 3 H), 1.8 (m, 2 H), 2.01 (s, 3 H), 3.47 (t, 1 H), 4.50 and 4.30 (AB quartet, J = 16.7 Hz, 2 H), and 7.12 (broad s, 5 H); mass spectrum; *m/e* (relative intensity) 220 (8, M^+), 158 (8), 119 (68), 117 (13), 115 (10), 101 (47), 91 (100), 77 (8), 73 (14), and 43 (49).

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.88; H, 7.32. Found: C, 70.83; H, 7.65.

2-Acetoxy-2-phenyl-3-pentanone (45) and **4-acetoxy-2-phenyl-3-pentanone (48)** (the latter as a mixture of erythro and threo diastereomers) were obtained as an inseparable mixture. The ratio of **45** to **48** was established by the ratio of the singlet at δ 1.85 (**45**) to the two overlapping doublets at δ 1.4 (the two diastereomers of **48**) in the NMR spectrum of the crude product. Upon preparative VPC **45** mostly decomposed to 2-phenyl-3-keto-1-pentene (**49**) (singlets at δ 5.75 and 6.00), which was eluted mixed with unreacted **45** and **48**. The mass spectrum of this mixture exhibited peaks at *m/e* (relative intensity) 220 (1, M^+),* 163 (18),* 160 (19),* 131 (7),* 122 (8), 121 (80),* 115 (15), 105 (29), 104 (10), 103 (55), 91 (3), 87 (8), 77 (21), 57 (27.6),* 51 (11), and 43 (100)* (peaks marked with an asterisk are associated with **45**).

1-Acetoxy-1,3-diphenyl-2-propanone (50). The crude product from mercury reduction of a mixture of *dl*- and *meso*-**10** in acetic acid was essentially pure **50**:[26] NMR δ 1.87 (s, 3 H), 3.41 and 3.45 (AB quartet, J = 15 Hz), 5.80 (s, 1 H), and 6.8–7.2 (m, 5 H).

Acknowledgment. Financial support was provided by the National Science Foundation, Wesleyan University, and Sigma Xi. The electrochemical reduction of 1-phenyl-1,3-dibromo-2-propanone was carried out by Mr. John O'Dea. The reduction of 1,3-diphenyl-1,3-dibromo-2-propanone by mercury was carried out by Mr. Gilbert Shuster. Computer time was provided by the Wesleyan University Computer Center.

Registry No.—erythro-**4**, 56764-08-0; *threo*-**4**, 56764-00-2; **5**, 66551-77-7; *erythro*-**6**, 66551-78-8; *threo*-**6**, 66551-79-9; **7**, 37988-51-5; **8**, 66551-80-2; *dl*-**10**, 51513-35-0; *meso*-**10**, 51513-34-9; **11**, 1007-32-5; **12**, 2893-05-2; **13**, 1528-39-8; **13** DNP, 66551-81-3; **14**, 7074-12-6; **15**, 16819-77-5; **16**, 20474-49-1; **17**, 100-09-4; **18**, 66552-46-3; **41**, 66551-82-4; **42**, 66551-83-5; **43**, 66551-84-6; **44**, 66551-85-7; **45**, 66551-86-8; **46**, 66551-87-9; **47**, 66551-88-0; *threo*-**48**, 66551-89-1; *erythro*-**48**, 66551-90-4; **49**, 66551-91-5; **50**, 66551-92-6; 3-methyl-1-phenyl-2-butanol, 705-58-8; phenylacetaldehyde, 122-78-1; isopropyl bromide, 75-26-3; phenylacetone, 103-79-7; ethyl iodide, 75-03-6; anisylacetone, 122-84-9; methyl iodide, 74-88-4.

References and Notes

(1) Abstracted in part from the M.A. Thesis of Jane Bujanauskas, Wesleyan University, November, 1976.
(2) Current address: Allied Chemical Corp., Morristown, N.J. 07960.
(3) A. J. Fry and J. J. O'Dea, *J. Org. Chem.*, **40**, 3625 (1975).
(4) A. J. Fry and D. Herr, *Tetrahedron Lett.*, 1721 (1978).
(5) A. Brandstrom and U. Junggren, *Tetrahedron Lett.*, 473 (1972).
(6) G. Claesson and A. Thalen, *Acta Chem. Scand.*, **17**, 1172 (1963).
(7) H. O. House, "Modern Synthetic Reactions", 2nd ed, W. A. Benjamin, New York, N.Y., 1972, p 459ff.
(8) V. Calo and L. Lopez, *J. Chem. Soc., Chem. Commun.*, 212 (1975).
(9) R. Breslow, T. Eicher, A. Krebs, R. A. Peterson, and J. Posner, *J. Am. Chem.*

Soc., 87, 1320 (1965).
(10) J. P. Dirlam, L. Eberson, and J. Casanova, J. Am. Chem. Soc., 94, 240 (1972).
(11) (a) A. R. Miller, J. Org. Chem., 41, 3599 (1976), and references therein; (b) H. M. R. Hoffmann, Angew. Chem., Int. Ed. Engl., 12, 819 (1973); (c) E. A. Schmidt and H. M. R. Hoffmann, J. Am. Chem. Soc., 94, 7832 (1972).
(12) C. A. Vernon, J. Chem. Soc., 423 (1954).
(13) (a) F. G. Bordwell, Acc. Chem. Res., 3, 281 (1970); (b) F. G. Bordwell and M. W. Carlson, J. Am. Chem. Soc., 92, 3370, 3377 (1970); (c) F. G. Bordwell and J. Almy, J. Org. Chem., 38, 575 (1973); (d) F. G. Bordwell, M. W. Carlson, and A. C. Knipe, J. Am. Chem. Soc., 91, 3949 (1969).
(14) (a) It is conceivable that the key intermediate in the formation of the α-acetoxy ketones is not oxyallyl cation 27 but rather an allene oxide,[14b] though we regard the latter as unlikely for reasons similar to those advanced by Bordwell;[13b] nevertheless, we are presently carrying out an experimental search for such intermediates;[14c] (b) B. S. Ong and T. H. Chan, Tetrahedron Lett., 3257 (1976); (c) Y. Migron, research in progress.
(15) (a) R. A. Sneen, J. Am. Chem. Soc., 83, 900 (1961); (b) R. H. De Wolfe and W. G. Young, Chem. Rev., 56, 753 (1956).
(16) A. J. Fry, "Synthetic Organic Electrochemistry", Harper and Row, New York, N.Y., 1972, Chapter 5.
(17) H. Budzikiewicz, C. Djerassi, and D. Williams, "Mass Spectrometry of Organic Compounds", Holden-Day, San Francisco, Calif., 1967, p 168.
(18) F. W. McLafferty, "Interpretation of Mass Spectra", 2nd ed, W. A. Benjamin, 1973.
(19) Program written by A.J.F.
(20) Reference 17, p 237.
(21) Reference 17, p 443.
(22) J. Levy and P. Jullien, Bull. Soc. Chim. Fr., 45, 941 (1929).
(23) A. Sosa, Ann. Chim. (Paris), [11], 14, 100 (1940).
(24) "Handbook of Chemistry and Physics", 47th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1966, p C-194.
(25) A referee has commented that thermal conductivity detector response factors were not established, thus introducing some inaccuracies into the data of Table I; while this is correct, it is unlikely that conclusions reached herein would be affected in any substantive way if this omission was corrected. In point of fact, whenever analyses were feasible by both NMR and VPC, the results agreed quite closely (±2–5%).
(26) C. Prevost and A. Sommiere, Bull. Soc. Chim. Fr., 2, 1151 (1935).

3,5-Dinitroperoxybenzoic Acid. A Crystalline, Storable Substitute for Peroxytrifluoroacetic Acid

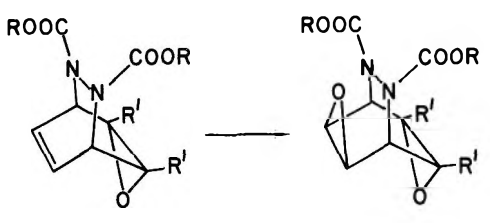
William H. Rastetter,* Thomas J. Richard, and Michael D. Lewis

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received January 27, 1978

Epoxidations and Baeyer-Villiger oxidations by 3,5-dinitroperoxybenzoic acid (3,5-DNPBA) are described. A preparation of 3,5-DNPBA is also given.

In the course of our syntheses of *sym*-oxepin oxides[1a-d] we were required to effect the difficult epoxidations of olefins **1a** and **1b**. Neither peroxytrifluoroacetic acid epoxidation nor high-temperature epoxidation by *m*-chloroperoxybenzoic acid proved preparatively useful in these systems. Under optimized conditions only low conversions of **1a** and **1b** to the corresponding epoxides could be achieved with peroxytrifluoroacetic acid. Buffered (Na_2CO_3 or Na_2HPO_4) peroxytrifluoroacetic acid reaction mixtures gave, at best, intractable mixtures of starting material, desired epoxide, and unidentified by-products.[2] Treatment of the parent system **1a** with 4,4′-thiobis(6-*tert*-butyl-3-methylphenol) (tbp)[3] stabilized *m*-chloroperoxybenzoic acid at elevated temperatures led to tarry reaction mixtures and low yields of diepoxide **2a**.[1a] Clean, efficient epoxidation of **1a** was achieved using *p*-nitroperoxybenzoic acid, stabilized by tbp,[3] in 1,2-dichloroethane at 90 °C (yield of crystalline **2a**, 65%).[1a] With the substituted derivative **1b**, however, the optimized yield utilizing *p*-nitroperoxybenzoic acid did not exceed 37%.[2] We have found that 3,5-dinitroperoxybenzoic acid (3,5-DNPBA) is an efficient reagent for achieving the conversion **1b** → **2b** (vide infra).[4] Herein we report on the synthetic utility of 3,5-DNPBA for difficult epoxidations and Baeyer-Villiger oxidations.



1a **1b** **2a** **2b**

1a and **2a**, R = CH_2CCl_3; R′ = H
1b and **2b**, R = CH_2CCl_3; R′, R′ = $-CH_2CH_2CH_2-$

Results and Discussion

To test the utility of 3,5-DNPBA we have chosen as substrates **1a, 1b,** and several other olefins or ketones for which literature oxidation procedures exist. Our results and a summary of literature oxidations are presented in Table I. An inspection of the table suggests that 3,5-DNPBA is not as reactive as peroxytrifluoroacetic acid (e.g., compare concentrations and reaction times for ethyl crotonate) but shows that yields for oxidations by these two peroxy acids are comparable.

It should be noted that similar weights of precursor per mole of peroxy acid are needed for 3,5-DNPBA and peroxytrifluoroacetic acid. The procedure for generation of methylene chloride solutions of peroxytrifluoroacetic acid[5] utilizes trifluoroacetic anhydride (mol wt 210.03) and hydrogen peroxide; buffers are routinely utilized to remove the trifluoroacetic acid which is also formed. By our procedure, crystalline samples of 3,5-DNPBA with active oxygen content >90% can be easily made from 3,5-dinitrobenzoic acid (mol wt 212.12).

Advantages of 3,5-DNPBA over peroxytrifluoroacetic acid are (1) no buffers are needed in 3,5-DNPBA oxidations and (2) 3,5-DNPBA can be stored for long periods without significant loss of active oxygen content. We have routinely stored 3,5-DNPBA in a freezer (<−10 °C) for periods up to 1 year without noticeable loss of reactivity. A more quantitative measure of the loss of active oxygen content from samples of 3,5-DNPBA and peroxytrifluoroacetic acid is given in Table II. At least some loss of active oxygen content from peroxytrifluoroacetic acid solutions is due to evaporation of the volatile peroxy acid. At ambient temperature sufficient evaporation occurs from an approximately 0.2 M solution of peroxytrifluoroacetic acid in methylene chloride to give an immediate, positive KI/starch test at the top of an ice–water cooled spiral condenser attached to a flask of the solution. Our studies of loss of active oxygen content from peroxytrifluo-

0022-3263/78/1943-3163$01.00/0

Table I. Oxidations by 3,5-DNPBA and Other Peroxy Acids

substrate/ peroxy acid/ additive	product	registry no.	equiv of peroxy acid	g of substrate/ amount of solvent	reaction time/ temp, °C	yield, %/ purification (lit. ref)
1a[e]/3,5-DNPBA[o]/ 1 wt % tbp[a]	**2a**	66511-15-7	3.78	0.237/1.0 mL ($ClCh_2CH_2Cl$)	55 min/75	52/crystallized
1a/*p*-nitroperoxybenzoic acid[p]/ 1 wt % tbp[a]	**2a**		3.97	2.39/7.5 mL ($ClCH_2CH_2Cl$)	2.5 h/90	65/crystallized (ref 1a)
1b[f]/3,5-DNPBA/ 1 wt % tbp[a]	**2b**	66402-64-0	4.06	2.58/12.0 mL ($ClCH_2CH_2Cl$)	1 h/75	59/crystallized
1b/*p*-nitroperoxybenzoic acid/ 1 wt % tbp[a]	**2b**		4.25	0.116/0.45 mL ($ClCH_2CH_2Cl$)	2 h/93	37/crystallized
1-octene[g]/ 3,5-DNPBA	1-octene oxide	2984-50-1	1.14	2.28/40.0 mL (CH_2Cl_2)	2 h/ambient temp	87/vacuum transferred[b]
1-octene/ CF_3CO_3H[h]/Na_2CO_3	1-octene oxide		1.50	22.4/250 mL (CH_2Cl_2)	30 min/reflux	87/distilled (ref 5)
1-decene[i]/ 3,5-DNPBA	1-decene oxide	2404-44-6	1.20	13.9/200 mL (CH_2Cl_2)	1.0 h/ice bath and 2.5 h/ ambient temp	80/distilled[c]
1-decene/ CH_3CO_3H	1-decene oxide		1.20	42/408 g of 0.9 M solution (CH_3COOH)	28 h/ambient temp	56/distilled (ref 6)
methyl methacrylate[j]/ 3,5-DNPBA	methyl α-methyl glycidate	58653-97-7	1.14	2.04/40 mL (CH_2Cl_2)	7.75 h/reflux	80/vacuum transferred[b]
methyl methacrylate/ CF_3CO_3H/ Na_2HPO_4	methyl α-methyl glycidate		1.25	20.0/250 mL (CH_2Cl_2)	30 min/reflux	84/distilled (ref 5)
ethyl crotonate[k]/3,5-DNPBA	ethyl β-methyl glycidate	19780-35-9	1.13	2.36/40 mL (CH_2Cl_2)	9.5 h/reflux	87/vacuum transferred[b]
ethyl crotonate/ CF_3CO_3H/ Na_2HPO_4	ethyl β-methyl glycidate		1.25	22.8/250 mL (CH_2Cl_2)	30 min/reflux	73/distilled (ref 5)
ethyl acrylate[l]/ 3,5-DNPBA	ethyl glycidate	4660-80-4	2.19	10.0/200 mL ($CHCl_3$)	8.0 h/reflux	79/distilled[c]
ethyl acrylate/ CF_3CO_3H Na_2HPO_4	ethyl glycidate		2.25	20.0/300 mL ($ClCH_2CH_2Cl$)	30 min/reflux	54/distilled (ref 5)
methyl cyclopropyl ketone[m]/ 3,5-DNPBA/ 1 wt % tbp[a,d]	cyclopropyl acetate	4606-06-8	2.50	15.4/366 mL ($CHCl_3$)	12.0 h/reflux	59 (GC yield) 53/distilled[c]
methyl cyclopropyl ketone/ CF_3CO_3H/ Na_2HPO_4	cyclopropyl acetate		2.00	16.8/300 mL (CH_2Cl_2)	1.0 h/reflux	53/distilled (ref 7)
BENZOPHENONE[n]/ 3,5-DNPBA/ 1 wt % tbp[a]	phenyl benzoate	93-99-2	2.50	3.72/51 mL ($ClCH_2CH_2Cl$)	3.5 h/reflux	87 (crude yield) 70/recrystallized (mp 68.5–69.5 °C)
benzophenone/ CF_3CO_3H/ Na_2HPO_4	phenyl benzoate		1.50	36.4/200 mL (CH_2Cl_2)	1.0 h/reflux	86 (crude yield, mp 65–67 °C) (ref 7)

[a] tbp is an abbreviation for 4,4′-thiobis(6-*tert*-butyl-3-methylphenol); see ref 3. [b] Product vacuum transferred with residual solvent at ambient temperature/P < 0.1 mmHg; ^1H NMR shows only the indicated product and residual solvent; yield determined by ^1H NMR. [c] Product >95% pure by GC and ^1H NMR. [d] This oxidation done prior to the peroxy acid stability study summarized in Table II; addition of tbp may not be necessary. [e] Registry no. 66511-146. [f] Registry no. 66358-47-2. [g] Registry no. 111-66-0. [h] Registry no. 359-48-8. [i] Registry no. 872-05-9. [j] Registry no. 80-62-6. [k] Registry no. 10544-63-5. [l] Registry no. 140-88-5. [m] Registry no. 765-43-5. [n] Registry no. 119-61-9. [o] Registry no. 66358-48-3. [p] Registry no. 943-39-5.

roacetic acid/methylene chloride solutions contradict Emmons' original finding[8] that "such a solution [concentration not given] lost essentially no active oxygen during a reflux period of 24 h."

Caution: All peroxy acids are potentially explosive. Oxidations using 3,5-DNPBA or the preparation of the peroxy acid should be conducted with adequate shielding and reaction temperatures should be carefully monitored. We have not been able to detonate 3,5-DNPBA by impact, nor have we experienced any problems during 3,5-DNPBA oxidations. We

Table II. Loss of Active Oxygen from Samples of 3,5-DNPBA and Peroxytrifluoroacetic Acid

3,5-DNPBA[d]			peroxytrifluoroacetic acid[c]		
storage or treatment	physical state	remaining fraction of active oxygen[a]	storage or treatment	physical state	remaining fraction of active oxygen[a]
114 days, <−10 °C	crystalline	93.5/93.5	2 h, reflux; straight bore condenser	0.210 M in CH_2Cl_2	0.189/0.210
16 days, ambient temp	crystalline	92.8/93.5			
80 days, ambient temp	crystalline	84.0/93.5	2 h, reflux; ice–water cooled spiral condenser	0.205 M in CH_2Cl_2	0.196/0.205
2 h, reflux	1 M in $CHCl_3$	79.0/93.5		0.205 M in CH_2Cl_2	0.193/0.205
2 h, reflux	1 M in $CHCl_3$, 1.5 wt % tbp[b]	79.0/93.5	2 h, reflux; straight bore condenser	0.703 M in CH_2Cl_2	0.560/0.703
2 h, reflux	1 M in $ClCH_2CH_2Cl$	7.5/93.5		0.750 M in CH_2Cl_2	0.583/0.750
2 h, reflux	1 M in $ClCH_2CH_2Cl$, 1.5 wt % tbp[b]	32.5/93.5		0.698 M in CH_2Cl_2	0.535/0.698
			24 h, ambient temp; sealed vessel	2.87 M in CH_2Cl_2	1.82/2.87
				2.95 M in $CHCl_3$	2.60/2.95
				2.94 M in $ClCH_2CH_2Cl$	2.31/2.94
			24 h, refrigerator (+5 °C); sealed vessel	1.50 M in CH_2Cl_2	1.32/1.50

[a] Percentage of active oxygen determined by iodometric titration. [b] tbp is an abbreviation for 4,4′-thiobis(6-*tert*-butyl-3-methylphenol); see ref 3. [c] Solutions of peroxytrifluoroacetic acid prepared by the method in ref 5. [d] Initial sample 93.5% active oxygen.

have deliberately detonated a 200-mg sample by heating the peroxy acid to just above its melting point (mp ~112 °C) (see also the caution outlined in ref 9).

Experimental Section

General. Melting points were determined in a capillary apparatus (Mel-Temp) and are uncorrected. Gas chromatographic analyses of reaction products were done on a $\frac{1}{8}$ in. × 8 ft aluminum column packed with 4.1% SE-30 on Chromosorb G. ^1H NMR spectra (60 MHz) were determined in $CDCl_3$ or $CDCl_3/CD_3OD$ solution (Me_4Si internal standard) on an Hitachi Perkin-Elmer R-24B or on a Varian T-60 spectrometer; IR spectra were determined on a Perkin-Elmer 567 grating infrared spectrophotometer.

For the preparation of 3,5-DNPBA, Aldrich (99%) 3,5-dinitrobenzoic acid was used without further purification; methanesulfonic acid was obtained from Aldrich (98%) or from Eastman (White Label); hydrogen peroxide (90%) was obtained from FMC Corp. Chlorinated solvents were purified by passage through basic alumina immediately prior to use. Iodometric titrations were done by the method of Silbert et al.[10] For solid 3,5-DNPBA samples, the peroxy acid was directly dissolved in acetic acid, omitting dissolution in benzene as indicated in ref 10.

Preparation of 3,5-Dinitroperoxybenzoic Acid (3,5-DNPBA). Our procedure is adapted from the method of Silbert, Siegel, and Swern[11] for the preparation of aliphatic and aromatic peroxy acids. 3,5-Dinitrobenzoic acid (81.90 g, 0.386 mol) and methanesulfonic acid (177 g) were mixed in a three-neck round-bottom flask[12] equipped with a thermometer, a mechanical stirrer, and a nitrogen inlet. Hydrogen peroxide (90% by weight) (40 mL; approximately 1.5 mol) was added in one portion with stirring under nitrogen. The reaction was maintained at 50 °C[13] for 2 h and 50 min and then cooled to 0 °C with an ice/salt bath. With external cooling still applied, crushed ice (120 g) was slowly added (temperature rose to 25 °C). The reaction mixture was cooled to 0 °C and the nearly white crystals of 3,5-DNPBA were collected by suction filtration through sintered glass. The peroxy acid was dried in a vacuum desiccator (yield, 79.8 g, 91%; active oxygen content 93.5%, determined by iodometric titration; ^1H NMR ($CDCl_3/CD_3OD$) δ (Me_4Si) 4.83 (br s, exchangeable proton), 8.82 (m, 2 H), 8.98 (m, 1 H); IR (Nujol mull) 1758, 1738, 1540, 1342 cm^{-1}). A small sample heated in a capillary apparatus melts at 113–115 °C with gas evolution, resolidifies, then remelts at 195–200 °C. A sample prepared by the above method without further purification and containing 95.0% active oxygen (by iodometric titration) was analyzed by combustion analysis: calculated for 95% $C_7H_4N_2O_7$ + 5% $C_7H_4N_2O_6$: C, 37.00; H, 1.78; N, 12.33. Found: C, 37.00; H, 1.93; N, 11.70.

Oxidations with 3,5-DNPBA. Two representative procedures are given.

Epoxidation of 1b by tbp[3]-Stabilized 3,5-DNPBA. Crystalline **1b** (3.001 g containing 14 wt % benzene, 5.01 mmol), 3,5-DNPBA (5.014 g, 92.5% active oxygen, 20.33 mmol active oxygen), and tbp[3] (54.3 mg) were thoroughly mixed and dried in high vacuum overnight. A thick-walled glass tube was charged with the mixture and with 1,2-dichloroethane (12.0 mL). The tube was flushed with nitrogen, sealed, and heated at 75 °C for 1 h. The reaction mixture was cooled to 0 °C and filtered through sintered glass with a $CHCl_3$ wash (40 mL). The resulting solution was washed with 20% aqueous $NaHSO_3$ (2 × 25 mL), saturated aqueous $NaHCO_3$ (3 × 25 mL), and saturated aqueous NaCl (3 × 25 mL). The organic layer was dried ($MgSO_4$), rotary evaporated to a yellow oil, and re-evaporated from benzene (twice) and from Et_2O, giving an off-white foam. Trituration with Et_2O (3.0 mL) and refrigeration overnight induced crystallization. Collection and drying of the white crystals (mp 137–139 °C) and similar crystallization of the mother liquors yielded 1.66 g of diepoxide **2b.** ^1H NMR of crystalline **2b** shows 94% diepoxide and 6% incorporated benzene; yield of **2b,** 59%.

Epoxidation of Ethyl Acrylate by 3,5-DNPBA. Ethyl acrylate (10.0 g, 0.10 mol) was added to $CHCl_3$ (200 mL) followed by a single portion of 3,5-DNPBA (52.0 g, 96.2% active oxygen, 0.22 mol active oxygen). The mixture was mechanically stirred and brought to reflux for 8 h. The reaction mixture was cooled with an ice bath, diluted with CH_2Cl_2 (100 mL), and filtered through sintered glass with CH_2Cl_2 wash (4 × 50 mL). The resulting solution was washed with 20% aqueous $NaHSO_3$ (1 × 100 mL) and the separated organic layer was drawn off. The aqueous phase (a suspension containing some organic layer) was diluted with an equal volume of saturated aqueous $NaHCO_3$, cautiously mixed, and the remainder of the organic layer was withdrawn. The combined organic layers were washed with saturated aqueous $NaHCO_3$ (3 × 100 mL, solid NaCl added to last wash), dried ($MgSO_4$), filtered, and distilled (105–108 °C (87 mmHg)) yielding 9.20 g (79%) of colorless ethyl glycidate.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. We also thank the M.I.T. Undergraduate Research Opportunities Program for support to M.D.L.

Registry No.—tbp, 96-69-5.

References and Notes

(1) (a) W. H. Rastetter, *J. Am. Chem. Soc.*, **98,** 6350 (1976), and D. D. Haas and W. H. Rastetter, *ibid.*, **98,** 6353 (1976); (b) W. H. Rastetter, T. J. Richard, N. D. Jones, and M. O. Chaney. *J. Chem. Soc., Chem. Commun.*, 377 (1978); (c) W. H. Rastetter and T. J. Richard, *Tetrahedron Lett.*, in press; (d) W. H. Rastetter, T. J. Richard, J. Bordner, and G. L. A. Hennessee, *J. Chem. Soc., Chem. Commun.*, submitted.
(2) Unpublished results.
(3) Y. Kishi, M. Aratani, H. Tanino, T. Fukuyama, T. Goto, S. Inoue, S. Sugiura, and H. Kakoi, *J. Chem. Soc., Chem. Commun.*, 64 (1972).
(4) The reagent of choice in the parent system (**1a** → **2a**) remains *p*-nitro-

peroxybenzoic acid; see Table I.
(5) W. D. Emmons and A. S. Pagano, *J. Am. Chem. Soc.*, **77**, 89 (1955).
(6) D. Swern, G. N. Billen, and J. T. Scanlan, *J. Am. Chem. Soc.*, **68**, 1504 (1946).
(7) W. D. Emmons and G. B. Lucas, *J. Am. Chem. Soc.*, **77**, 2287 (1955).
(8) W. D. Emmons, *J. Am. Chem. Soc.*, **76**, 3468 (1954).
(9) A. I. Meyers, S. Schwartzman, G. L. Olson, and H. Cheung, *Tetrahedron Lett.*, 2417 (1976).
(10) L. S. Silbert, E. Siegel, and D. Swern, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 904.
(11) L. S. Silbert, E. Siegel, and D. Swern, *J. Org. Chem.*, **27**, 1336 (1962).
(12) The procedure outlined in ref 11 utilizes an open beaker for the peroxy acid preparation. We found this procedure to be unsatisfactory on humid days, yielding peroxy acid samples with low active oxygen content.
(13) The temperature of the reaction mixture should be carefully monitored. If the mixture is heated above 53 °C a steady rise in the internal reaction temperature may be seen. The exotherm may lead to frothing, spillage, and peroxy acid batches with low active oxygen content.

Cyanohydrin Synthesis of 2,3-Dihydroxy-2,3-dimethylbutanoic Acid

Jack E. Powell,* Carl Osuch, Harvey R. Burkholder, Santi Kulprathipanja, James H. Miller, Leon G. Stadtherr, and Russell G. Baughman

Ames Laboratory, DOE and Department of Chemistry, Iowa State University, Ames, Iowa 50011

Received January 18, 1978

From 3-hydroxy-3-methyl-2-butanone (**1**) via cyanohydrin synthesis and subsequent hydrolysis, the intermediates 2,3-dihydroxy-2,3-dimethylbutanonitrile (**2**), 3-chloro-1,2-dihydroxy-2,3-dimethylbutanimine hydrochloride (**3**), 3-chloro-1,2-dihydroxy-2,3-dimethylbutanamide (**4**), and 2,3-dihydroxy-2,3-dimethylbutanamide (**5**) have been isolated en route to 2,3-dihydroxy-2,3-dimethylbutanoic acid (**6**). Compound **2** reverted to **1** in the presence of base. In aqueous NaOH or NaOMe in Et_2O, compounds **3** and **4** gave (by HCl abstraction) 2,3-epoxy-1-hydroxy-2,3-dimethylbutanimine (**7**), tautomeric with 2,3-epoxy-2,3-dimethylbutanamide (**8**). Acid hydrolysis of **2** (at 40–50 °C) led principally to **5**, but at higher temperatures to 3-methyl-2-butanone (**9**) via a pinacol–pinacolone type rearrangement involving the intermediates 2,2-dimethyl-3-oxobutanamide (**10**) and 2,2-dimethyl-3-oxobutanoic acid (**11**), which decarboxylates spontaneously to **9**. In the acid hydrolysis of **2** to obtain **5** and **6** directly, substantial amounts of the byproduct 2-hydroxy-2,3-dimethyl-3-butenoic acid (**12**) were encountered; better yields of the desired products were obtained when the dihydroxynitrile (**2**) was first treated with 2 mol of acetic anhydride per mole to form its diacetate and somewhat diluted hydrochloric acid was used in lieu of saturated aqueous HCl.

Interest in the effects of adding a second methyl group to the β-carbon atom of 2,3-dihydroxy-2-methylbutanoic acid on the acid ionization constant and the chelating properties of the ligand moiety prompted an attempt to synthesize 2,3-dihydroxy-2,3-dimethylbutanoic acid from 3-hydroxy-3-methyl-2-butanone (via a route used in preparing 2,3-dihydroxy-2-methylpropanoic acid and 2,3-dihydroxy-2-methylbutanoic acid from acetol and acetoin precursors, respectively[1,2]). After several failures to obtain the expected amide and acid from unisolated cyanohydrin, using standard procedures, it was decided to perform a step-by-step isolation (by ion-exclusion chromatography and anion exchange when appropriate) of the various intermediates, in order to ascertain at what point the process failed.

While no one (to date) has reported the synthesis of either 2,3-dihydroxy-2,3-dimethylbutanamide (DHDMB amide) or DHDMB acid, Cantacuzène and Ricard[3] prepared the corresponding DHDMB nitrile by acid hydrolysis (dilute H_2SO_4) of 2,3-epoxy-2,3-dimethylbutanonitrile and reported its ^1H NMR spectra in $CDCl_3$, benzene, and DMF and its IR spectrum in CCl_4. Since they failed to obtain the nitrile in crystalline form, only its boiling point [130 °C (15 Torr)] was given.

It was immediately ascertained that DHDMB nitrile could be prepared in good yield from the KCN-catalyzed combination of 3-hydroxy-3-methyl-2-butanone and excess liquid HCN (the reaction temperature being controlled at ~30 °C by refluxing of the HCN). The cyanohydrin (DHDMB nitrile) was readily obtained as a white crystalline solid (mp 67–69 °C) from ethyl acetate, whose ^1H NMR spectrum in $CDCl_3$ coincided with the liquid prepared by Cantacuzène and Ricard[3] from 2,3-epoxy-2,3-dimethylbutanonitrile. Typical of cyanohydrins, our DHDMB nitrile yielded the original ketone and NaCN (instantaneously and quantitatively) when treated with excess aqueous NaOH.

Acid hydrolysis of the DHDMB nitrile posed a problem in that undesired dark byproducts were obtained copiously at elevated temperatures, and conversion of the nitrile was inordinately slow in concentrated hydrochloric acid or dilute acid at room temperature. When the nitrile was dissolved in hydrochloric acid and saturated with HCl gas below 35 °C (a standard procedure), the tertiary 3-hydroxyl was replaced by chloride, and 3-chloro-1,2-dihydroxy-2,3-dimethylbutanimine hydrochloride (rather than the expected DHDMB amide) resulted. This hydrochloride (upon recovery and washing with ether) decomposed spontaneously at room temperature (over a 24-h period) to the corresponding 3-chloro-2-hydroxy-2,3-dimethylbutanamide by evolving HCl.

Dilute (~1 M) aqueous solutions of 3-chloro-2-hydroxy-2,3-dimethylbutanamide (CHDMB amide) slowly generate H_3O^+ via hydrolysis (replacement of the tertiary –Cl by –OH). The resulting DHDMB amide then presumably undergoes very slow hydrolytic conversion to DHDMB acid. At temperatures as low as 80 °C, when either CHDMB amide or DHDMB amide is hydrolyzed in dilute HCl, CO_2 is evolved at an appreciable rate and the major product isolated (and positively identified by its ^1H NMR spectrum) is 3-methyl-2-butanone. The characteristic odor of this ketone could be detected after a day even in conversions carried out at 45 °C. Isolation of 2,2-dimethyl-3-oxobutanamide (mp 120–122 °C),[4] whose oxime melts at 162–164 °C,[5] in the acid hydrolysis of both CHDMB amide and DHDMB amide indicates that DHDMB amide readily undergoes a pinacol–pinacolone type of rearrangement. As the resulting 2,2-dimethyl-3-oxobutanamide hydrolyzes to 2,2-dimethyl-3-oxobutanoic acid, decarboxylation of this unstable substance occurs. The chief product obtained is 3-methyl-2-butanone.

If 3-chloro-2-hydroxy-2,3-dimethylbutanamide in aqueous solution is treated with excess base, abstraction of HCl, rather than replacement of –Cl by –OH, occurs. An epoxyhydroxy-

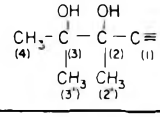
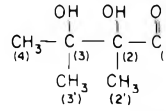
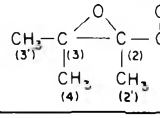
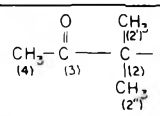
0022-3263/78/1943-3166$01.00/0

Table I. Melting Points and ^1H NMR Chemical Shifts of 2,3-Dihydroxy-2,3-dimethylbutanoic Acid and Derivatives

compd	registry no.	mp, °C	^1H NMR[a]	
2	26429-38-9	67–69	$CDCl_3$:	1.30 (s, 3 H), 1.44 (s, 3 H), 1.51 (s, 3 H), 2.87 (b, 1 H), 4.03 (b, 1 H)
			D_2O:	1.31 (s, 6 H), 1.57 (s, 3 H)
4	66483-60-1	139–141	$CDCl_3$:	1.57 (s, 3 H), 1.68 (s, 3 H), 1.74 (s, 3 H)
			D_2O:	1.51 (s, 3 H), 1.68 (s, 6 H)
5	66483-61-2	111–113	$CDCl_3$:	1.29 (s, 6 H), 1.46 (s, 3 H)
			D_2O:	1.22 (s, 6 H), 1.38 (s, 3 H)
6	66483-62-3	102–104	$CDCl_3$:	1.34 (s, 6 H), 1.48 (s, 3 H)
			D_2O:	1.27 (s, 6 H), 1.42 (s, 3 H)
7	66483-63-4	157–158	$CDCl_3$:[b]	1.379 (s, 6 H), 1.545 (s, 3 H), 6.299 (s, 2 H)
		[lit.[6] 157–158][c]	CCl_4:	1.34 (s, 6 H), 1.44 (s, 3 H)
10	66483-64-5	122–124	$CDCl_3$:[b]	1.408 (s, 6 H), 2.333 (s, 3 H), 6.136 (s, 2 H)
		[lit.[4] 121–122]	D_2O:	1.39 (s, 6 H), 2.25 (s, 3 H)
12	17891-10-0	85–57	$CDCl_3$:	1.61 (s, 3 H), 1.83 (d-d, 3 H), 5.02 (d-d, 1 H) 5.21 (t, 1 H), 7.41 (b, 2 H)
		[lit.[7] 87–88]		[lit.:[7] 1.59 (s), 1.82 (d-d), 5.03 (q), 5.22 (q), 7.52 (s)]

[a] Chemical shift in ppm relative to Me_4Si ($CHCl_3$, CCl_4) and DSS (D_2O). [b] Recorded at 90 MHz on Brucker HX-90 spectrophotometer. [c] Previously identified as a different compound; see text.

Table II. ^{13}C Chemical Shifts[a]

COMPOUND	STRUCTURE	C-1	C-2	C-3	C-4	C-3'	C-2'	C-2''
2		121.406	74.495	75.210	22.517 & 22.387		25.051	—
5		180.855	78.458	74.430	26.220 & 24.401		22.127	—
7		174.359	65.464	63.710		20.308	15.565	—
10		175.008	55.978	208.859	26.090	—		22.452

[a] In ppm from internal Me_4Si.

imine, less soluble than the CHDMB amide, is obtained. The identity of this substance was at first puzzling, as the ^1H NMR (in CCl_4, $CDCl_3$) showed only two peaks with a ratio of 2:1. All of the NMR data are summarized in Tables I and II. The compound was eventually determined by X-ray diffraction to be 2,3-epoxy-1-hydroxy-2,3-dimethylbutanimine.

This epoxyhydroxyimine appears to be identical with the substance (mp 157–158 °C) obtained by Delbaère[6] on heating 2,3-epoxy-2,3-dimethylbutanonitrile a few minutes with dilute aqueous NaOH (mistakenly identified by Delbaère as 2,3-dihydroxy-2,3-dimethylbutanonitrile). It is now apparent that rapid hydrolysis of the epoxynitrile to the imine occurred in Delbaère's reaction, rather than opening of the ether linkage.

Another substance isolated in substantial amounts in attempts to convert 3-chloro-2-hydroxy-2,3-dimethylbutanamide to 2,3-dihydroxy-2,3-dimethylbutanoic acid (which helps to confirm the position of the Cl in CHDMB amide) was the known compound 2-hydroxy-2,3-dimethyl-3-butenoic acid.

Formation of CHDMB amide, 2-hydroxy-2,3-dimethyl-3-butenoic acid, 2,2-dimethyl-3-oxobutanamide, 3-methyl-2-butanone, and unidentified dark-colored substances is repressed by converting the isolated nitrile to its diacetate ester and utilizing somewhat diluted (~8 M) hydrochloric acid at 50 °C in converting DHDMB nitrile to DHDMB amide. Conversion under these conditions requires about 40 h.

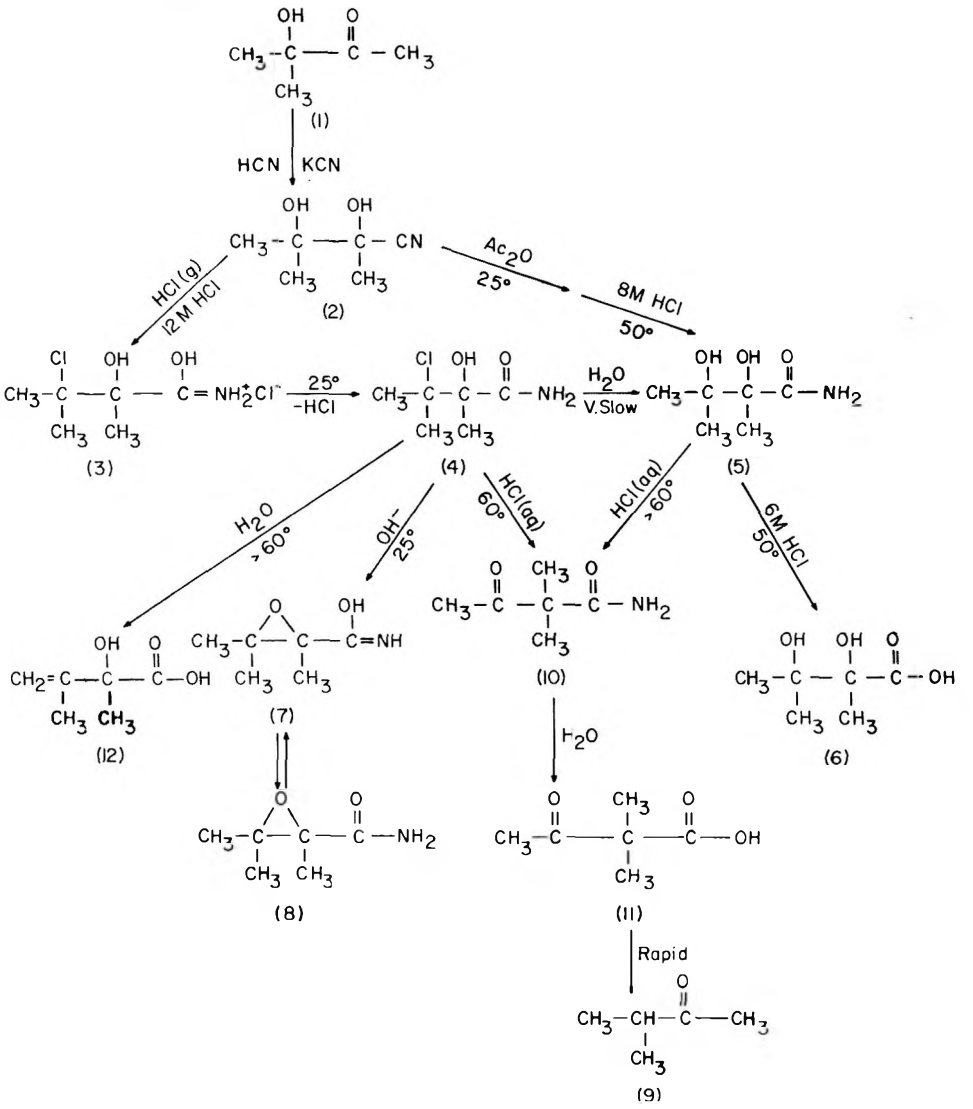
Although DHDMB acid was obtained by basic hydrolysis of DHDMB amide, better yields were obtained via slow hydrolysis in 6 M HCl at 50 °C (2 weeks).

Experimental Section

The melting points were taken on an electrothermal melting point apparatus and are uncorrected. The proton magnetic resonance spectra were measured on a Varian A-60 or Hitachi Perkin-Elmer R-20 B spectrometer. The ^{13}C NMR spectra were recorded on a Brucker HX-90 spectrometer. Some ^1H spectra were also obtained using pulsed Fourier transform at 90 MHz on the Brucker HX-90. All chemical shifts were measured in parts per million relative to internal Me_4Si (or DSS in D_2O).

2,3-Dihydroxy-2,3-dimethylbutanonitrile (2, see Scheme I). 3-Hydroxy-3-methyl-2-butanone (1; 1 mol, 120 g of 85%) at 0 °C was mixed with 5 mol (135 g) of freshly prepared, chilled, anhydrous, liquid HCN (in a 3-L, three-neck, round-bottom flask equipped with an ice-water-cooled reflux condenser, a thermometer, and a magnetic stirrer and immersed in an ice bath *in an efficient hood*). Solid KCN catalyst (0.1 g) was added, and the assembly was raised just out of the bath to initiate the reaction. When the temperature began to rise rapidly (at about 15 °C) the assembly was lowered to touch the ice bath, after which the reaction continued at the reflux temperature (~30 °C). When (upon seeding) solid cyanohydrin (2) separated copiously (in the course of about 30 min), an additional 3.2 mol of chilled 1 was added at a rate sufficient to maintain the reaction at 30–35 °C. Nitrile 2 accumulated eventually to the extent that the magnetic stirrer could no longer handle the load. At this point the reversible reaction was stopped by adding 8 mL of glacial acetic acid in 500 mL

Scheme I. Relationships between Intermediate, Products, and Byproducts Observed.



of ethyl acetate. The flow of ice water in the reflux condenser was then stopped, and the flask was gently warmed in a heating mantle to distill off excess HCN and bring the ethyl acetate to a state of reflux.

After recooling to about 18 °C, the mixture was transferred to an open beaker *in the hood,* seeded with a few crystals of **2**, and then chilled to near 0 °C. The snow-white crystalline product was recovered by filtration, and the filtrate was evaporated first to 300 mL and then to 150 mL to obtain two additional crops of nitrile. The pale-yellow residual liquid was principally **1**, containing a small amount of **2**.

The crystalline cyanohydrin weighed 413 g (3.2 mol = 76% yield) and melted (after recrystallization from ethyl acetate) at 67–69 °C. Anal. Calcd for $C_6H_{11}NO_2$: C, 55.79; H, 8.58; N, 10.84; O, 24.77. Found: C, 55.8; H, 8.5; N, 11.1; O, 24.6. The equivalent weight computed from base-liberated CN^- was 129 (theoretical 129.16). Note: In the open **2** reverts slowly to **1** and HCN.

3-Chloro-1,2-dihydroxy-2,3-dimethylbutanimine Hydrochloride (3). **2** (0.5 mol, 64.5 g) in 63 mL of 12 N HCl was saturated with HCl gas at such a rate that the temperature reached about 35 °C. After 4 h, and a weight gain of 19.9 g, considerable **3** separated. The mixture was allowed to stand overnight and was then resaturated with HCl, giving an additional gain of 11.2 g. It was then allowed to stand for 48 h, at which time a qualitative test revealed no **2** remaining. At this point, the crystalline **3** was filtered off and rinsed with 30 mL of anhydrous ether (5 mL at a time). After a 1-h exposure to the air, the produce weighed 52.5 g and appeared dry (although reeking of HCl).

3-Chloro-2-hydroxy-2,3-dimethylbutanamide (4). In two separate experiments, 25.5 g and 17.0 g of **3** lost 5.3 g and 3.5 g, respectively, on standing 24 h at 23 °C in the open. Recrystallized from ethyl acetate, the residual material melted at 139–141 °C and exhibited an equivalent weight of 166.3, based on an independent analysis for Cl ($C_6H_{12}ClNO_2$ = 165.62). Anal. Calcd for $C_6H_{12}ClNO_2$: C, 43.51; H, 7.30; Cl, 21.40; N, 8.45; O, 19.32. Found: C, 43.4; H, 7.4; Cl, 21.1; N, 8.5; O, 19.6.

2,3-Epoxy-1-hydroxy-2,3-dimethylbutanimine (7). A 3.31-g sample of **4** (0.02 mol), dissolved in 30 mL of diethyl ether, was combined with 0.02 mol of NaOMe in ether. NaCl separated immediately, and after 0.5 h the salt was filtered off and washed with ether. When a vacuum was pulled on the filtrate to reduce the volume, silky-white needles separated from the cold solution. The yield was nearly quantitative, and when recrystallized from ether, ethyl acetate, or water, the product (**7**) melted at 157–158 °C (with sublimation). Anal. Calcd for $C_6H_{11}NO_2$: C, 55.79; H, 8.58; N, 10.84; O, 24.77. Found: C, 55.7; H, 8.6; N, 11.0; O, 24.7.

2,3-Dihydroxy-2,3-dimethylbutanamide (5). When 20.7 g (0.125 mol) of **4** and 26.0 g (0.128 mol) of **3** were dissolved, each in 100 g of H_2O, they slowly generated H_3O^+. In dilute solution the replacement of –Cl by –OH appears to be first order with respect to **4** and independent of the H_3O^+ concentration. The rate constants at 23 and 45 °C are 0.004 and 0.16 h^{-1}, respectively.

After 72 h at room temperature followed by 48 h at 45 °C, the products of the parallel experiments above were combined, diluted to 500 mL, and pumped into a 1-in. system (three, 4-ft beds in series) of −40 + 50 mesh, H^+-form, Dowex 50W-X8, cation-exchange resin (at a rate of 1.25 mL/min). The mixture was then subjected to ion-exclusion separation by eluting the system with deionized water at the same rate. The effluent solution was collected in a series of 30 95-mL fractions. Samples 5–14 contained primarily the expected 3/8 mol of HCl. A weak acid and **5** eluted principally in fractions 14–21. Fractions 22–26 yielded a second nitrogen-containing substance subsequently identified as 2,2-dimethyl-3-oxobutanamide[4] (by its empirical formula and melting point, 121–122 °C). Upon evaporation of fractions 16–20 (under vacuum at 35 °C) to a thick syrup and dissolving this in 15 mL of hot ethyl acetate, 6.0 g of **5** was obtained as

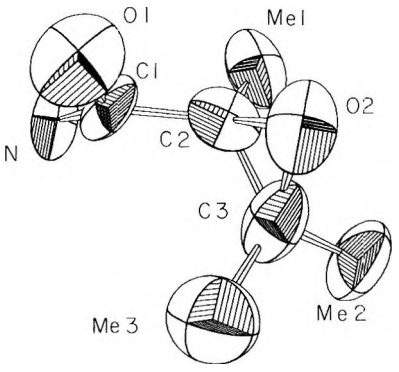


Figure 1. The molecular structure of 2,3-epoxy-1-hydroxy-2,3-dimethylbutanimine, with thermal ellipsoids drawn at the 50% probability level.

a first crop on cooling. Recrystallized from $CHCl_3$, **5** melted at 111–113 °C. The mother liquor from fractions 16–20, after heating with base and removal of the Na^+ by cation exchange, yielded (instead of the expected DHDMB acid (**6**)) 3.2 g of 2-hydroxy-2,3-dimethylbutenoic acid (**12**) melting at 85–87 °C (lit.[7] 87–88 °C).

Subsequently, as one of a series of experiments intended to optimize conversion of **2** to **5**, 0.3 mol of **2** was treated with 0.6 mol of acetic anhydride and a drop of H_2SO_4 to form the diacetate ester of the dihydroxynitrile. Hydrolysis of the CN functional group was then carried out by adding 83 mL of 12 N HCl and 36 mL of H_2O and heating at 40 °C for 15 h. The yield of **5** (isolated by ion exclusion as described above) was 81.6%. The formula weight by base-evolved NH_3 was 147 ($C_6H_{13}NO_3$ = 147.18). Anal. Calcd for $C_6H_{13}NO_3$: C, 48.96; H, 8.90; N, 9.52; O, 32.61. Found: C, 48.4; H, 8.8; N, 9.5; O, 33.3.

2,3-Dihydroxy-2,3-dimethylbutanoic acid (6). A 14-g sample of **5** (0.095 mol) was dissolved in 150 mL of H_2O, treated with 40 g (1 mol) of NaOH pellets, and refluxed for 2 h. The mixture was then diluted to 250 mL and passed through a bed containing a 50% excess of −40 + 50 mesh, H^+-form, Dowex 50W-X8, cation-exchange resin. The acidic effluent was collected and evaporated at 40 °C. The residue was recrystallized from $CHCl_3$ to a white monobasic acid (mp 102–104 °C) which exhibited a formula weight of 151.7 ($C_6H_{12}O_4$ = 148.16). Anal. Calcd for $C_6H_{12}O_4$: C, 48.64; H, 8.16; O, 43.20. Found: C, 48.4; H, 8.3; O, 43.3. The ^1H NMR spectrum of the acid (**6**) was indistinguishable from that of the amide (**5**) in D_2O (Table I).

DHDMB acid (**6**) was also obtained via consecutive prolonged acid hydrolyses of the diacetate ester of DHDMB nitrile and DHDMB amide. For example, 300 g of the nitrile (**2**) was first converted to the diacetate ester by adding a slight excess of acetic anhydride and a few drops of H_2SO_4. After 1 h, the reaction mixture was treated with 325 mL of H_2O and 650 mL of concentrated HCl. At 50 °C, the conversion of nitrile to amide was found to be nearly complete in 40 h (conclusion based on qualitative test for cyanohydrin). The mixture was diluted to 4 L, passed onto a system consisting of a series of six 4-in. × 4-ft, H^+-cycle, −40 + 50 mesh, Dowex 50W-X8, cation-exchange beds at a rate of about 1 L/h, and then ion-exclusion eluted with deionized water at the same rate. The fractions free of HCl and containing DHDMB amide (and some **6**) were combined and vacuum evaporated at 50 °C to a solid mass. This mixture was then dissolved in 4 L of 6 N HCl and maintained at 50 °C for 2 weeks. The DHDMB acid was finally isolated along with some unconverted amide by a repetition of the ion-exclusion process above. The amide was next eliminated by adsorbing the acid on an acetate-cycle anion-exchange column, and the acid was recovered by displacing it with 0.25 M HCl. When the residue, obtained by vacuum evaporation of the effluent, was recrystallized from $CHCl_3$, the combined crops of **6** totaled 151 g.

Table III. Selected Interatomic Distances (Å) for 2,3-Epoxy-1-hydroxy-2,3-dimethylbutanimine

C(1)–O(1)	1.41 (2)	C(2)–O(2)	1.463 (27)
C(1)–N	1.17 (3)	C(3)–O(2)	1.416 (34)
C(1)–C(2)	1.53 (3)	C(3)–Me(2)	1.55 (3)
C(2)–Me(1)	1.45 (3)	C(3)–Me(3)	1.54 (4)
C(2)–C(3)	1.485 (33)		

Table IV. Bond Angles (deg) for 2,3-Epoxy-1-hydroxy-2,3-dimethylbutanimine

O(1)–C(1)–N	126.4 (2.5)	O(2)–C(2)–C(3)	57.4 (1.8)
O(1)–C(1)–C(2)	110.8 (2.2)	C(2)–O(2)–C(3)	62.1 (1.4)
N–C(1)–C(2)	122.3 (2.0)	C(2)–C(3)–O(2)	60.5 (1.8)
C(1)–C(2)–Me(1)	114.9 (2.4)	C(2)–C(3)–Me(2)	120.6 (2.7)
C(1)–C(2)–O(2)	117.3 (2.0)	C(2)–C(3)–Me(3)	121.8 (2.4)
C(1)–C(2)–C(3)	115.7 (2.5)	O(2)–C(3)–Me(2)	115.9 (2.5)
Me(1)–C(2)–O(2)	118.4 (2.3)	O(2)–C(3)–Me(3)	114.3 (2.3)
Me(1)–C(2)–C(3)	121.2 (2.7)	Me(2)–C(3)–Me(3)	112.8 (2.8)

X-Ray Crystallographic Data. A single crystal of the compound $C_6H_{11}NO_2$, mp 157–158 °C, d = 1.14, was mounted on a glass fiber and placed on a four-circle diffractometer and submitted to a routine crystal and molecular structure determination. The data fit obtained indicated that the compound should be considered the epoxyhydroxyimine (**7**) rather than the epoxyamide (**8**). The molecular structure is depicted in Figure 1, and pertinent bond angles and distances are listed in Tables III and IV.

Acknowledgments. We would like to thank Dr. R. A. Jacobson and the members of his group for the use of the X-ray diffractometer. This work was supported by U.S. Department of Energy, Division of Basic Energy Sciences.

Registry No.—**1**, 115-22-0; **3**, 66483-65-6.

Supplementary Material Available: Complete details of the structural determination of **7**, including procedure, *F* tables, and final positional and thermal parameters (3 pages). Ordering information is given on any current masthead page.

References and Notes

(1) J. E. Powell, H. R. Burkholder, and J. L. Farrell, *J. Chromatogr.*, **57**, 309 (1971).
(2) J. E. Powell, S. Kulprathipanja, D. A. Johnson, and H. R. Burkholder, *J. Chromatogr.*, **74**, 265 (1972).
(3) J. Cantacuzène and D. Ricard, *Bull. Soc. Chim. Fr.*, 1587 (1967).
(4) H. Meyer, *Monatsh. Chem.*, **27**, 1085 (1906).
(5) O. N. Wallach, *Justus Liebigs Ann. Chem.*, **248**, 165 (1888).
(6) P. Delbaëre, *Bull. Soc. Chim. Belg.*, **51**, 1 (1942).
(7) J. D. Edwards, Jr., T. Hase, and N. Ichikawa, *J. Heterocycl. Chem.*, **4**, 487 (1967).

Proton and Carbon-13 Nuclear Magnetic Resonance Spectra of Para-Bisannelated Benzenes

Randolph P. Thummel* and Wutichai Nutakul

Department of Chemistry, University of Houston, Houston, Texas 77004

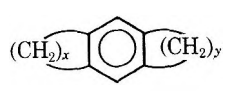
Received January 12, 1978

A complete proton and carbon-13 NMR analysis has been carried out for a series of benzo[1,2:4,5]dicycloalkenes where the fused cycloalkene portions contain all possible combinations of four-, five-, and six-membered rings. With decreasing size of the annelated rings the chemical shift of the unsubstituted aromatic carbon moves upfield and the bridgehead carbons move downfield. The aromatic proton chemical shift of the benzocyclobutene derivatives show anomalous behavior but the aromatic C–H coupling constant increases very consistently with decreasing size of the annelated rings. Comparison is made with the methylenecycloalkanes and interpretations are set forth in terms of local anisotropy effects as well as a rehybridization theory associated with bond angle distortions. CNDO/2 calculations lend support to these observations.

The chemical and physical properties of the benzocycloalkenes have been the subject of a variety of investigations.[1] These systems present a convenient means for studying the effect of regularly increasing steric strain on a simple aromatic nucleus without complicating or competing electronic perturbations. Manatt and Cooper have reported a detailed analysis of the ^{1}H NMR spectra of the benzocycloalkenes with particular regard to changes in proton–proton spin–spin couplings with changes in strain.[2] They conclude that although certain definite trends are present no direct correlation with "Mills–Nixon" type bond alternation can be made without more accurate structural information.

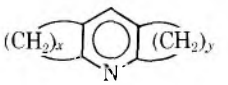
^{13}C NMR provides a more sensitive probe of nuclear shielding effects and affords a useful correlation to ^{1}H NMR data. An early report on the carbon chemical shifts of the benzocycloalkenes misassigned the unsubstituted aromatic carbons.[3] This situation was later corrected by two independent groups utilizing a variety of instrumental techniques as well as specifically deuterated or fluorinated derivatives.[4,5] General trends were pointed out in that the bridghead carbon atom chemical shifts move downfield with increasing strain thus evidencing a deshielding effect. Similarly, the aromatic carbons ortho to the fused ring move upfield with increasing strain. Benzocyclopropene does not correlate well with its higher homologues and this behavior is attributed to the substantial shielding effect of the cyclopropene ring system.[6] Semiempirical[7] as well as ab initio[8] theoretical treatments have afforded some accordance with experimental results. It is still not clear, however, to what extent the observed shielding trends for strained aromatic systems depend upon changes in bond order, charge density, or rehybridization effects.[9]

In a recent paper we reported an interesting anomaly regarding the aromatic proton chemical shifts and ^{13}C–H coupling constants of the series of para-bisannelated benzenes **1–3**.[10] As the size of the rings fused to benzene is decreased the ^{13}C–H coupling constant is observed to increase (Table II). Such an increase has often been associated with an increase in s character of the bond in question.[11] This observation is consistent with a rehybridization theory set forth by Streitweiser[12] and also by Finnegan[13] in which it is claimed that for small ring fused benzocycloalkenes the bridgehead carbon



1, $x = 2; y = 2$
2, $x = 2; y = 3$
3, $x = 3; y = 3$
4, $x = 2; y = 4$
5, $x = 3; y = 4$
6, $x = 4; y = 4$

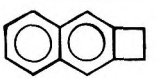
rehybridizes to use orbitals of higher p character in bonding to the small ring. This leaves an orbital of higher s character to bond to the ortho carbon which results in an inductive polarization of the ortho aromatic C–H bond evidenced by the increased ^{13}C–H coupling constant. Such polarization should result in an increase in the acidity of the aromatic proton and therefore a lower field chemical shift. What is observed, instead, is a substantial shift to higher field from δ 7.08 for **3** to δ 6.64 for **1**. On the other hand, a similar study in the pyridine



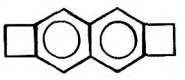
7, $x = 3; y = 3$
8, $x = 3; y = 4$
9, $x = 4; y = 4$

series **7–9** shows a consistent downfield shift for the aromatic proton from δ 7.02 for **9** to δ 7.30 for **7**.[14]

It therefore became of interest to extend the benzene study through the higher homologues **4–6**, thus providing a series consisting of all possibilities of para-bisannelated benzenes in which the fused rings contain four, five, or six carbon atoms. The analysis of trends resulting from strain effects on the NMR spectra should be more reliable than in the simple monoannelated series benzocyclobutene, indan, tetralin where only three molecules are available for comparison. Cyclopropene-fused analogues have been purposely omitted due to the complicating electronic features mentioned above. A parallel study comparing naphtho[*b*]cyclobutene (**10**) with the corresponding naphtho[*b*,*e*]dicyclobutene (**11**) has dem-



10



11

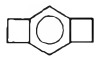
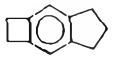
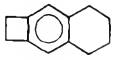
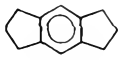
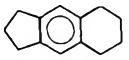
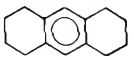
onstrated that strain effects evidenced by the fusion of one small ring are amplified by the linear fusion of a second small ring.[15]

Assignment of Chemical Shifts

As compared to the benzocycloalkenes, the assignment of carbon resonances in the benzodicycloalkenes is considerably simplified by the additional degree of symmetry inherent in systems **1**, **3**, and **6**. Benzo[1,2:4,5]dicyclobutene (**1**) shows only two aromatic and one aliphatic resonance. In the proton-coupled spectrum, the unsubstituted aromatic carbon splits into a doublet, assuring its identity. At the same time the bridghead aromatic carbon of **1** (B4) shows a four-line pattern due to long-range coupling (ca. 2.5 Hz) with the aromatic and benzylic protons. This same characteristic pattern appears clearly in the proton-coupled spectra of **2** and **4** assuring the assignment of their cyclobutene bridgehead carbons. The

0022-3263/78/1943-3170$01.00/0

Table I. Carbon-13 and Proton Chemical Shifts of Benzo[1,2:4,5]dicycloalkenes (in ppm Downfield from Me_4Si)[a]

	registry no.	carbons									protons					
		A	B4	B5	B6	4α	5α	5β	6α	6β	A	4α	5α	5β	6α	6β
 1	1610-51-1	117.3	143.4			29.3					6.64	2.99				
 2	60582-10-7	118.9	143.1	142.1		28.5	33.1	25.3			6.91	3.08	2.86	2.00		
 4	65957-33-7	122.9	142.9		135.6	29.2			30.0	23.3	6.68	3.04			2.67	1.69
 3	495-52-3	120.0		141.9			32.4	25.8			7.08		2.85	2.05		
 5	1624-25-5	124.8		141.5	134.7		32.5	25.7	29.6	23.6	6.91		2.82	2.01	2.74	1.76
 6	1079-71-6	134.1			129.3				28.9	23.4	6.74				2.67	1.74

[a] A = aromatic carbon or proton. B4, B5, B6 = bridgehead carbon fused to four-, five-, or six-membered ring. 4, 5, 6 (α or β) = α or β methylene carbon or proton in the four-, five-, or six-membered ring.

long-range coupling exhibited by cyclopentene and cyclohexene bridgehead carbons is more complex and less well resolved due to additional coupling with the nonbenzylic methylene protons. Further support for the assignment of bridgehead carbons in the unsymmetrically fused benzenes **2, 4,** and **5** comes from the close analogy of their chemical shifts with the more symmetrical homologues **1, 3,** and **6.** With no attempt being made to normalize relaxation time effects or to suppress the Nuclear Overhauser effect, the aromatic carbon is always found to be the most intense downfield peak even when statistically outnumbered 2:1 by the bridgehead carbons.

The aliphatic ring carbons of **1, 3,** and **6** are also assigned with comparative ease. The benzylic methylene carbons appear at lower field than their nonbenzylic counterparts. Again, assignments for the unsymmetrically annelated systems were made by close analogy with their more symmetrical homologues.

The proton-coupled spectra showed downfield doublets for the aromatic C–H coupling and upfield triplets for the aliphatic methylenes. Of the aliphatic couplings, only those on the four-membered rings vary significantly from the range of 124–129 Hz. In all cases, fine structure resulting from long-range effects was observed but detailed analysis was not attempted at this time.

The ^1H NMR spectra were assigned with little difficulty. Each system showed one sharp aromatic singlet downfield. The cyclobutene methylene appeared as a slightly broadened singlet, while the remaining benzylic protons gave multiplets in the region of δ 2.67–2.86 and the nonbenzylic methylenes appeared at δ 1.69–2.05. Analysis of the proton–proton couplings was not carried out although J values of about 7.5 Hz were typical.

Discussion of NMR Data

The ^{13}C chemical shifts for the benzo[1,2:4,5]dicycloalkenes show very smooth and consistent trends throughout the homologous series (see Table I). The unsubstituted aromatic carbon (A) moves upfield with increasing strain from a value of 134.1 ppm for **6** to 117.3 ppm for **1.** Compound **4,** in which the annelated rings differ by two methylene units, is consistent in both the series **6** > **5** > **4** and **4** > **2** > **1** where one ring is held constant and the other is varied. The bridgehead carbon chemical shifts move downfield with decreasing size of the annelated ring from a high field value of 129.3 ppm for **6** to 143.4 ppm for **1.** The bridgehead carbons of a ring fused to one side of the benzene nucleus are even sensitive to changes in the ring fused to the other side. In the series **6, 5, 4; 5, 3, 2;** and **4, 2, 1** small downfield shifts are observed for the bridgehead carbons of the ring whose size is held constant as the size of the other ring is decreased. It should be noted that the olefinic resonances of the series cyclohexene (δ 126.5), cyclopentene (δ 129.9), cyclobutene (δ 136.3) also move downfield with increasing strain[16] although the magnitude of the overall shift is somewhat less. The aliphatic methylene carbons do not show any very distinctive or characteristic variation, exhibiting chemical shifts that correlate reasonably well with those observed for the corresponding cycloalkenes.[16]

Table II. Aromatic ^{13}C–H Coupling Constants for Benzo[1,2:4,5]dicycloalkenes (in Hz ±0.4)[a]

compd	A	4α	5α	5β	6α	6β
1	160.2	138.4				
2	158.7	137.6	129.4	128.9		
4	157.3	136			124	126
3	155.1		127.5	126.6		
5	153.8		128.0	126.9	125.6	127.6
6	152.3				127.0	127.5

[a] A = aromatic carbon or proton. B4, B5, B6 = bridgehead carbon fused to the four-, five-, or six-membered ring. 4, 5, 6 (α or β) = α or β methylene carbon or proton in the four-, five-, or six-membered ring.

The aromatic proton chemical shifts for the series **1–6** show the lowest field peak at δ 7.08 for **3** and high field values of δ 6.64 for **1** and δ 6.75 for **6.** The unsymmetrical systems **2** and **5** fall in between, both showing a peak at δ 6.91 (Table II). Compound **4,** to which is fused both a four- and a six-membered ring, shows an aromatic resonance at δ 6.68, intermediate between the values observed for **1** and **6.**

The aromatic C–H coupling constant increases very consistently from a low value of 152.3 Hz for **6** to 160.2 Hz for **1.** These values may be compared with the J_{CH} value for durene (148.1 Hz) and that of benzene (159 Hz). To a first approxi-

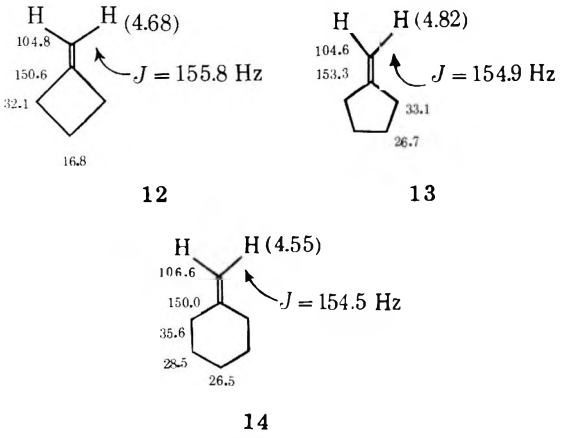


Figure 1. NMR data for methylenecycloalkanes (in ppm, proton chemical shifts in parentheses).

mation one might attribute the observed increments in J_{CH} to a lessening of the alkyl inductive effect. The larger coupling constants also reflect the higher degree of s character associated with the bond in question. The same trend of increasing aromatic C–H coupling has been observed along the benzocycloalkene series increasing from a value of 155 Hz for tetralin to a value of 162 Hz for benzocyclobutene.[4]

Any attempt to analyze the chemical shift trends exhibited by the aromatic carbon and proton as well as the corresponding coupling between these atoms for the series of benzo[1,2:4,5]dicycloalkenes must confront a variety of potential influencing factors. As was already mentioned, there are rehybridization effects functioning in the σ framework. Anisotropy effects could result either from perturbations of the aromatic ring current or simply from factors involving the local environment of the C–H bond. Finally, geometric distortions of the benzene ring involving changes in bond lengths and angles could be important.

As was stated previously, rehybridization of the bridgehead carbon atom of a benzocycloalkene would cause the orbital used in bonding to the adjacent unsubstituted aromatic carbon to become higher in s character as the size of the fused ring is decreased from six carbons to four. According to Streitweiser, this effect would then cause the neighboring carbon to contribute an orbital higher in p character to preserve the C–C bond order.[12] Such rehybridization would therefore leave the aromatic C–H bond enriched in s character and polarized toward carbon. Such polarization might explain the higher field shift of this carbon atom with decreasing size of the fused rings on benzene. Also consistent with this model is the observed increase in the aromatic C–H coupling constant. The aromatic proton chemical shift moves downfield along the series **6, 5, 3,** again consistent with increasing polarization of the C–H bond, but then anomalously moves upfield in the cyclobutene-fused systems **1, 2,** and **4.**

A useful model for a portion of the benzocycloalkenes would be the methylenecycloalkanes **12–14** (Figure 1). The orientation of the vinylic hydrogens of these molecules with respect to the cyclic portion of the system should be quite similar to the orientation of the aromatic protons of **1–6** with respect to the fused rings. Although there appears to be little discernible trend or relationship between the ^{13}C chemical shifts of **12–14** with **1–6,** the vinylic ^{13}C–H coupling constant is seen to increase with decreasing ring size although much less dramatically than for the bisannelated compounds. Most noticeably, the proton chemical shifts show the same unusual behavior with a decided downfield shift apparent for methylenecyclopentane. Therefore the possibility cannot be ignored that this shift is partly attributable to a local anisotropy effect caused by the orientation of the small ring rather than any perturbation of the aromatic ring current.

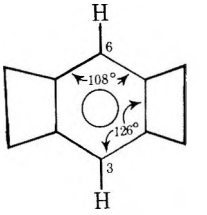


Figure 2. Aromatic bond angles in benzo[1,2:4,5]dicyclobutene (ref 17).

Table III. CNDO Calculated s-Orbital Overlap for Varying Benzene Geometries

internal C_a–C_b–C_c bond angle (θ), deg	$P^2_{C_b(s)H_b(s)}$	internal C_a–C_b–C_c bond angle (θ), deg	$P^2_{C_b(s)H_b(s)}$
108	0.3169	122	0.2625
112	0.3020	124	0.2535
116	0.2869	126	0.2447
120	0.2707		

An X-ray crystal study of **1** has shown a severe pinching effect to be imposed on the aromatic ring by the fused cyclobutene rings. This pinching results in an opening of the interior bridgehead angle to 126° and a closing down of the interior angle at the unsubstituted aromatic carbon to 108°.[17] The net result of this distortion is to move carbons 3 and 6 and their attached hydrogens away from the geometric center of the molecule. Such a move should decrease the deshielding effect experienced by this proton and perhaps account for its upfield chemical shift.

To test the effect of these geometric distortions on a simple benzene nucleus, we carried out CNDO calculations for a set of model benzene systems in which the internal angles of a planar benzene ring were modified from 120° at all six carbons to the limiting values shown for the structure in Figure 2. All bond lengths were held constant with C–C equal to 1.39 Å and C–H equal to 1.09 Å. The square of the carbon-s hydrogen-s bond order should thus be proportional to s character and thereby related to the ^{13}C–H coupling constant for this same bond.[18] Table III presents the results of these calculations and demonstrates clearly that as an internal C_a–C_b–C_c benzene bond angle (θ) is compressed, the s character of the C_b–H_b bond increases substantially in very good accord with what is observed for compound **1.** The relationship between angle θ and $P^2_{C_b(s)H_b(s)}$ is almost linear. It will be of interest to design systems in which a proton is attached to the apical carbon of an expanded benzene bond angle to see if it exhibits an unusually small ^{13}C–H coupling constant.

Experimental Section

The preparation of benzodicycloalkenes 1–4 has been previously described.[10,15] Clemmensen reduction[19] of 6,7-trimethylene-1-tetralone[20] gave a 77% yield of 6,7-trimethylene-1,2,3,4-tetrahydronaphthalene (**5**), bp 90–95 °C (0.15 mm) (lit.[21] bp 125–126 °C (6 mm)). Similar Clemmensen reduction of 6,7-tetramethylene-1-tetralone[20] gave an 80% yield of 1,2,3,4,5,6,7,8-octahydroanthracene (**6**), bp 128–135 °C (0.3 mm), mp 73–74 °C (lit.[22] mp 73–74 °C). Methylenecyclobutane was prepared from pentaerythrityl tetrabromide according to the procedure of Roberts and Sauer.[23] Methylenecyclopentane was obtained from Chemical Samples Co., Columbus, Ohio 43220. Methylenecyclohexane was prepared by the Wittig reaction of methylenetriphenylphosphorane and cyclohexanone.[24]

^1H and ^{13}C NMR spectra were obtained at 32 °C for 5–10% solutions in $CDCl_3$ and chemical shifts in ppm are referred to internal Me_4Si. The proton spectra were measured at 100.06 MHz and the carbon-13 spectra were measured at 25.15 MHz with a flip angle of

20–40° and a 3–8 s delay time. All spectra were recorded on a Varian Associates XL-100 spectrometer equipped with a Nicolet TT-100 Data System and an NT-440 Multinuclear Probe. Slight deviations of the ^{13}C–H couplings for compounds 1–3 from earlier reported values[10] obtained from ^{13}C satellites in the ^{1}H NMR spectra are well within the range of experimental error.

Molecular Orbital Calculations were carried out using the CNDO/2 program (No. 141) from the Quantum Chemistry Program Exchange, Chemistry Department, Indiana University.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. We would also like to thank Mr. Steven Silber for his assistance in obtaining NMR spectra. The Varian XL-100 NMR spectrometer was obtained with a major equipment grant from the National Science Foundation.

Registry No.—**12,** 1120-56-5; **13,** 1528-30-9; **14,** 1192-37-6.

References and Notes

(1) For leading references see P. J. Garratt and D. N. Nicolaides, *J. Org. Chem.*, **39,** 2222 (1974), as well as ref 2 and 6 below.
(2) M. A. Cooper and S. L. Manatt, *J. Am. Chem. Soc.*, **92,** 1605 (1970).
(3) E. L. Motell, D. Lauer, and G. E. Maciel, *J. Phys. Chem.*, **77,** 1865 (1973).
(4) H. Gunther, G. Jikeli, H. Schmickler, and J. Prestien, *Angew Chem., Int. Ed. Engl.*, **12,** 762 (1973).
(5) W. Adcock, B. D. Gupta, T. C. Khor, D. Doddrell, D. Jordan, and W. Kitching, *J. Am. Chem. Soc.*, **96,** 1595 (1974).
(6) W. Adcock, B. D. Gupta, T. C. Khor, D. Doddrell, and W. Kitching, *J. Org. Chem.*, **41,** 751 (1976).
(7) (a) C. S. Cheung, M. A. Cooper, and S. L. Manatt, *Tetrahedron*, **27,** 701 (1971); (b) M. Randic and Z. B. Maksic, *J. Am. Chem. Soc.*, **93,** 64 (1971).
(8) A. Streitweiser, P. H. Owens, R. A. Wolf, and J. E. Williams, *J. Am. Chem. Soc.*, **96,** 5448 (1974).
(9) See for example: (a) A. J. Jones, P. J. Garratt, and K. P. C. Vollhardt, *Angew. Chem., Int. Ed. Engl.*, **12,** 241 (1973); (b) W. M. Beckenbaugh, S. R. Wilson, and P. A. Loeffler, *Tetrahedron Lett.*, 4821 (1972).
(10) R. P. Thummel and W. Nutakul, *J. Org. Chem.*, **42,** 300 (1977).
(11) N. Muller and D. E. Pritchard, *J. Chem. Phys.*, **31,** 768 (1959).
(12) A. Streitweiser, Jr., G. Ziegler, P. Mowery, A. Lewis, and R. Lawler, *J. Am. Chem. Soc.*, **90,** 1357 (1968).
(13) R. A. Finnegan, *J. Org. Chem.*, **30,** 1333 (1965).
(14) R. P. Thummel and D. K. Kohli, *J. Org. Chem.*, **42,** 2742 (1977).
(15) R. P. Thummel and W. Nutakul, submitted for publication.
(16) D. E. Dorman, M. Jautelat, and J. D. Roberts, *J. Org. Chem.*, **36,** 2757 (1971).
(17) J. L. Lawrence and S. G. G. MacDonald, *Acta Crystallogr., Sect. B*, **25,** 978 (1969).
(18) G. E. Maciel, J. W. McIver, Jr., N. S. Ostlund, and J. A. Pople, *J. Am. Chem. Soc.*, **92,** 1 (1970).
(19) L. F. Feiser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley, New York, N.Y., 1968, p 1287.
(20) H. Christol, D. D. Koulodo, M. Mousseron, and F. Plenat, *Bull. Soc. Chim. Fr.*, 1576 (1960).
(21) S. Chandra and S. Gupta, *J. Indian Chem. Soc.*, **16,** 89 (1939).
(22) G. Schroeter, *Chem. Ber.*, **57B,** 2003 (1924).
(23) J. D. Roberts and C. W. Sauer, *J. Am. Chem. Soc.*, **71,** 3925 (1949).
(24) G. Wittig and U. Schoellkopf, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 751.

Addition of Dichloroketene to Silyl Enol Ethers. Synthesis of Functionalized Cyclobutanones[1]

Larry R. Krepski and Alfred Hassner*

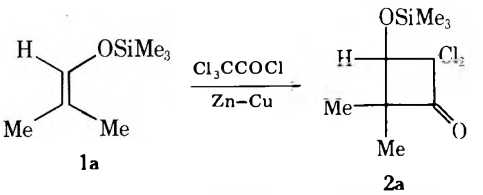
Department of Chemistry, University of Colorado, Boulder, Colorado 80302, and Department of Chemistry, State University of New York at Binghamton, Binghamton, New York 13901

Received October 27, 1977

Dichloroketene, generated from trichloroacetyl chloride and activated zinc, has been found to react readily with silyl enol ethers. In most cases, good yields of 3-siloxy-substituted dichlorocyclobutanones could be isolated. The reaction appears to be both regio- and stereospecific. Mild acid hydrolysis of the siloxycyclobutanones afforded the corresponding 3-hydroxydichlorocyclobutanones. In some cases, cyclobutane ring opening or elimination to generate a dichlorocyclobutenone was observed. The silyl enol ethers derived from acetophenone and pinacolone, on the other hand, afforded only acyclic products from the dichloroketene. The possibility that these acyclic products may result from ring opening of initially formed cyclobutanones is discussed.

General Reaction Scheme. The cycloaddition of dichloroketene[2] to reactive olefins constitutes a convenient synthesis of cyclobutanones.[3] In view of the considerable synthetic utility of silyl enol ethers[4] as masked enols and our[5] own interest in these species, we investigated the reaction of dichloroketene with silyl enol ethers as a possible route to functionalized cyclobutanones.

When trichloroacetyl chloride was slowly added to a stirred mixture of the trimethylsilyl enol ether **1a** and activated zinc in dry ether, a mildly exothermic reaction occurred and a one to one adduct was obtained in 92% yield after workup. A strong high-frequency (1805 cm^{-1}) carbonyl absorption in the IR spectrum indicated cyclobutanone **2a** as the product of this cycloaddition (eq 1). Regiochemistry was assigned in accord with known examples of diphenylketene cycloadditions with enol ethers.[6] Several other silyl enol ethers were found to react smoothly with dichloroketene to afford good yields of substituted cyclobutanones (see Table I). The yields are generally higher than in cycloadditions of dichloroketene to simple olefins.



1a **2a** (1)

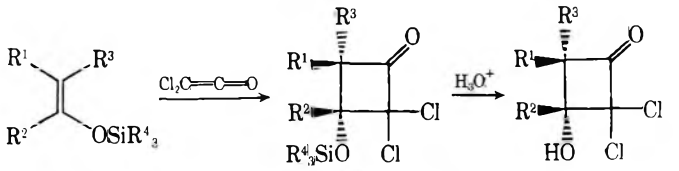
Hydrolysis of the trimethylsilyl group of the cycloadducts was readily accomplished by treating a tetrahydrofuran or methanol solution of the siloxycyclobutanone with dilute hydrochloric acid. As indicated in Table I, this afforded high yields of the hydroxy-substituted cyclobutanones (**3a–f**).

Generation of dichloroketene by the triethylamine dehydrohalogenation of dichloroacetyl chloride in the presence of silyl enol ethers did not lead to cycloadducts. For instance, in the case of **1b,** conversion to cyclopentanone appeared to be the major reaction, accompanied by minor amounts of **4** (eq

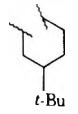
* Address correspondence to State University of New York at Binghamton.

0022-3263/78/1943-3173$01.00/0

Table I

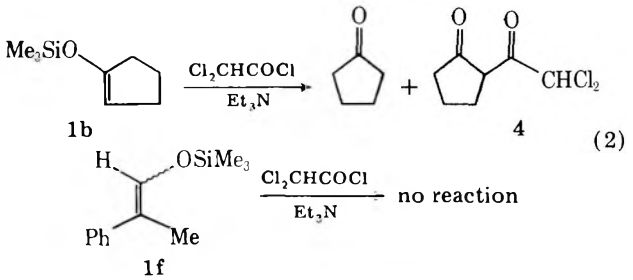


1 2 3

	R1	R2	R3	R4	Registry no.	Yield of 2,[a] %	Registry no.	Yield of 3,[a] %	Registry no.
1a	Me	H	Me	Me	6651-34-9	92[b]	66324-00-3	83	66324-05-8
1b	-(CH2)3-		H	Me	19980-43-9	79	66324-01-4	88	66324-06-9
1c	-(CH2)4-		H	Me	6651-36-1	81	66402-59-3	85	66324-07-0
1d			H	Me	19980-19-9	95[b]	66402-60-6	73	66324-08-1
1e			H	t-Bu(Me)2	66323-98-6	92	66324-02-5	c	
1f[d]	Ph	H	Me	Me		86[b,e]	66324-03-6	85[e]	66324-09-2
1g[f]	H	Ph	Me	Me	66323-99-7	94[f,g]	66324-04-7	h	
(E)-1h	Ph	Me	H	Me	19980-25-7	59[i,j]		k	
(Z)-1h	H	Me	Ph	Me	19980-24-6				

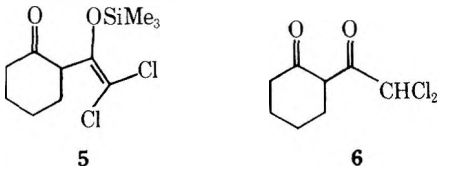
[a] Yield after distillation. [b] Crude yield; attempted distillation led to partial hydrolysis of the trimethylsilyl group. [c] Not hydrolyzed. [d] E/Z ratio was 70:30. [e] Stereochemistry unknown. [f] Apparently stereochemically homogeneous by NMR and GC. [g] Crude yield; attempted distillation led to partial conversion to the ring-opened product 7 (see text). [h] Hydrolysis afforded cyclobutenone 9 (see text) in 78% yield. [i] Adducts are thermally sensitive (see Experimental Section). [j] Ratio of cyclobutanones is identical to E/Z ratio of 1h. [k] Hydrolysis afforded cyclobutenone 10 (see text) in 81% yield.

2). The silyl enol ether **1f** was found to be completely unreactive toward dichloroacetyl chloride and triethylamine.



Therefore, we used the zinc dehalogenation procedure to generate dichloroketene, and in addition we found it advantageous to use the trichloroacetyl chloride within 2 to 3 days of its distillation and zinc within 1 week of its activation. Reactions were conveniently carried out in dry ether. Under these conditions, undesirable partial hydrolysis of silyl enol ethers to the parent carbonyl compounds was avoided. The reactions of dichloroketene with silyl enol ethers were followed by either GC or NMR spectroscopy and were usually complete within 2 to 3 h after addition of the acid chloride. The disappearance of acid chloride and silyl enol ether was monitored by GC; however, nearly all of the siloxycyclobutanone products **2** were found to decompose readily on gas chromatography. Attempted chromatography of **2** on silica gel or neutral alumina also led to extensive decomposition, but purification was achieved by bulb to bulb distillation at reduced pressure. Even under these conditions, however, several of the siloxycyclobutanones suffered partial conversion to the corresponding hydroxycyclobutanones (see Experimental Section).

Siloxycyclobutanone Ring Opening. In the dichloroketene reactions described thus far, the trimethylsilyl enol ether from cyclohexanone, **1c**, was found to be the most sensitive. For example, if trichloroacetyl chloride was not freshly distilled prior to reaction or if the acid chloride was added too rapidly to the suspension of zinc and **1c**, the reaction became quite vigorous and little, if any, cyclobutanone **2c** could be isolated. Instead, products **5** and **6** were formed in high yield. In addition, the hydrolysis of siloxycyclobutanone **2c** to the hydroxycyclobutanone **3c** was found to be extremely erratic. Often, even brief (1 min) treatment of a methanol or tetrahydrofuran solution of **2c** with dilute acid gave exclusively the ring-opened product **6**.

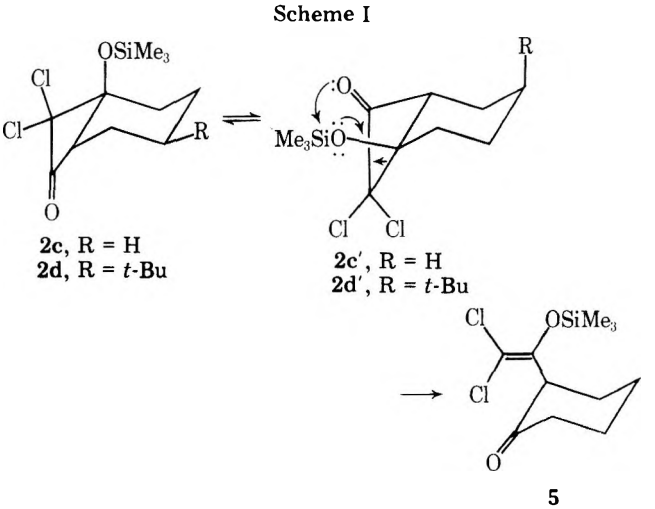


5 6

Enol ether **5** was readily hydrolyzed to **6** with dilute acid. For comparison, compound **6** was also synthesized by an alternative route[7] described by Murai, namely, the reaction of dichloroacetyl chloride with silyl enol ether **1c**.

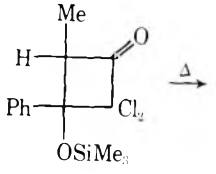
As suggested in Scheme I, the flexibility of the cyclohexyl adduct **2c** may account for its relative instability. In one (**2c'**) of the possible conformations, the system appears to be well set up for a migration[8] of silicon from one oxygen to the other with consequent opening of the four-membered ring. This process may be catalyzed by zinc chloride present in the reaction mixture (see discussion below).

Scheme I

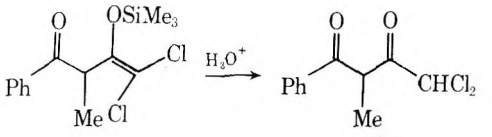


The less conformationally mobile 4-*tert*-butyl analogue **1d**, on the other hand, reacted smoothly with dichloroketene to afford the siloxycyclobutanone **2d**.[9] In no instances were any ring-opened products isolated in this reaction. In contrast to **2c**, the 4-*tert*-butyl analogue **2d** underwent clean hydrolysis to the hydroxycyclobutanone **3d**, a stable crystalline solid. This is attributable to the fact that conformation **2d′**, necessary for the ring-opening process, is unfavorable because of severe diaxial interactions. These results lend credence to the idea that a conformation such as **2c′** is involved in the ring-opening process.

Ring-opening reactions were also observed with the siloxycyclobutanone **2g**. Attempted distillation of **2g** led to partial conversion to the ring-opened product **7** (eq 3). Heating the

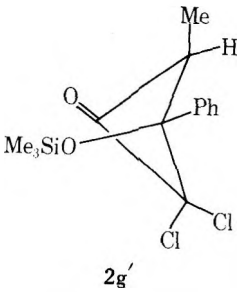


2g



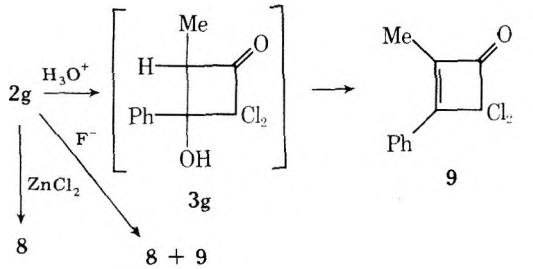
7 **8** (3)

crude product **2g** or the distillate at 200 °C for 2 h led to complete ring opening to **7**. In this case, as for **2c′**, the favorable conformation has the siloxy group axial and the large phenyl substituent equatorial to the puckered cyclobutanone ring (**2g′**).



2g′

Although **7** was readily hydrolyzed to **8** with dilute acid, the siloxycyclobutanone **2g** proved to be resistant to conditions that completely hydrolyzed the other siloxycyclobutanones. Under more rigorous hydrolysis conditions (see Experimental Section), **2g** afforded cyclobutenone **9** in good yield (eq 4);

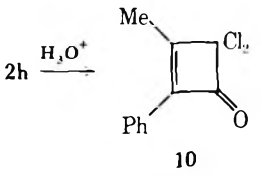


8 **8 + 9** **3g** **9** (4)

evidently, the hydroxy intermediate **3g** underwent loss of water (in a diaxial fashion from **2g′**).

Treatment of siloxycyclobutanone **2g** with tetrabutylammonium fluoride[10] in tetrahydrofuran solution at room temperature led to the rapid formation of the ring-opened product **8** and cyclobutenone **9**. Finally, complete ring opening of **2g** to afford **8** could be accomplished by stirring an ether solution of **2g** and zinc chloride at room temperature overnight.

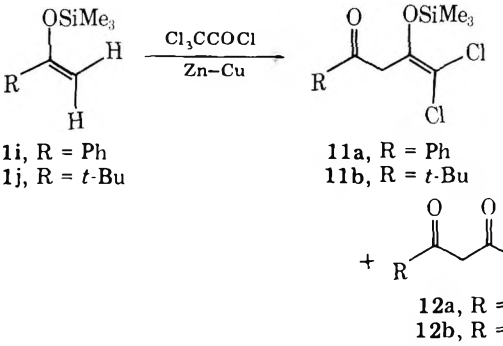
In contrast to **2g**, a mixture of siloxycyclobutanones (*E*)- and (*Z*)-**2h** was readily hydrolyzed with dilute acid. Again in



10 (5)

this case, however, hydroxycyclobutanones were not isolated, but rather the cyclobutenone **10**[12] (eq 5).

The reaction of dichloroketene with silyl enol ethers **1i** and **1j**, from acetophenone and pinacolone, respectively, took a different course (eq 6). No cyclobutanone products could be



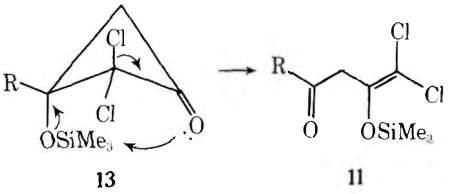
1i, R = Ph
1j, R = *t*-Bu

11a, R = Ph
11b, R = *t*-Bu

12a, R = Ph
12b, R = *t*-Bu (6)

detected in either case. Instead, the acylic products **11** and **12** were isolated in high yields. That these products were not arising from the workup was demonstrated by NMR examination of the reaction mixtures prior to completion. Treatment of **11** with dilute acid led to **12**. Attempts to isolate cyclobutanones from the reaction of dichloroketene with **1i** at lower temperatures were to no avail.

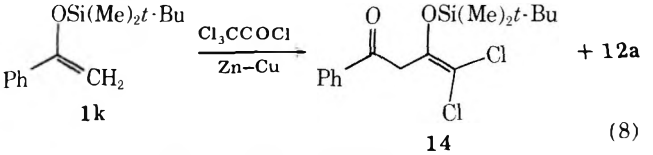
One explanation for the formation of products **11** is a ring opening of an initially formed cyclobutanone species **13** (eq 7). The bulky substituent (R = Ph or *tert*-butyl) might prefer



13 **11** (7)

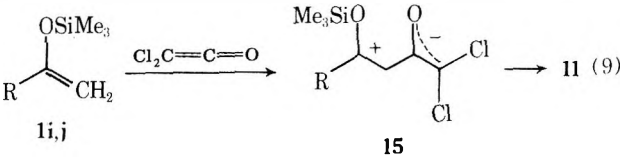
to occupy an equatorial conformation, forcing the trimethylsiloxy group into an axial conformation. Thus, a situation similar to that suggested for the cyclohexyl system **2c** might occur; attack of carbonyl oxygen on silicon might initiate ring opening to afford the observed products.

Since the *tert*-butyldimethylsilyl[10] group is much less susceptible to nucleophilic attack than the trimethylsilyl group, it was thought that enol ether **1k** might yield a stable cyclobutanone. However, this was found not to be the case (eq 8), and enol ether **1k** afforded only **14** and **12a** (R = Ph) under the usual reaction conditions.



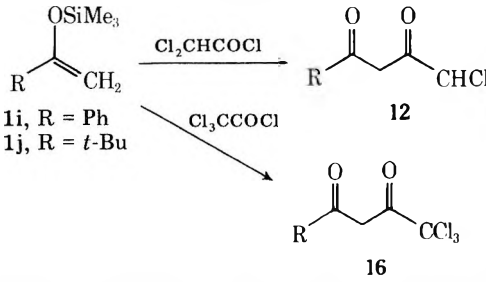
1k **14** + **12a** (8)

Another possibility for the generation of acyclic products in the reactions of **1i** and **1j** with dichloroketene is that cyclobutanone formation is not involved at all and that dichloroketene simply acylates the enol ether to give an initial zwitterionic species **15** which collapses to **11** (eq 9). The ste-



1i,j **15** **11** (9)

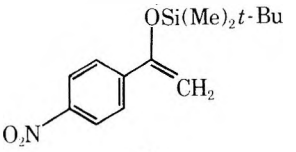
reospecificity of the cycloaddition observed for **1h** (see below) would speak against an ionic intermediate. On the other hand, Murai has reported[7] that silyl enol ethers **1i** and **1j** react with di- and trichloroacetyl chlorides to afford, after hydrolysis, fair (60–67%) yields of the 1,3-diketones **12** and **16**, respectively (eq 10). Although no products corresponding to **16** were



(10)

detected in our reactions (by mass spectral analysis), dichloroketene would of course be expected to be a much more reactive acylating reagent than either di- or trichloroacetyl chloride.

The possibility of destabilizing a zwitterionic species **15** with an electron-withdrawing substituent on the aromatic ring was investigated next. However, silyl enol ether **11** was unchanged

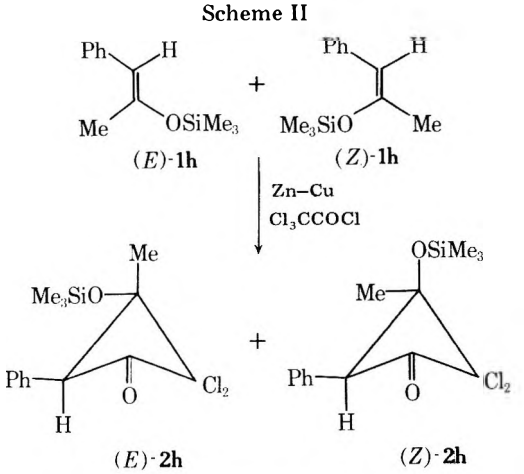


11

after a 3-day reaction with dichloroketene, as evidenced by NMR examination of aliquots from the reaction mixture, and therefore did not provide any positive evidence.

Stereochemistry. An opportunity to study the stereochemistry of the reaction of dichloroketene with silyl enol ethers was presented by the silyl enol ethers **1h**, derived from phenylacetone. The isomeric ratio is clearly evident from the NMR spectrum since the chemical shifts of the vinyl protons are distinct (δ 5.7 for the *E* isomer and δ 5.4 for the *Z* isomer).[11] Since the *E* and *Z* isomers could not be completely separated by either GC or spinning band distillation, various *E*/*Z* mixtures of **1h** were allowed to react with dichloroketene. This led to mixtures of cyclobutanones [(*E*)- and (*Z*)-**2h**] (Scheme II), the ratios of which were identical with the *E*/*Z* ratios of starting material (**1h**). These results suggest that an intermediate dipolar species capable of free rotation is not involved in the cycloadditions described thus far and that the reaction

Scheme II



E/*Z* 1h	*E*/*Z* 2h
1:16	1:16
1:1	1:1
7:1	7:1

of dichloroketene with these silyl enol ethers is a concerted stereospecific cycloaddition.

The siloxycyclobutanones (*E*)- and (*Z*)-**2h** were also found to be sensitive to heating, but ring-opened products, if formed, were not isolated. Thus, bulb to bulb distillation [120 °C (0.02 mm)] of a mixture of (*E*)- and (*Z*)-**2h** led to less than 70% recovery of material, although the IR and NMR spectra of crude and distilled products were superimposable; a dark tar remained in the distillation flask.

In summary, silyl enol ethers have been found to react readily with dichloroketene, affording in most cases good yields of cyclobutanones. Although the regiochemistry of the cyclobutanones suggests electronic control with the possibility of a dipolar intermediate, the stereochemical results indicate that such species do not have an appreciable lifetime.

Experimental Section[13]

General. The silyl enol ether adducts **2** were either partially hydrolyzed to the alcohols upon attempted purification or underwent partial ring opening or elimination during attempted distillation. Hence, they were not submitted to elemental analysis but were identified by consistent IR, NMR, and mass spectra and hydrolysis to **3**.

Trichloroacetyl Chloride. This procedure is a slight modification of the literature procedure.[14]

To a stirred mixture of 97.0 g (0.59 mol) of Cl_3CCO_2H and 3.0 mL of DMF at 85 °C was added 51.0 mL (84.5 g, 0.71 mol) of thionyl chloride dropwise. When addition was complete, heating at this temperature was continued for 2 h. The bath temperature was lowered to 60–65 °C, and the product was distilled (40–45 °C at 20–25 mm) and collected in an ice-cooled receiver. The first few milliliters were discarded. The product was distilled one more time at reduced pressure and finally at atmospheric (625 mm) pressure (collected at 108–110 °C) to yield 74.3 g (70%) of trichloroacetyl chloride.

Activation of Zinc. This procedure is a slight modification of the procedure of Brady.[2a]

A stirred suspension of 10.0 g (0.15 mol) of zinc dust in 40 mL of water was degassed by bubbling N_2 through it for 15 min. Then 750 mg (4.7 mmol) of $CuSO_4$ was added at once. The black suspension was stirred while N_2 bubbled through it for 45 min more. The Zn–Cu couple was collected on a sintered glass funnel under a stream of N_2 and washed successively with 100 mL of degassed water and acetone. The Zn–Cu couple was transferred to a small flask under a stream of N_2 and dried at reduced pressure (0.2 mm) for 2 h. Nitrogen was admitted to the system when the vacuum was broken, and the Zn–Cu couple was stored under N_2 in a tightly stoppered flask.

General Procedure for the Addition of Dichloroketene to Silyl Enol Ethers. The trimethylsilyl enol ethers were prepared by House's procedure[11] and have been previously described. Trichloroacetyl chloride was used within 2 to 3 days of its distillation and zinc within 1 week of its activation.

A 100-mL three-neck flask equipped with a condensor, addition funnel, magnetic stirrer, and N_2 inlet was flame dried while being purged with N_2. When cool, the flask was charged with 5.0 mmol of the silyl enol ether, 7.5 mmol of activated zinc, and 40 mL of anhydrous ether. The mixture was stirred under N_2, and a solution of 6.5 mmol of Cl_3CCOCl in 15 mL of anhydrous ether was added dropwise over a 45-min period. Stirring at room temperature was continued until NMR or GC (a 5 ft × 0.25 in, 10% DC-550 column was used) analysis of aliquots indicated that the silyl enol ether had been consumed. The reaction mixture was then filtered through a pad of Celite and the unreacted zinc washed with a few milliliters of ether. The solution was concentrated in vacuo to ca. 25% of its original volume, an equal volume of pentane was added, and the solution was stirred for a few minutes to precipitate the zinc salts. The solution was decanted from the residue, washed with a cold saturated $NaHCO_3$ solution and brine, and dried over K_2CO_3, and the solvent was removed in vacuo to afford the crude product, which was purified by bulb distillation at reduced pressure.

General Procedure for the Hydrolysis of the Trimethylsilyl Group of the Dichloroketene Adducts. Hydrolysis of the trimethylsilyl group was accomplished by dissolving the dichloroketene adduct in methanol or THF (ca. 1 mmol/10 mL), adding a few drops of a 5% HCl solution, and stirring at room temperature for 1 h. The solvent was removed in vacuo, the residue was dissolved in ether, and the solution was washed with water and brine and dried over K_2CO_3.

The solvent was removed in vacuo and the product purified by bulb to bulb distillation at reduced pressure or by recrystallization.

2,2-Dichloro-3-trimethylsiloxy-4,4-dimethylcyclobutanone (2a). The reaction of 2.0 g (13.8 mmol) of trimethylsilyl enol ether **1a** by the general procedure (9 h) afforded 3.25 g (92%) of **2a** as a yellow oil. Attempted distillation of **2a** led to partial hydrolysis of the trimethylsilyl group. Siloxycyclobutanone **2a:** IR (neat) 1805, 1270, and 860 cm^{-1}; NMR (CCl_4) δ 4.22 (s, 1 H), 1.27 (s, 3 H), 1.17 (s, 1 H), and 0.17 (s, 9 H); MS *m/e* (%) 256 (M + 2, 1.1), 254 (M^+, 1.7), 241 (2.2), 239 (3.2), 193 (4.0), 191 (12.3), 144 (27.2), 129 (14.3), 75 (62.3), 73 (100), and 70 (71.2).

2,2-Dichloro-3-hydroxy-4,4-dimethylcyclobutanone (3a). Hydrolysis of 1.0 g (3.9 mmol) of siloxycyclobutanone **2a** afforded 0.71 g (99%) of a yellow oil which was purified by bulb to bulb distillation (oven 60 °C, 5 mm) to afford 0.59 g (83%) of **3a:** IR (neat) 3600–3350, 1799, 1470, 1130, and 860 cm^{-1}; NMR (CCl_4) δ 4.40 (s, 1 H), 3.9 (broad, OH, 1 H), 1.41 (s, 3 H), and 1.31 (s, 3 H); MS *m/e* (no M^+) 119 (3.1), 114 (1.4), 112 (2.3), 109 (6.8), 72 (17.8), 71 (10.3), 70 (100), 57 (13.3), 44 (7.3), 43 (17.8), 42 (35.7), and 41 (20.6).

Anal. Calcd for $C_6H_8O_2Cl_2$: C, 39.37; H, 4.40. Found: C, 39.28; H, 4.39.

7,7-Dichloro-1-trimethylsiloxybicyclo[3.2.0]heptan-6-one (2b). The reaction of 5.0 g (32 mmol) of trimethylsilyl enol ether **1b** by the general procedure (2 h) afforded 7.2 g (85%) of **2b** as a viscous orange oil. Bulb to bulb distillation (oven 95 °C, 0.02 mm) afforded 6.7 g (79%) of **2b** as a colorless oil which solidified upon refrigeration: IR (neat) 1805 cm^{-1}; NMR (CCl_4) δ 3.6 (broad, 1 H), 2.77–1.43 (6 H), and 0.25 (s, 9 H); MS *m/e* 268 (M + 2, 2.4), 266 (M^+, 3.6), 253 (3.5), 251 (5.4), 225 (4.7), 223 (7.1), 205 (7/[(= 2]3 (23.2), 156 (30.4), 95 (16.1), 93 (32.1), 79 (46.4), 75 (32.1), and 73 (100).

7,7-Dichloro-1-hydroxybicyclo[3.2.0]heptan-6-one (3b). Hydrolysis of 66.0 g (22.6 mmol) of siloxycyclobutanone **2b** afforded 3.87 g (88%) of **3b** which was recrystallized from hexane to afford 3.0 g (68%) of **3b:** mp 57–58 °C; IR (CCl_4) 3560, 1800, 1330, and 110 cm^{-1}; NMR (CCl_4) δ 3.60 (broad, 1 H), 3.23 (broad, OH, 1 H), and 2.8–1.0 (6 H); MS *m/e* 196 (M + 2, 1.4), 194 (M^+, 2.1), 160 (11.6), 158 (17.6), 151 (15.5), 149 (23.5), 133 (6.10), 131 (93.0), 115 (17.6), 113 (52.9), 110 (73.2), 95 (64.7), 85 (88.2), 84 (70.6), 67 (76.5), and 55 (100).

Anal. Calcd for $C_7H_8Cl_2O_2$: C, 43.10; H, 4.13. Found: C, 43.50; H, 4.11.

Generation of Dichloroketene from Dichloroacetyl Chloride in the Presence of 1b. To a stirred solution of 1.0 g (6.4 mmol) of silyl enol ether **1b** and 0.96 mL (1.47 g, 10 mmol) of $Cl_2CHCOCl$ in 30 mL of anhydrous ether was added dropwise a solution of 2.05 mL (1.5 g, 15 mmol) of triethylamine in 15 mL of anhydrous ether. The mixture was stirred for 12 h after addition of the solution was completed and then washed with a 5% HCl solution, a saturated $NaHCO_3$ solution, and brine. The solution was dried over K_2CO_3 and the solvent removed in vacuo to afford 0.62 g of a dark oil, shown to contain mainly (>60%) cyclopentanone by coinjection with an authentic sample into the GC instrument (a 10 ft × 3/8 in, 15% DC-550 column was used for this analysis). At least three minor products were present in the mixture. The presence of **4** in the mixture was implicated by the spectra of the mixture: IR (neat) 3500 tailing to 2500, 1740, 1650–1550, and 1220 cm^{-1}; NMR (CCl_4) δ 12.4 (broad), 6.0 (s), and 3.0–1.2; MS *m/e* 196 and 194. (Compare spectra of **6** below.)

8,8-Dichloro-1-trimethylsiloxybicyclo[4.2.0]octan-7-one (2c). The reaction of 2.0 g (11.7 mmol) of trimethylsilyl enol ether **1c** by the general procedure at 0 °C (3 h) afforded 3.0 g (91%) of **2c** as a viscous yellow oil. Bulb to bulb distillation (oven 110 °C, 0.02 mm) afforded 2.7 g (81%) of **2c** as a slightly yellow oil: IR (neat) 1805, 1270, 1235, and 865 cm^{-1}; NMR (CCl_4) δ 3.7 (broad, 1 H), 2.7–1.2 (8 H), and 0.28 (s, 9 H); MS *m/e* 282 (M + 2, 1.6), 280 (M^+, 2.7), 267 (2.5), 265 (4.1), 219 (5.5), 217 (17.8), 170 (30.1), 155 (15.1), 109 (16.4), 75 (45.2) and 73 (100).

8,8-Dichloro-1-hydroxybicyclo[4.2.0]octan-7-one (3c). Hydroxycyclobutanone **3c** was obtained by a short (45 s) hydrolysis of siloxycyclobutanone **2c** in methanol: IR (CCl_4) 3600–3250, 1805, 1305, 1265, 1230, and 860 cm^{-1}; NMR (CCl_4) δ 3.70 (broad, 1 H), 3.15 (broad, 1 H), and 2.8–1.0 (8 H).

2-(2′,2′-Dichloro-1′-trimethylsiloxyvinyl)cyclohexanone (5). Compound **5** was formed when the Cl_3CCOCl was added too rapidly to a suspension of silyl enol ether **1c** and zinc or when Cl_3CCOCl was used without previous distillation. Compound **5:** IR (neat) 1710, 1620, 1260, 1130, 1050, 980, and 860 cm^{-1}; NMR (CCl_4) δ 3.6 (broad, 1 H), 2.7–1.5 (8 H), and 0.27 (s, 9 H); MS *m/e* 282 (M + 2, 4.3), 280 (M^+, 6.5), 267 (5.8), 265 (9.3), 217 (9.7), 171 (25.8), 155 (9.7), 127 (11.3), 125 (21.0), 95 (6.5), 93 (19.8), 75 (19.4), and 73 (100).

2-Dichloroacetylcyclohexanone (6). Hydrolysis of 1.0 g (3.6 mmol) of **5** afforded 0.72 g (96%) of **6:** IR (CCl_4) 3500 tailing to 2600, 1650–1550, 1270, 1180, 820, and 750 cm^{-1}; NMR (CCl_4) δ 14.6 (broad, 1 H), 6.22 (s, 1 H), and 3.0–1.2 (8 H); MS *m/e* 210 (M + 2, 2.9), 208 (M^+, 4.3), 192 (2.8), 190 (4.1), 165 (12.9), 163 (18.4), 147 (12.2), 145 (36.7), 98 (49.0), 92 (38.8), 91 (32.7), 70 (24.5), and 55 (100).

Preparation of 6 from 1c and Dichloroacetyl Chloride. A solution of 0.5 g (2.9 mmol) of silyl enol ether **1c** and 0.28 mL (0.43 g, 2.9 mmol) of $Cl_2CHCOCl$ in 15 mL of methylene chloride was stirred for 3 days, and then the solvent was removed in vacuo, 10 mL of methanol and 2 drops of a 5% HCl solution were added, and the solution was refluxed for 1 h. The solvent was removed in vacuo to afford 0.53 g of a brown oil, a mixture (ca. 1:1) of cyclohexanone and **6** which was not separated. The spectra of the mixture had absorptions identical with those reported above for **6.**

8,8-Dichloro-1-trimethylsiloxy-4-*tert*-butylbicyclo[4.2.0]-octan-7-one (2d). The reaction of 1.0 g (4.4 mmol) of silyl enol ether **1d** by the general procedure (2 h) afforded 1.4 g of a yellow oil which was purified by bulb to bulb distillation (oven 100 °C, 0.02 mm) to afford 1.25 g of a mixture (ca. 4:1) of **2d** and **3d.** Siloxycyclobutanone **2d:** IR (neat) 1805, 1377, 1270, and 860 cm^{-1}; NMR (CCl_4) δ 3.90–3.40 (1 H), 2.25–0.90 (7 H), 0.93 (s, 9 H), and 0.30 (9 H).

8,8-Dichloro-1-hydroxy-4-*tert*-butylbicyclo[4.2.0]octan-7-one (3d). Hydrolysis of 0.20 g of a mixture of **2d** and **3d** afforded 0.15 g of **3d,** which was recrystallized from hexane to afford 0.12 g of **3d:** mp 118–119 °C; IR (CCl_4) 3550, 1805, and 1377 cm^{-1}; NMR (CCl_4) δ 4.0–3.3 (1 H), 2.90 (broad, OH, 1 H), 2.3–1.2 (7 H), and 1.0 (s, 9 H); MS *m/e* 266 (M + 2, 3.3), 264 (M^+, 5.2), 251 (2.2), 249 (3.3), 203 (8.2), 201 (11.7), 137 (25.2), 69 (23.3), and 57 (100).

Anal. Calcd for $C_{12}H_{18}Cl_2O_2$: C, 54.35; H, 6.84. Found: C, 54.21; H, 6.93.

1-*tert*-Butyldimethylsiloxy-4-*tert*-butylcyclohexene (1e). A solution of 10.0 g (65 mmol) of 4-*tert*-butylcyclohexanone in 40 mL of anhydrous THF was added dropwise to a stirred suspension of 4.0 g (0.1 mol) of potassium hydride in 100 mL of anhydrous THF under N_2. After stirring for 1 h, a solution of 10.6 g (70 mmol) of *tert*-butyldimethylsilyl chloride in 80 mL of anhydrous THF was added dropwise. Stirring was continued for 12 h, excess potassium was destroyed by the cautious addition of a few milliliters of *tert*-butyl alcohol, and the solvent was removed in vacuo. The residue was taken up in 150 mL of ether, and the solution was washed with a 5% HCl solution, a saturated $NaHCO_3$ solution, and brine and dried over K_2CO_3. The solvent was removed in vacuo. Distillation of the residue afforded 10.3 g (59%) of **1e:** bp 100–104 °C (0.7 mm); IR (neat) 1600, 1475, 1375, 1270, 1210, and 900 cm^{-1}; NMR ($CDCl_3$) δ 4.65 (m, 1 H), 2.15–−0.88 (7 H), 0.90 and 0.87 (2 s, 18 H), and 0.08 (s, 6 H).

8,8-Dichloro-1-*tert*-butyldimethylsiloxy-4-*tert*-butylbicyclo[4.2.0]octan-7-one (2e). The reaction of 1.0 g (3.7 mmol) of silyl enol ether **1e** by the general procedure (2 h) afforded 1.4 g of a yellow oil which was purified by bulb to bulb distillation (oven 130 °C, 0.02 mmol) to afford 1.28 g (92%) of **2e:** IR (neat) 1805, 1475, 1375, 1270, 860, and 800 cm^{-1}; NMR (CCl_4) δ 3.92–3.37 (1 H), 2.25–1.1 (7 H), 0.98 (s, 9 H), 0.92 and 0.88 (2 s, 9 H), 0.28 (s, 3 H), and 0.23 (s, 3 H).

2,2-Dichloro-3-trimethylsiloxy-4-methyl-4-phenylcyclobutanone (2f). The reaction of 0.50 g (2.43 mmol) of silyl enol ether **1f** (*E*/*Z* = 70:30)[11] by the general procedure (3 h) afforded 0.66 g (86%) of **2f.** Attempted distillation of **2f** led to partial hydrolysis of the trimethylsilyl group. Siloxycyclobutanone **2f:** IR (neat) 1805, 1265, 1200, 910, 860, 780, and 720 cm^{-1}; NMR (CCl_4) δ 7.32 (s, 5 H), 4.80 (s, 1 H), 1.57 (s, 3 H), and 0.33 (s, 9 H); MS *m/e* (no M^+) 255 (1.7), 235 (2.5), 240 (1.8), 238 (2.8), 208 (18.0), 165 (5.7), 163 (8.3), 134 (23.6), 133 (100), 105 (52.8), 93 (12.5), and 73 (65.3).

2,2-Dichloro-3-hydroxy-4-methyl-4-phenylcyclobutanone (3f). Hydrolysis of 0.50 g (1.58 mmol) of siloxycyclobutanone **2f** followed by bulb to bulb distillation (oven 120 °C, 0.02 mm) afforded 0.33 g (85%) of **3f:** IR (neat) 3600–3300, 1800, 1500, 1450, 1170, 860, 775, and 715 cm^{-1}; NMR (CCl_4) δ 7.38 (s, 5 H), 4.90 (s, 1 H), 3.57 (broad s, 1 H), and 1.62 (s, 3 H); MS *m/e* (no M^+) 183 (3.1), 181 (9.4), 165 (6.3), 163 (14.1), 133 (100), 105 (32.8), and 77 (57.8).

2,2-Dichloro-3-phenyl-3-trimethylsiloxy-4-methylcyclobutanone (2g). The reaction of 2.0 g (9.7 mmol) of silyl enol ether **1g** by the general procedure (2 h) afforded 2.88 g (94%) of **2g.** Attempted distillation (120 °C, 0.02 mm) of **2g** led to partial ring opening. Siloxycyclobutanone **2g:** IR (neat) 1810, 1450, 1260, 1160, 1040, 910, 860, and 710 cm^{-1}; NMR (CCl_4) δ 7.42 (s, 5H); 4.25 (q, J = 7 Hz, 1 H), 1.38 (d, J = 7 Hz, 3 H), and −0.013 (s, 9 H); MS *m/e* (no M^+) 284 (2.1), 282 (5.4), 262 (4.4), 260 (7.0), 129 (10.4), 122 (10.0), 117 (8.6), 106 (8.8), 105 (100), 93 (8.0), 77 (26.2), 75 (8.5), and 73 (35.7).

1,1-Dichloro-2-trimethylsiloxy-3-methyl-4-phenylbut-1-en-4-one (7). Heating 1.4 g (4.4 mmol) of siloxycyclobutanone **2g** for 2 h at 200 °C followed by bulb to bulb distillation (oven 115 °C, 0.02 mm) afforded 0.96 g of a mixture (ca. 1:1) of **7** and **8.** Compound **7:** IR

(neat) 1690 cm^{-1}; NMR (CCl_4) δ 7.9–7.5 (5 H), 4.65 (q, J = 7 Hz, 1 H), 1.32 (d, J = 7 Hz, 3 H), and 0.08 (s, 9 H). The spectral properties of 8 are reported below.

1,1-Dichloro-3-methyl-4-phenylbutane-2,4-dione (8). A solution of 0.20 g (0.63 mmol) of siloxycyclobutanone **2g** and 0.20 g (1.5 mmol) of zinc chloride in 15 mL of ether was stirred for 15 h. It was then poured into 25 mL of pentane, the solution was washed with a saturated $NaHCO_3$ solution and dried over K_2CO_3, and the solvents were removed in vacuo to afford 144 mg (94%) of **8:** IR (neat) 1740, 1675, 1450, 1280, 975, and 710 cm^{-1}; NMR (CCl_4) δ 8.07 (m, 2 H), 7.60 (m, 3 H), 6.08 (s, 1 H), 5.13 (q, J = 7 Hz, 1 H), and 1.50 (d, J = 7 Hz, 3 H); MS m/e (no M^+) 210 (1.4), 208 (4), 174 (10.4), 161 (4.0), 134 (4.0), 117 (15.0), 116 (13.0), 115 (4.0), 105 (100), and 77 (42.0).

2,2-Dichloro-3-phenyl-4-methylcyclobutenone (9). A solution of 0.50 g (1.5 mmol) of siloxycyclobutanone **2g** and 3 drops of concentrated HCl in 15 mL of THF was refluxed for 15 h. The solvent was removed in vacuo, 25 mL of ether was added to the residue, and the solution was washed with a saturated $NaHCO_3$ solution. The solution was dried over K_2CO_3 and the solvent removed in vacuo to afford 0.34 g of a yellow oil which was purified by bulb to bulb distillation (oven 120 °C, 0.02 mm) to afford 0.28 g (78%) of **9:** IR (CCl_4) 1780, 1610, 1450, 1350, and 860 cm^{-1}; NMR (CCl_4) δ 8.0 (m, 2 H), 7.67 (m, 3 H), and 2.20 (s, 3 H); MS m/e 228 (M + 2, 7.8), 226 (M^+, 12.3), 165 (7.6), 163 (22.7), 161 (7.2), 128 (8.2), 127 (6.3), 122 (9.6), 77 (100), and 51 (17.1).

Reaction of 2g with Fluoride Ion. A solution of 0.50 g (1.6 mmol) of siloxycyclobutanone **2g** and 0.42 g (1.6 mmol) of tetrabutylammonium fluoride in 15 mL of THF was stirred for 1 h, the solvent was removed in vacuo, and 40 mL of hexane was added to the residue. The solution was washed with water and dried over K_2CO_3, and the solvent was removed in vacuo to afford 0.35 g of a mixture (ca. 2:1) of 8 and 9 as determined by NMR spectroscopy.

2,2-Dichloro-3-methyl-3-trimethylsiloxy-4-phenylcyclobutanone [(*E*)- and (*Z*)-2h]. The reaction of 1.0 g (4.85 mmol) of a mixture (*E*/*Z*, 1:16)[12] of silyl enol ethers **1h** by the general procedure (3 h) afforded 1.4 g of a mixture (1:16 by NMR spectroscopy) of (*E*)- and (*Z*)-**2h.** Bulb to bulb distillation (oven 100 °C, 0.02 mm) afforded 0.9 g (59%) of an identical mixture. The spectra of the crude and distilled mixtures were identical. The mixture: IR (neat) 1805, 1260, 1210, 1030, 860, and 710 cm^{-1}; MS m/e (no M^+) 282 (4.4), 280 (6.7), 228 (5.5), 226 (8.3), 165 (3.3), 163 (11.7), 149 (20.0), 148 (40.0), 147 (100), 105 (21.7), 95 (5.8), 93 (15.0), 77 (20.2), 75 (22.2), and 73 (61.7). Siloxycyclobutanone (*E*)-**2h:** NMR (CCl_4) δ 7.2 (broad s, 5 H), 5.02 (s, 1 H), 1.23 (s, 3 H), and 0.28 (s, 9 H). Siloxycyclobutanone (*Z*)-**2h:** NMR (CCl_4) δ 7.2 (broad s, 5 H), 4.75 (s, 1 H), 1.82 (s, 3 H), and −0.12 (s, 9 H).

The reaction of a 7:1 *E*/*Z* mixture of silyl enol ethers **1h** afforded (*E*)-**2h** and (*Z*)-**2h** in a ratio of 7:1. The reaction of other *E*/*Z* mixtures also yielded (*E*)- and (*Z*)-**2h** in ratios identical with those of the starting silyl enol ether.

2,2-Dichloro-3-methyl-4-phenylcyclobutenone (10). Hydrolysis of 0.50 g (1.58 mmol) of a mixture of siloxycyclobutanones (*E*)- and (*Z*)-**2h** afforded 0.34 g of a yellow oil which was purified by bulb to bulb distillation (oven 110 °C, 0.02 mm) to afford 0.29 g (81%) of **10:** IR (CCl_4) 1780, 1620, 1380, 930, 850, and 700 cm^{-1}; NMR (CCl_4) δ 7.7 (m, 2 H), 7.5 (m, 3 H), and 2.55 (s, 3 H); MS m/e 228 (M + 2, 8.3), 226 (M^+, 12.7), 163 (27.3), 161 (9.0), and 77 (100).

1,1-Dichloro-2-trimethylsiloxy-4-phenylbut-1-en-4-one (11a). The reaction of 5.0 g (26 mmol) of silyl enol ether **1i** by the general procedure (2 h) afforded 7.5 g of a yellow oil as a 4:1 mixture of **11a** and **12a.** Distillation (90–95 °C, 0.02 mm) led to a 2.5:1 mixture of **11a** and **12a.** Compound **11a:** IR (neat) 1690, 1270, 1040, 1000, 870, 780, and 710 cm^{-1}; NMR (CCl_4) δ 7.9 (m, 2 H), 7.4 (m, 3 H), 3.9 (s, 2 H), and 0.15 (s, 9 H).

1,1-Dichloro-4-phenylbutane-2,4-dione (12a). Hydrolysis of 2.0 g of a mixture of **11a** and **12a** afforded, after bulb to bulb distillation (oven 110 °C, 0.02 mm), 1.3 g of **12a:** IR (neat) 3400 tailing to 2600, 1650–1550, 1270, 775, and 720 cm^{-1}; NMR (CCl_4) δ 14.3 (broad, 1 H), 7.9 (m, 2 H), 7.4 (m, 3 H), 6.58 (s, 1 H), and 5.93 (s, 1 H); MS m/e 232 (M + 2, 4.3), 230 (M^+, 6.3), 196 (2.7), 194 (4.2), 168 (8.3), 147 (100), 105 (33.3), 77 (47.9), and 69 (74.8).

1,1-Dichloro-2-trimethylsiloxy-5,5-dimethylhex-1-en-4-one (11b). The reaction of 2.0 g (11.6 mmol) of silyl enol ether **1j** by the general procedure (7 h) afforded 3.0 g of a mixture (ca. 4:1) of **11b** and **12b.** Compound **11b:** IR (neat) 1720, 1630, 1470, 1300, 1270, 1040, 1020, and 870 cm^{-1}; NMR (CCl_4) δ 3.42 (s, 2 H), 1.12 (s, 9 H), and 0.17 (s, 9 H).

1,1-Dichloro-5,5-dimethylhexane-2,4-dione (12b). Hydrolysis of 0.50 g of a mixture of **11b** and **12b** followed by bulb to bulb distillation (oven 90 °C, 0.02 mm) afforded 0.31 g of **12b:** IR (neat) 1650–1550, 1375, 1320, 1235, 1150, and 800 cm^{-1}; NMR (CCl_4) δ 14.3 (broad, 1 H), 5.96 (s, 1 H), 5.76 (s, 1 H), and 1.18 (s, 9 H); MS m/e 212 (M + 2, 10.4), 210 (M^+, 15.3), 155 (45.4), 153 (73.7), 127 (100), 120 (34.0), 118 (63.8), and 57 (70.3).

1-*tert*-Butyldimethylsiloxy-1-phenylethylene (1k). Silyl enol ether **1k** was prepared by a reaction analogous to that described for **1e.** Distillation afforded a 35% yield of **1k:** bp 95–100 °C (3 mm); IR (neat) 1600 cm^{-1}; NMR (CCl_4) δ 7.6–7.0 (m, 5 H), 4.75 (broad s, 1 H), 4.27 (broad s, 1 H), 0.95 (s, 9 H), and 0.12 (s, 6 H).

1,1-Dichloro-2-*tert*-butyldimethylsiloxy-4-phenylbut-1-en-4-one (14). The reaction of 0.50 g of silyl enol ether **1k** by the general procedure (1 h) afforded 0.66 g of a mixture (ca. 2.5:1) of **14** and **12a.** Compound **14:** IR (neat) 1690 cm^{-1}; NMR (CCl_4) δ 7.92 (m, 2 H), 7.45 (m, 3 H), 3.92 (s, 2 H), 0.85 (s, 9 H), and 0.15 (s, 6 H).

1-*tert*-Butyldimethylsiloxy-1-(4-nitrophenyl)ethylene (1l). Silyl enol ether **1l** was prepared by a reaction analogous to that described above for **1e.** Distillation afforded a 22% yield of **1l:** bp 125–128 °C (0.1 mm); IR (neat) 1590, 1520, 1350, 1320, 1260, 1110, 1020, 850, and 800 cm^{-1}; NMR (CCl_4) δ 8.27 (d, J = 8 Hz, 2 H), 7.73 (d, J = 8 Hz, 2 H), 5.0 (d, J = 2 Hz, 1 H), 4.55 (d, J = 2 Hz, 1 H), 1.0 (s, 9 H), and 0.22 (s, 6 H).

Acknowledgment. This investigation was supported by Grant CA-19203 awarded by the National Cancer Institute, DHEW.

Registry No.—(*E*)-**1f,** 51425-64-0; **1i,** 13735-81-4; **1j,** 17510-46-2; **1k,** 66324-10-5; **1l,** 64600-20-0; (*E*)-**2h,** 66323-87-3; (*Z*)-**2h,** 66323-88-4; **4,** 66323-95-3; **5,** 66323-89-5; **6,** 66323-90-8; **7,** 66323-91-9; **8,** 66323-92-0; **9,** 66323-93-1; **10,** 34647-96-6; **11a,** 66323-94-2; **11b,** 66323-97-5; **12a,** 37471-43-5; **12b,** 26709-24-0; **14,** 66323-96-4; Cl_3CCO_2H, 76-03-9; Cl_3CCOCl, 76-02-8; $Cl_2C{=}C{=}O$, 4591-28-0; $Cl_2CHCOCl$, 79-36-7; 4-*tert*-butycyclohexanone, 98-53-3; *tert*-butyldimethylsilyl chloride, 18162-48-6.

References and Notes

(1) Cycloadditions. 24. For Part 23, see A. Hassner, H. W. Pinnick, and J. Ansell, *J. Org. Chem.*, **43,** 1774 (1978).

(2) (a) W. T. Brady, *Synthesis,* 415 (1971); (b) L. Ghosez, R. Montaigne, A. Roussel, H. Vanlierde, and P. Mollett, *Tetrahedron,* **27,** 615 (1971); (c) V. R. Fletcher and A. Hassner, *Tetrahedron Lett.,* 1071 (1970).

(3) (a) For a comprehensive review of cyclobutanones, see D. Seebach, S. Beckman, and H. Geiger, *Methoden Org. Chem. (Houben-Weyl), 4th Ed., 1971,* **4** (1971). (b) For elegant examples of the synthetic utility of cyclobutanones, see B. M. Trost, *Top. Curr. Chem.,* **41,** 1 (1973), *Acc. Chem. Res.,* **7,** 85 (1974), and *Pure Appl. Chem.,* **43,** 563 (1975).

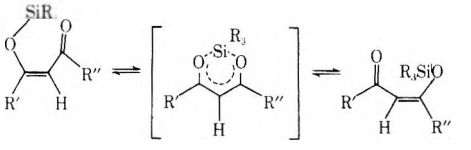
(4) For a recent review, see J. K. Rasmussen, *Synthesis,* 91 (1977).

(5) (a) J. K. Rasmussen and A. Hassner, *Tetrahedron Lett.,* 2783 (1973); (b) R. H. Reuss and A. Hassner, *J. Org. Chem.,* **39,** 785 (1974); (c) J. K. Rasmussen and A. Hassner, *ibid.,* **39,** 2558 (1974); (d) A. Hassner, R. H. Reuss, and H. W. Pinnick, *ibid.,* **40,** 3427 (1975).

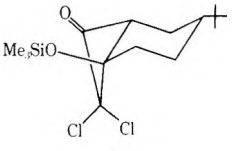
(6) (a) R. Huisgen, L. Feiler, and G. Binsch, *Angew. Chem.,* **76,** 893 (1964); (b) R. Huisgen and L. Feiler, *Chem. Ber.,* **102,** 3391 (1969).

(7) S. Murai, Y. Kerroki, K. Hasegawa, and S. Tsutsumi, *J. Chem. Soc., Chem. Commun.,* 946 (1972).

(8) T. J. Pinnavaia and J. A. McClarin, *J. Am. Chem. Soc.,* **98,** 3012 (1974), have found that certain acyclic silyl enol ethers undergo a rapid 1,5 silyl group migration between the two oxygen centers.



(9) The cycloaddition of dichloroketene to cyclohexene systems has been demonstrated [A. Hassner, V. R. Fletcher, and D. P. G. Hamon, *J. Am. Chem. Soc.,* **93,** 264 (1971)] to be highly regioselective; that is, the newly formed bond of the carbonyl carbon will prefer to be axial with respect to the six-membered ring. On this basis, the cycloaddition of dichloroketene to silyl enol ether **1d** is assumed to generate siloxycyclobutanone **2d** rather than the other possible isomer, A (*tert*-butyl and siloxy trans).



A

(10) E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.,* **94,** 6190 (1972).

(11) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.,* **34,** 2324 (1969).

(12) For an alternate synthesis of cyclobutenone **10,** see W. Reid and H. Kohl, *Synthesis,* 542 (1971).

(13) Melting points were determined on a Fisher-Johns block and are uncorrected. Infrared spectra were obtained of liquid films or carbon tetrachloride solutions as noted on a Perkin-Elmer 457 instrument. NMR spectra were recorded on Varian A-60A or EM-360 spectrometers with Me_4Si as an internal standard. GC data were recorded on a Varian Aerograph A90-P3 instrument with a thermal conductivity detector. Mass spectra were recorded on a Varian MAT CH5 instrument. Elemental analyses were performed by Atlantic Microlabs, Inc., Atlanta, Ga.

(14) H. H. Bosshard, R. Mory, M. Schmid, and H. Zollinger, *Helv. Chim. Acta*, **42**, 1653 (1959).

Synthesis of 2-Substituted 4-Oxahomoadamantanes

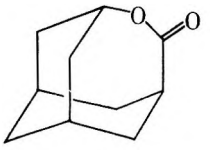
David L. Goff and Roger K. Murray, Jr.*[1]

Department of Chemistry, University of Delaware, Newark, Delaware 19711

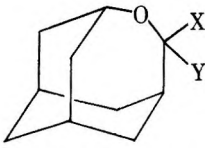
Received February 21, 1978

An entry into 2-substituted 4-oxahomoadamantanes has been developed. Treatment of bicyclo[3.3.1]non-6-ene-3-*endo*-methanol with *m*-chloroperbenzoic acid gives 2-*exo*-hydroxy-4-oxahomoadamantane (**8**). Jones oxidation of **8** provides the corresponding ketone, which undergoes reduction with sodium borohydride to give exclusively 2-*endo*-hydroxy-4-oxahomoadamantane. Extensions of this reaction permit the preparation of 2,5-disubstituted and 2,5,5-trisubstituted 4-oxahomoadamantanes. An improved synthesis of 4-oxahomoadamantane is also noted, and its ^{13}C NMR spectrum is reported.

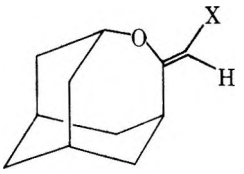
The synthesis, chemistry, and pharmacology of heteroadamantanes and related cage compounds have attracted considerable attention.[2] With the exception of 4-oxahomoadamantan-5-one[3,4] (**1**) and its derivatives,[5] the only substituted 4-oxahomoadamantanes which are known are compounds **2–6**.[6] We now wish to report the stereoselective



1



2, X = OH; Y = CH_3
3, X = OH; Y = CH_2Cl
4, X = I; Y = CH_2I



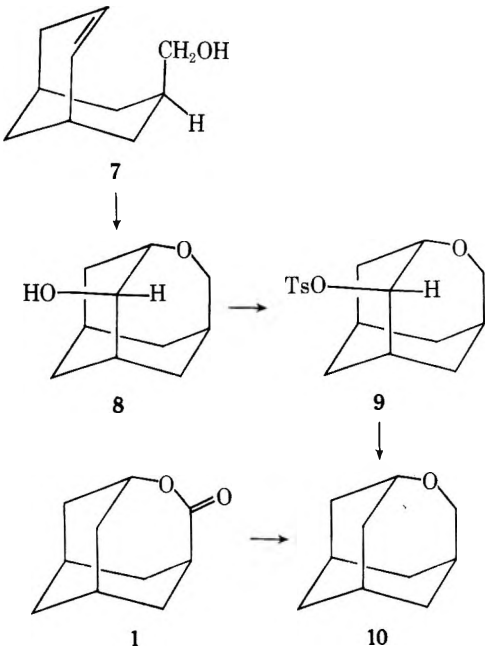
5, X = H
6, X = I

synthesis of both 2-*exo*-hydroxy- and 2-*endo*-hydroxy-4-oxahomoadamantane.[7] Extensions of the reactions employed to prepare these compounds permit the synthesis of 2,5-disubstituted and 2,5,5-trisubstituted 4-oxahomoadamantanes.

Results and Discussion

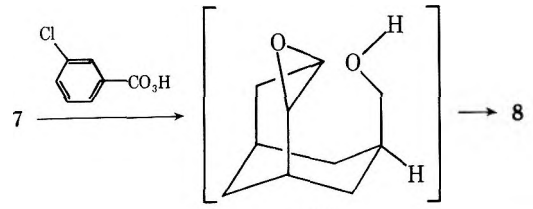
Treatment of bicyclo[3.3.1]non-6-ene-3-*endo*-methanol[3a,4a] (**7**) with *m*-chloroperbenzoic acid affords 2-*exo*-hydroxy-4-oxahomoadamantane (**8**) in ca. 70% yield. The skeletal framework of **8** follows from its conversion to the known ether,[3a,8] 4-oxahomoadamantane (**10**). Reaction of **8** with *p*-toluenesulfonyl chloride in pyridine gives exo tosylate **9**. Subsequent treatment of **9** with lithium aluminum hydride provides **10**. Owing to some minor discrepancies between the ^1H NMR parameters observed for **10** and those previously reported for this compound,[9] ether **10** was also synthesized by an independent route. Treatment of lactone **1** with boron trifluoride etherate and lithium aluminum hydride provides **10** in 95% yield. The physical and spectral properties of **10** prepared by these independent routes are identical. Moreover, consistent with the presence of a plane of symmetry in **10**, the ^{13}C NMR spectrum of **10** contains only seven signals and three of these signals are twice as intense as the others.[10] Since the reported syntheses of **10** all either proceed in low yield and/or give mixtures of reaction products[3a,8] and since **1** can readily be prepared from commercially available 2-adamantanone[3] (**11**), the route **11** → **1** → **10** appears to be the method of choice for the synthesis of 4-oxahomoadamantane.

The assigned skeletal position and stereochemistry of the hydroxyl substituent in **8** follow in part from its mode of synthesis. Thus, **7** → **8** is rationalized as occurring by initial epoxidation of **7** from the less sterically encumbered face of the carbon–carbon double bond to give **12**, which then undergoes intramolecular nucleophilic attack by the hydroxylic oxygen to provide **8**. In order to firmly establish the stereochemistry at C-2 in **8**, the C-2 epimer of **8** was also prepared. Oxidation of **8** with Jones reagent gives 4-oxahomoadamantan-2-one (**13**), and sodium borohydride reduction of **13** provides 2-*endo*-hydroxy-4-oxahomoadamantane (**14**). In an earlier study we were not able to devise GLC conditions



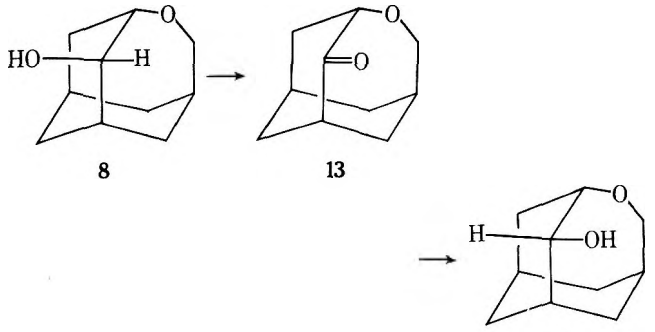
7 **8** **9** **1** **10**

0022-3263/78/1943-3179$01.00/0



12

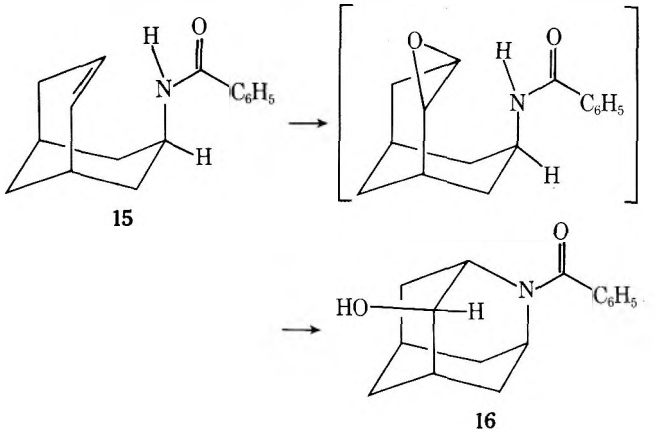
for the effective separation of 2-*exo*- and 2-*endo*-hydroxyhomoadamantane.[11] However, apparently due to the significant intramolecular hydrogen bonding present in **14**, epimeric alcohols **8** and **14** could be readily resolved by GLC. Analysis of the crude reaction mixture from **13** → **14** showed that endo



8 13 14

alcohol **14** is obtained from this reaction in greater than 99% stereochemical purity. This result is consistent with an examination of molecular models which clearly indicates that attack at the carbonyl carbon in **13** across the face of the seven-membered ring should be significantly impeded by the endo hydrogen at C-5. By contrast, there is no apparent steric hindrance to attack at the carbonyl carbon in **13** across the face of the six-membered ring.

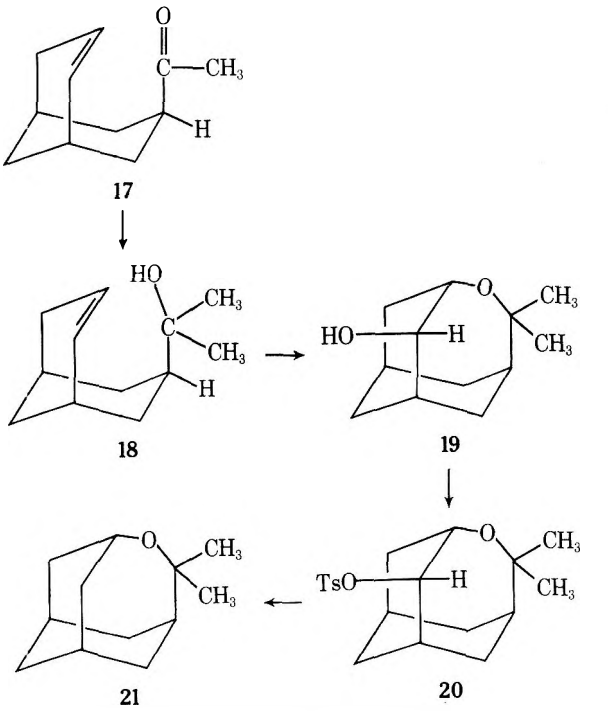
The formation of **8** from **7** parallels the earlier observation by Staas and Spurlock that treatment of bicyclo[3.3.1]non-6-en-3-*endo*-ylbenzamide (**15**) with *m*-chloroperbenzoic gives exclusively 4-*anti*-hydroxy-*N*-benzoyl-2-azaadamantane (**16**).[5a] This reaction was also rationalized as occurring by



15 16

spontaneous intramolecular attack on an initially formed epoxide intermediate.[5a] Other reactions of *m*-chloroperbenzoic acid with olefins which have neighboring functional groups are well known.[12]

Since a variety of α-substituted secondary alcohols and α,α-disubstituted tertiary alcohols related to **7** can readily be prepared, the reaction **7** → **8** offers a route for the synthesis of a number of 2,5-disubstituted and 2,5,5-trisubstituted 4-oxahomoadamantanes.[13] In order to illustrate this point, we have prepared 5,5-dimethyl-2-*exo*-hydroxy-4-oxahomoadamantane (**19**). Treatment of ketone **17** with an excess of methyllithium gives tertiary alcohol **18**. Subsequent reaction of **18** with *m*-chloroperbenzoic acid provides **19** in 95% yield.



17 18 19 20 21

Consistent with the structure assignment, the ^{1}H NMR spectrum of **19** contains a broad multiplet for the C-2 and C-3 methine protons at δ 3.87–3.67 and two singlets for the constitutionally heterotopic C-5 methyls at δ 1.29 and 1.26. The skeletal framework of **19** was firmly established by its conversion to 5,5-dimethyl-4-oxahomoadamantane (**21**). Reaction of **19** with *p*-toluenesulfonyl chloride in pyridine gives tosylate **20** which is readily reduced with lithium aluminum hydride to provide **21**. The ^{1}H NMR spectrum of **21** shows a sharp singlet at δ 1.25 for the enantiotopic methyls at C-5.

Experimental Section

Melting points were obtained in sealed capillary tubes using a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were obtained on Perkin-Elmer 180 or 337 spectrophotometers. Proton magnetic resonance spectra were recorded with Varian A-60A or Perkin-Elmer R-12B 60-MHz spectrometers and are referenced to an internal standard of tetramethylsilane. Apparent splittings are reported in all cases. Unless noted otherwise, yields were obtained by integration of appropriate signals in the ^{1}H NMR spectrum of the product(s) vs. the signal of a predetermined amount of an added standard (generally chloroform or trichloroethylene) and are regarded as being accurate to ca. ±10%. Elemental analyses were performed by Micro-Analysis, Inc., Wilmington, Del.

2-*exo*-Hydroxy-4-oxahomoadamantane (8). A solution of 85% *m*-chloroperoxybenzoic acid (1.22 g, 6 mmol) in methylene chloride (25 mL) was added dropwise to a stirred solution of bicyclo[3.3.1]-non-6-ene-3-*endo*-methanol[3a,4a] (760 mg, 5 mmol) in methylene chloride (50 mL) which was maintained at 0 °C. The reaction was stirred at room temperature for 36 h, at which time the excess peracid present was destroyed by the addition of 10% aqueous sodium sulfite until a negative starch–iodide test was obtained. The reaction mixture was diluted with methylene chloride (50 mL), washed successively with 5% aqueous sodium bicarbonate (4 × 25 mL) and water (2 × 15 mL), and then dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure gave 605 mg of **8** (72% yield) as a white solid which was homogeneous by GLC analysis (10 ft × 0.25 in DC-550 column; 200 °C). Purification of the product by GLC (above conditions) provided **8**: mp 302–303 °C; NMR δ ($CDCl_3$) 4.14–3.73 (m, 4 H) and 2.51–1.13 (m, 12 H); IR ν (CCl_4) 3635, 3420, 2915, 1460, 1440, 1145, 1100, 1075, 1060, and 1035 cm^{-1}.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.53; H, 9.41.

2-*exo*-*p*-Toluenesulfonyloxy-4-oxahomoadamantane (9). Purified[14] *p*-toluenesulfonyl chloride (1.2 g, 59 mmol) was added to a solution of **8** (500 mg, 20 mmol) in freshly distilled dry pyridine (15 mL) at 0 °C. The reaction was stirred until a homogeneous solution was obtained, and it was then stored at 5 °C for 24 h. At this point the reaction was quenched by pouring it into a slurry of ice and water (50

mL) and stirring it vigorously for 15 min. A white solid resulted which was suction filtered. The crude tosylate was dissolved in a minimal amount of petroleum ether at room temperature, treated with Darco G-60, and cooled in a dry ice–acetone bath until crystallization was complete. The crystals were collected by suction filtration and dried under vacuum at room temperature to afford 150 mg of **9** (16% yield) as a white powder: NMR δ ($CDCl_3$) 8.35–7.5 (d of d, 4 H, aromatic protons), 4.61 [br s, 1 H, CH(OTs)], 4.26–3.88 (br m, 3 H, –CH–O– and $–CH_2–O–$), and 2.79–0.96 (br m, 14 H; containing a methyl singlet at δ 2.54); IR ν (CCl_4) 2920, 1365, 1190, 1180, 1150, 1100, 1065, and 1000 cm^{-1}.

4-Oxahomoadamantane (10). A. A solution of **9** (150 mg, 0.5 mmol) in anhydrous ether (15 mL) was added dropwise to a stirred suspension of lithium aluminum hydride (90 mg, 2.7 mmol) in anhydrous ether (35 mL) and heated at reflux for 48 h. The reaction mixture was cooled in an ice bath, and the excess lithium aluminum hydride present was destroyed by the dropwise addition of ice-cold water (5 mL). The resulting white suspension was dissolved by the addition of 10% aqueous hydrochloric acid (25 mL). The aqueous layer was separated and extracted with ether (2 × 25 mL). The combined organic layers were washed successively with 5% aqueous sodium bicarbonate (3 × 25 mL) and water (25 mL) and dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure afforded 70 mg of **10** (ca. quantitative yield) as a white solid which was homogeneous by GLC analysis (10 ft × 0.25 in DC-550 column; 175 °C). Purification by GLC (above conditions) provided **10** as a white solid: mp 271–272 °C (lit.[3a] mp 268–269 °C); ^1H NMR δ ($CDCl_3$) 4.38–4.12 (m, 1 H, –CH–O–), 3.93 (d, J = 2.5 Hz, 2 H, $–CH_2–O–$), and 2.21–1.43 (br m, 13 H); ^{13}C NMR[10] δ ($CDCl_3$) (tentative assignments) 74.3 (C-5), 72.1 (C-3), 37.8 (C-2 and C-11), 37.0 (C-7 and C-10), 35.4 (C-9), 34.4 (C-6), and 26.7 (C-1 and C-8); IR ν (CCl_4) 2915, 2850, 1440, 1255, 1145, 1110, 1065, 995, and 880 cm^{-1}.

B. A solution of lactone **1**[3] (530 mg, 3.2 mmol) and 45% boron trifluoride etherate complex (12 mL) in anhydrous ether (75 mL) was added dropwise to a stirred suspension of lithium aluminum hydride (1.0 g, 26 mmol) in anhydrous ether (100 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 45 min and then at reflux for 2 h. The reaction was then cooled to room temperature, and the excess lithium aluminum hydride present was destroyed by the dropwise addition of 10% aqueous hydrochloric acid (25 mL). The aqueous layer was separated and extracted with ether (2 × 50 mL). The combined organic layers were then washed successively with 5% aqueous sodium bicarbonate (4 × 25 mL) and water (25 mL) and dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure gave 456 mg of **10** (95% yield) as a white solid. GLC analysis (10 ft × 0.25 in DC-550 column; 175 °C) of this material showed the presence of a single component. Purification of the product by GLC (above conditions) gave a white solid whose physical and spectral properties were identical with those of **10** obtained by procedure A.

4-Oxahomoadamantan-2-one (13). To a stirred solution of **8** (500 mg, 3 mmol) in acetone (30 mL) at 0 °C was added 4 mL of a freshly prepared solution of Jones reagent (2.8 g of chromic anhydride, 4.5 mL of sulfuric acid, and 12 mL of water). The reaction was stirred at 0 °C for 1 h and at room temperature for 3 h, diluted with water (15 mL), and stirred for an additional hour. At this point the reaction mixture was saturated with sodium chloride and extracted with ether (4 × 25 mL). The combined ether extracts were washed successively with saturated aqueous sodium bicarbonate (4 × 15 mL) and water (2 × 15 mL) and dried over anhydrous magnesium sulfate. The solvent was evaporated at reduced pressure, and the residue was sublimed (90 °C at 0.05 mm) to give 370 mg of **13** (74% yield) as a white solid. GLC analysis (10 ft × 0.25 in DC-550 column; 200 °C) showed the presence of a single component. Purification by GLC (above conditions) afforded **13** as a white solid: mp 277–278 °C; NMR δ (CCl_4) 4.12–4.03 (m, 3 H, –CH–O– and $–CH_2–O–$) and 2.68–1.47 (br m, 11 H); IR ν (CCl_4) 2925, 2860, 1726, 1460, 1440, 1280, 1200, 1135, and 1060 cm^{-1}.

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.53; H, 8.57.

2-*endo*-Hydroxy-4-oxahomoadamantane (14). A solution of sodium borohydride (265 mg, 7 mmol) in methanol (10 mL) was added to a stirred solution of **13** (290 mg, 1.7 mmol) in methanol (25 mL) at 0 °C. The reaction was stirred at 0 °C for 45 min and then at room temperature for 45 min, at which point the reaction was quenched by the addition of water (10 mL). The resulting solution was saturated with sodium chloride and extracted with ether (3 × 50 mL), and the combined extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure provided 275 mg of **14** (96% yield) as a white solid. GLC analysis (10 ft × 0.25 in SE-30 column; 190 °C) indicated a single component. Purification by GLC (above conditions) afforded **14** as a white solid: mp 314–315 °C; NMR δ (CCl_4) 4.18–3.96 (m, 1 H, –CH–O–), 3.90–3.73 (m, 2 H, $–CH_2–O–$), 3.48 [dt, J = 4 and 1 Hz, 1 H, CH(OH)], 2.76 (s, 1 H, OH), and 2.23–1.25 (br m, 11 H); IR ν (CCl_4) 3555, 3400, 2920, 2860, 1445, 1390, 1135, 1105, 1080, and 1050 cm^{-1}.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.60; H, 9.43.

Oxidation of **14** with Jones reagent by the procedure described for **8** → **13** regenerated **13**.

3-*endo*-Acetylbicyclo[3.3.1]non-6-ene (17). An ethereal solution of methyllithium (80 mL of a 1.65 M solution; ca. 132 mmol) was added dropwise to a vigorously stirred solution of 3-*endo*-carboxybicyclo[3.3.1]non-6-ene[4a] (9.8 g, 59 mmol) in anhydrous ether at 0 °C at such a rate that the temperature of the reaction mixture did not exceed 5 °C. Following this addition, the reaction was stirred at 0 °C for 30 min and at room temperature for 4 h. The reaction was quenched by slowly pouring the reaction mixture into a saturated solution of ammonium chloride. The aqueous layer was separated and extracted with ether (4 × 50 mL). The combined ether layers were washed with 5% aqueous sodium bicarbonate (4 × 50 mL; acidification of the combined basic washes afforded a 300-mg recovery of unreacted starting material) and water (2 × 50 mL) and then dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure provided a yellow liquid. Vacuum distillation of this material gave 7.9 g (84% yield) of ketone **17** as a colorless liquid: bp 70–73 °C (0.5 mm); NMR δ ($CDCl_3$) 5.71–5.18 (br m, 2 H, –CH=CH–) and 2.68–1.28 (br m, 14 H; containing a methyl singlet at δ 2.05); IR ν (CCl_4) 3020, 2925, 2905, 2855, 1704, 1430, 1350, 1210, 1190, 1170, and 1105 cm^{-1}.

The semicarbazone derivative of **17** was prepared according to the procedure outlined by Fieser,[15] mp 209–210 °C.

Anal. Calcd for $C_{12}H_{19}N_3O$: C, 65.13; H, 8.65; N, 18.99. Found: C, 64.89; H, 8.87; N, 18.87.

α,α-Dimethylbicyclo[3.3.1]non-6-ene-3-*endo*-methanol (18). A 2 M ethereal methyllithium solution (5 mL, ca. 10 mmol) was added to a stirred solution of **17** (300 mg, 1.8 mmol) in anhydrous ether (60 mL) at 0 °C at such a rate that the temperature of the reaction mixture did not exceed 5 °C. The reaction mixture was stirred at 0 °C for 2 h and then carefully quenched by the dropwise addition of water (40 mL). The reaction mixture was extracted with ether (3 × 40 mL), and the combined ether extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure gave 290 mg of **18** (89% yield) as a viscous liquid. The crude product was purified by GLC (10 ft × 0.25 in SE-30 column; 200 °C) which afforded **18** as a colorless oil: NMR δ (CCl_4) 6.03–5.30 (m, 2 H, –CH=CH–) and 2.52–0.94 (br m, 18 H; containing the gem dimethyl singlet at δ 1.09); IR ν (CCl_4) 3625, 3500–3400, 3020, 2935, 2905, 2840, 1380, 1370, 935, 925, and 910 cm^{-1}.

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.80; H, 10.97.

2-*exo*-Hydroxy-5,5-dimethyl-4-oxahomoadamantane (19). A solution of 85% *m*-chloroperoxybenzoic acid (625 mg, 3 mmol) in methylene chloride (50 mL) was added dropwise to a stirred solution of **18** (500 mg, 2.8 mmol) in methylene chloride (100 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 23 h. Workup of the reaction mixture followed the procedure described for **7** → **8**. Evaporation of the solvent at reduced pressure gave 520 mg of **19** (95% yield) as a colorless liquid which solidified on standing. Analysis of the crude reaction mixture by GLC (10 ft × 0.25 in SE-30 column; 225 °C) indicated the presence of a single component. Purification of this material by GLC (above conditions) afforded **19** as a white solid: mp 55.5–57 °C; NMR δ (CCl_4) 3.87–3.67 [m, 2 H, –CH–O– and CH(OH)], 2.86 (s, 1 H, OH), and 2.43–1.10 (br m, 17 H; containing methyl singlets at δ 1.29 and 1.26); IR ν (CCl_4) 3625, 3400, 2910, 1550, 1460, 1445, 1380, 1365, 1145, 1050, and 1035 cm^{-1}.

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.40; H, 10.24.

5,5-Dimethyl-4-oxahomoadamantane (21). Purified[14] *p*-toluenesulfonyl chloride (180 mg, 0.9 mmol) was added to a solution of **19** (175 mg, 0.9 mmol) in freshly distilled dry pyridine (4 mL) at 0 °C. The reaction mixture was stirred at 0 °C until a homogeneous solution was obtained, and then it was stored at ca. 5 °C for 3 days. The reaction was quenched by pouring it into a slurry of ice and water (25 mL) and then stirring it vigorously for 30 min. The resulting pale yellow solid was filtered by suction and dried under vacuum at room temperature to provide 100 mg (ca. 30% yield) of **2-*exo*-*p*-toluenesulfonyloxy-5,5-dimethyl-4-oxahomoadamantane (20)** as an off-white powder.

A solution of **20** (100 mg, 0.3 mmol) in anhydrous ether (10 mL) was added dropwise to a stirred suspension of lithium aluminum hydride

(50 mg, 1.3 mmol) in anhydrous ether (50 mL) and heated at reflux for 48 h. Workup of the reaction mixture followed the procedure described for **9** → **10**. Evaporation of the solvent at room temperature afforded 42 mg (81% yield) of **21** as a colorless liquid. Analysis of the crude reaction mixture by GLC (10 ft × 0.25 in DC-550 column; 175 °C) indicated only a single component. Purification by GLC (above conditions) provided pure **21** as an oil: NMR δ (CCl_4) 4.18–3.93 (br s, 1 H, –CH–O–), 2.34–1.43 (br m, 13 H), and 1.25 (s, 6 H, gem dimethyls); IR ν (CCl_4) 2975, 2905, 2850, 1460, 1440, 1385, 1360, 1255, 1215, 1145, 1120, 1095, 1070, and 1050 cm^{-1}.

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 80.02; H, 11.08.

Acknowledgment. This work was supported by grants from the Research Corporation and the University of Delaware Research Foundation.

Registry No.—**1**, 21898-84-0; **7**, 21932-99-0; **8**, 66483-52-1; **9**, 66483-53-2; **10**, 21898-86-2; **13**, 66483-54-3; **14**, 66537-45-9; **17**, 66483-55-4; **17** semicarbazone, 66483-56-5; **18**, 28644-53-3; **19**, 66483-57-6; **20**, 66483-58-7; **21**, 66483-59-8; 3-*endo*-carboxybicyclo[3.3.1]non-6-ene, 21932-98-9.

References and Notes

(1) Recipient of a Camille and Henry Dreyfus Teacher-Scholar Grant Award, 1976–1981.
(2) For recent reviews, see R. C. Fort, Jr., "Adamantane: The Chemistry of Diamond Molecules", Marcel Dekker, New York, N.Y., 1976, pp 267–357, and C. Ganter, *Top. Curr. Chem.*, **67**, 15 (1976).
(3) (a) A. C. Udding, H. Wynberg, and J. Strating, *Tetrahedron Lett.*, 5719 (1968); (b) D. Faulkner and M. A. McKervey, *J. Chem. Soc. C*, 3906 (1971); (c) P. Soucy, T.-L. Ho, and P. Deslongchamps, *Can. J. Chem.*, **50**, 2047 (1972); (d) J. Vodicka, J. Hlavaty, and S. Landa, *Collect. Czech. Chem. Commun.*, **38**, 3302 (1973); (e) G. Mehta and P. Pandey, *Synthesis*, 404 (1975).
(4) (a) T. Sasaki, S. Eguchi, and T. Toru, *J. Org. Chem.*, **35**, 4109 (1970); (b) H. Keul, *Chem. Ber.*, **108**, 1207 (1975).
(5) (a) 2-Bromo-4-oxahomoadamantan-5-one: W. H. Staas and L. A. Spurlock, *J. Org. Chem.*, **39**, 3822 (1974); ref. 4a. (b) 4-Oxahomoadamantane-5,9-dione: H. Stetter and U. P. Dorsch, *Justus Liebigs Ann. Chem.*, 1406 (1976). (c) 9-Bromo-, 9-chloro-, and 9-iodo-2-oxahomoadamantane-3,7-diones: M. Keller and G. Snatzke, *Tetrahedron*, **29**, 4013 (1973).
(6) For **2–4** and **6**, see R. M. Black and G. B. Gill, *Chem. Commun.*, 172 (1971). For the X-ray crystal structure determination of **3**, see M. J. Begley, G. B. Gill, and D. C. Woods, *J. Chem. Soc., Perkin Trans. 2*, 74 (1975). For **2** and **5**, see D. P. G. Hamon and G. F. Taylor, *J. Org. Chem.*, **39**, 2803 (1974).
(7) We have adopted the convention that a substituent is designated as endo if it is oriented toward the larger ring of a polycyclic skeleton and exo if it faces the smaller ring.
(8) (a) R. Durand and P. Geneste, *C. R. Hebd. Seances Acad. Sci., Ser. C*, **277**, 1051 (1973); (b) T. A. Wnuk, J. A. Tonnis, M. J. Dolan, S. J. Padegimas, and P. Kovacic, *J. Org. Chem.*, **40**, 444 (1975); (c) J.-H. Liu and P. Kovacic, *ibid.*, **40**, 1183 (1975).
(9) The chemical shift of the $-CH_2-O-$ protons in **10** has been reported as being δ 3.08[3a] and 3.87.[8a]
(10) The carbon magnetic resonance spectrum was recorded at an operating frequency of 22.63 Hz on a Brüker HFX-90 spectrometer equipped for Fourier transform pulsed NMR with a Nicolet 1085 data acquisition system and is referenced to an internal standard of tetramethylsilane.
(11) R. K. Murray, Jr., K. A. Babiak, and T. K. Morgan, Jr., *J. Org. Chem.*, **40**, 2463 (1975).
(12) B. Capon, J. Farquarson, and D. J. McNeillie, *J. Chem. Soc., Perkin Trans. 2*, 914 (1977), and references cited therein.
(13) Derivatives of **7** with substituents at C-3, C-6, C-7, and/or C-8 can also be conveniently prepared.
(14) S. W. Pelletier, *Chem. Ind. (London)*, 1034 (1953).
(15) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley-Interscience, New York, N.Y., 1967, p 1000.

Insect Antifeedants. 1. Diels–Alder Approach to the Synthesis of Ajugarin I

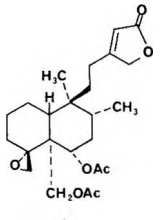
David J. Goldsmith,* Gabriel Srouji, and Cecil Kwong

Department of Chemistry, Emory University, Atlanta, Georgia 30322.

Received February 24, 1978

An approach to the synthesis of the antifeedant ajugarin I (**7**) employing a Diels–Alder reaction for the preparation of the decalin position of the molecule is described. Cycloaddition of 2,4-pentadien-1-ol (**5**) and carbomethoxy-*p*-benzoquinone (**6**) affords a mixture of hemiacetals **8** and **9** having the same gross regio- and stereochemistry. The structures of the adducts are determined by spectroscopic means and X-ray crystallography of their reduced transformation products **10** and **11**. Conversion of the initial adduct mixture to a potentially synthetically useful intermediate **31** is accomplished by reductive cleavage of a γ-keto unsaturated acetal, **29**.

Ajugarin I (**1**) isolated from *Ajuga remota* (Labitae) exhibits significant antifeeding activity against African army worms.[1] It is a member of the clerodane class[2] of rearranged diterpenes, many of which have also been shown to act as in-

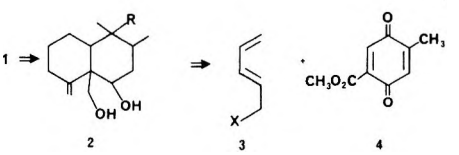


1

sect antifeedants.[3] The structure and activity of ajugarin I were recently described by Nakanishi and associates.

We are presently embarked on a project directed toward the synthesis of ajugarin I and its congeners. In this paper, we report some of the results of a Diels–Alder approach to the construction of the decalin portion of the structure of the natural product.

The placement and the nature of the groups about the periphery of the bicyclic unit of **1** suggested to us the retrosynthetic plan illustrated in brief form in the scheme **1** → **2** → **3** + **4**. As shown, we visualized a rapid and efficient construction of the decalin system by a cycloaddition reaction of suitably substituted diene–dienophile partners. In terms of the specific structural requirements of the Diels–Alder combination, the choice of a 1-heteroalkyl-substituted butadiene **3** and a carboalkoxy-*p*-quinone[4] seemed most appropriate.



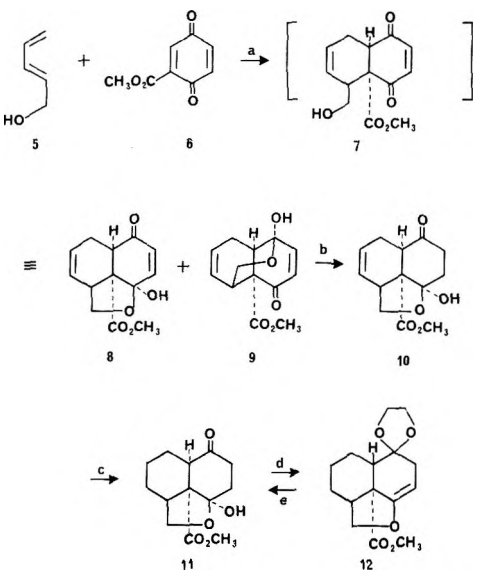
2 **3** **4**

Our initial efforts in an experimental realization of this synthetic plan have been focused on the addition of several substituted butadienes to the unsubstituted carbomethoxy-*p*-benzoquinone (**6**).[4] The discussion to follow is concerned with the structural and stereochemical outcome of two of these cycloadditions and with the results of several transformations carried out with the initial Diels–Alder adducts.

The first problem to be faced in the Diels–Alder approach to ajugarin I was the question of orientation in the proposed cycloaddition reaction. Dienes substituted at the 1 position are generally assumed to follow an "ortho" rule in Diels–Alder

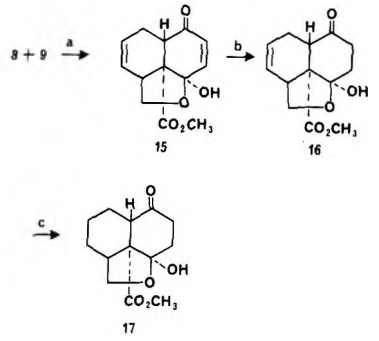
0022-3263/78/1943-3182$01.00/0

Scheme I



[a] C_6H_6, 25 °C; [b] Zn, HOAc; [c] H_2, Pd; [d] $HOCH_2CH_2OH$, *p*-TSOH; [e] H_3O^+.

Scheme II



[a] Dabco, 25 °C; [b] Zn, HOAc; [c] H_2, Pd.

additions,[5] and a number of theoretical–calculational reports[6] have appeared recently to support the empirical generalization. Specific additions of 1-aryl-substituted butadienes to carbomethoxyquinone **6** have also been studied by Ansell and co-workers.[7] Based on this work as well as on a study we have made of the addition of *trans*-piperylene to **6**,[8] the interaction of 1-hydroxymethylbutadiene (**5**) with **6** was expected to yield predominantly a product with the regiochemistry and stereochemistry shown in Scheme I for structure **7**.

In practice, the reaction of **5** and **6** occurs rapidly at room temperature[9] to yield a solid, mp 108–114 °C, which proved to be a mixture of two adducts. Although these products could not be separated and individually examined, the spectral and chemical evidence to be outlined below leaves little doubt that they are the isomeric hemiketals **8** and **9**, both having been formed with the anticipated geometry and molecular organization.

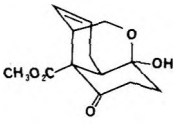
Treatment of the adduct mixture with diazabicyclononane afforded a new substance **15**, mp 142–145 °C (Scheme II), spectrally distinct from either component of the original product. That **15** is the trans-fused isomer of **8** was apparent from a comparison of the proton spectra of **15** and the mixture of **8** and **9**. In the spectrum of **15** a singlet at 3.62 ppm is observed corresponding to the ester methyl group. In contrast the ^1H NMR spectrum of the mixture shows two singlets at lower field, 3.69 and 3.71 ppm, respectively. An upfield shift of approximately 7–8 Hz in going from cis- to trans-fused aryl-substituted esters similar to **8**, **9**, and **15** has been noted by Ansell[10] for the resonance position of the carbomethoxy protons. Although the shift which we have observed is smaller than that found by Ansell, our results parallel his. We have found, moreover, that the same effect occurs in the saturated analogues of these compounds and is not limited to the Diels–Alder adducts and their epimers only. The finding here that both components of the adduct mixture are converted to a common trans isomer **15** (the epimer of **9** being of course sterically unattainable) removes both compound **15** and any substance stereoisomeric at the ring-A oxymethyl group from consideration as one of the components of the product from the cycloaddition.

Examination of the proton spectrum of **15** also helped to establish the regiochemical outcome of the Diels–Alder reaction. This spectrum displays a doublet of doublets centered at 2.81 ppm for the junction proton with coupling constants of 4 and 7 Hz. Such a pattern is consistent only with the regio- and stereochemistry of **15**. The compound must be trans fused with coupling of an axial angular proton to adjacent equatorial and axial neighbors.

The last aspect of the structure of the Diels–Alder product, the presence of a hemiketal group, was apparent first from the ^{13}C spectra of the adduct mixture and of the isomerized compound **15**. In the ^{13}C NMR spectrum of **8** and **9** each of the expected 13 peaks is doubled. More important, however, is the fact that both substances in the mixture show only two carbonyl carbons each. The "missing" carbonyl carbons appear instead as a pair of peaks at 95.1 and 100.6 ppm, indicative of hemiketal carbons.[11] In a similar fashion the isomerized trans compound **15** shows two carbonyl carbons at 196.6 and 169.9 ppm and a hemiketal carbon at 101.5 ppm.

Further evidence that the products of the Diels–Alder reaction are interconvertible hemiketals was provided by the result of zinc–acetic acid reduction of the adduct mixture. This reaction carried out at room temperature for 10 min afforded a single crystalline product **10**, mp 140–142 °C, in 93% yield. Despite the acidic conditions of this reduction, no change other than saturation of the enone double bond and formation of only a five-membered hemiketal ring occurs. The assignment of ring-junction stereochemistry is made again on the basis of the position of the carbomethoxy methyl group in the proton spectrum of **10** relative to the equivalent absorption in the spectrum of the corresponding trans isomer **16** (Scheme II). The latter material was prepared both by isomerization of **10** on silica gel and by zinc reduction of **15**.

Formulation of the hemiketal ring of **10** as five rather than six membered was made originally on conformational grounds. Saturation of the enone double bond of **9** would lead to the 3,3,1 bicyclic system **13**. Depending upon the specific con-



13

formation of the compound, this system would suffer either a severe nonbonded interaction on the concave side of the molecule or a boat 1,4 interaction on the top face of the ketone ring. As a consequence, **13** should be conformationally unfavorable compared to the considerably less hindered five-membered hemiketal **10**. Verification of this conclusion was provided by the result of an X-ray structure determination. As shown in Figure 1, the dihydro material is indeed the five-membered hemiketal isomer.

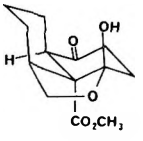
As shown in Scheme I, the next step in the transformation of the Diels–Alder product to an appropriate ajugarin I precursor is saturation of the ring-A double bond. Catalytic hydrogenation of **10** over palladium proceeded smoothly to afford the tetrahydro compound **11**, mp 142–145 °C, in 96%

Table I. X-ray Structure Determination of Compounds 10 and 11[a]

crystal data	10	11
unit-cell parameters		
a	14.08866 (6) Å	14.18523 (7) Å
b	7.09289 (6) Å	21.14905 (11) Å
c	13.19149 (10) Å	8.08458 (6) Å
	90.0222°	90.03551° (6)
	116.0957°	90.09968° (6)
	90.0400°	89.89425° (3)
volume	1184.5 Å^3	2425.4 Å^3
d_{calcd}	1.41	1.39
d_{dis}	1.43	1.41
formula wt.	252	254
Z	4	8
crystal system	monoclinic	orthorhombic
space group	$P2_1/C$	P_{bca}
data collection		
radiation	Mo Kα^- = 0.71069 Å	
mode	θ–2θ scan	
scan rate	5.85–29.3° min^{-1}	7.20–29.3° min^{-1}
scan range	[2θ(Kα_1) − 1.0]° → [2θ(Kα_1) + 1.2]°	
scan width	2°	2°
check reflect.	measured every 100 reflect.	
2θ range	up to 50°	
reflect. measured	2199	2158
reflect. accepted for refinement		
with $I_o \geq 3.0\ \sigma(I_o)$	1989	1982
R	0.049	0.053
R_w	0.070	0.066

[a] The structures were solved by direct methods. Normalized structure factors (*E* values) were calculated using overall scale factors and isotopic thermal parameters obtained from Wilson plots. The 350 strongest peaks (*E* values >1.33 for **10** and E values >1.35 for **11**) were used as input for the program MULTAN. An *E* map based on the phase set showing the highest figure of merit revealed the positions of all nonhydrogen atoms. Hydrogen positions were obtained from a difference map made after several isotropic refinement cycles, and they were refined using a fixed isotropic thermal parameter of 5.0. They were then held fixed for further isotropic and also during subsequent anisotropic refinement. During the last least-square cycle, no parameter shifted more than 0.001σ and a final difference map showed no peaks greater than 0.27 e/Å^3 for **10** and 0.35 e/Å^3 for **11**.

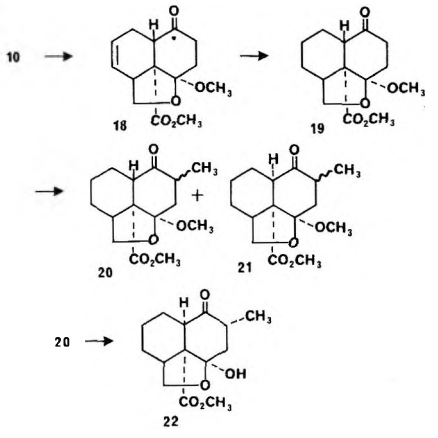
yield. That the stereochemistry of **11** should be as shown is by no means obvious from simple considerations of possible strain in the tricyclic ring system. The inference drawn from molecular models is that the isomeric structure **14**, in which the hemiketal hydroxyl group has a β configuration, should be of lower energy than **11**. In contrast, the stereochemistry shown for **11** dictates that one of the carbocyclic rings be a



14

boat. Despite this, the molecule does in fact have the latter geometry at least in the crystalline form. Figure 2 illustrates the structure obtained from X-ray analysis and shows that it is the carbonyl-containing ring which has a twist-boat conformation. Remarkably, the cis-fused isomer **11** also appears to be of lower energy than its trans-fused epimer **17**, mp 153–155 °C (Scheme II). When either of these isomers is absorbed on silica gel to effect ring-junction isomerization, the predominant component of the resulting eluent is the cis compound **11**.[12]

Following the establishment of the regio- and stereochemical course of the Diels–Alder reaction of **5** and **6** and of the isomerizations and reductive transformations already discussed, we focused our attention on two critical problems. Both of these synthetic concerns arise from the particular choice of the original Diels–Alder components. The initial dienophile **6**, although readily available, lacks the eventual C-8 methyl group of ajugarin I. The first problem to be faced then was the practicality of introducing this methyl by al-



kylation of an intermediate along the synthetic trail. Should this step prove particularly inefficient or unachievable it would be necessary to return to the initial cycloaddition reaction and use the appropriate methyl-substituted quinone **4**, a compound requiring a considerable lengthier preparation than **6**. Methylation was achieved in the following way. The *cis*-dihydro material **10** was converted to the *trans*-methyl ketal **18**, mp 91–92.5 °C, by the action of methanol and acid. Hydrogenation of the latter gave the saturated ketal **19**, mp 70–73 °C. Methylation was then effected in 50% yield by means of enolate formation with lithium diisopropylamide and alkylation with methyl iodide. After chromatography, two methylated products **20**, mp 76–80 °C, and **21** were obtained in a ratio of 4:1.[13] Hydrolysis of **20** in acidic medium afforded the methylated hemiketal **22**.

The second and more critical problem arising from the specific Diels–Alder approach discussed so far is that of the

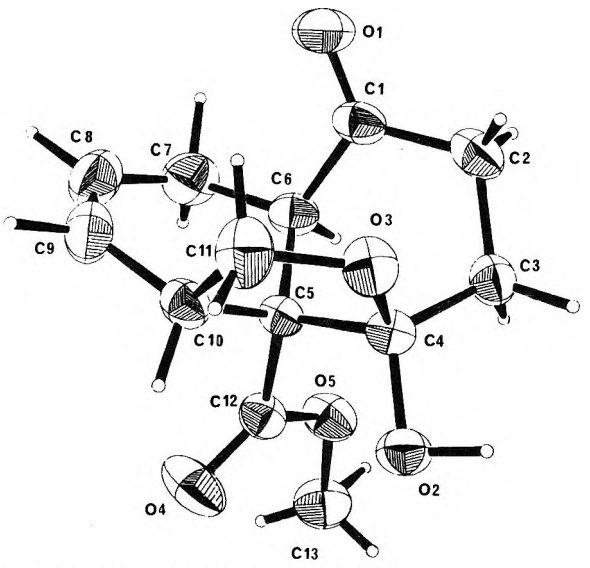


Figure 1. A perspective drawing of **10.**

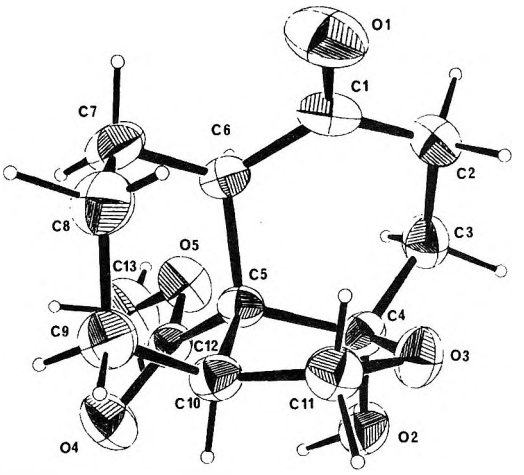


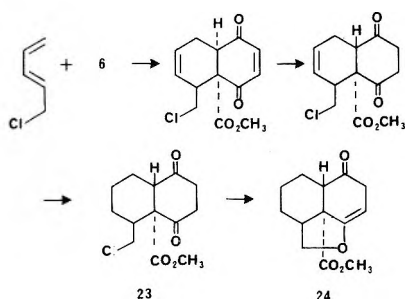
Figure 2. A perspective drawing of **11.**

opening of the hemiketal ring. Neither the initial Diels–Alder mixture or its isomerized and/or reduced transformation products show any indication of containing the corresponding hydroxymethyl diketone tautomers. Furthermore, attempts to open any of these hemiketals by trapping some small concentration of free primary alcohol have been generally unsuccessful.[14] For example, the treatment of **10** with base (sodium hydride or pyridine) and acylating agents (acetyl chloride, methanesulfonyl chloride, or toluenesulfonyl chloride) yields no recognizable acetate or sulfonate derivatives.

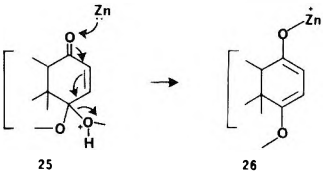
On the basis that the C-9 ketone group in the saturated compounds might be undergoing reaction under the basic conditions used to try to cleave the hemiketal ring, we moved to protect the carbonyl function through ketal formation. However, when **11** was exposed to ethylene glycol and acid, considerably more than simple ketal formation transpired. The intended carbonyl-masking process was accompanied by ring-junction isomerization and dehydration, yielding the cyclic enol ether[15] ketal **12** (Scheme I). The structure of **12** follows from its ^{13}C spectral characteristics as well as from the fact that it is reconverted to **11** upon treatment with aqueous acid.

Our efforts to open the hemiketal ring being thus frustrated, we turned to an alternative approach using a different Diels–Alder adduct; one incapable of forming the adamantine hemiketal unit. To this end, we prepared the chloromethyl diketone **23,** mp 123–125 °C, by the sequence illustrated in Scheme III. Attempted elimination of hydrogen chloride from this molecule to form the exocyclic olefin was unsuccessful. Treatment of **23** with DBN, for example, led only to the keto *enol ether* **24,** which upon acid hydrolysis gave hemiketal **11** again. Clearly, the proximity of the keto group at C-6 to the chloromethyl unit allows the ketone oxygen to participate in the dehydrochlorination process.

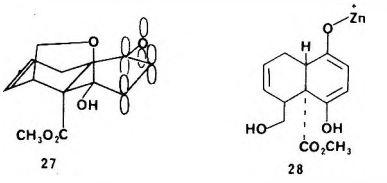
Scheme III



The problem of opening the hemiketal ring was solved finally by recourse to a reaction we had routinely employed in the early stages of this work; zinc in acetic acid reduction of a γ-alkoxyenone.[16] The mechanism for the conversion of **8** and **9** to **10** or of **15** to **16** presumably entails the elimination of one of the γ-oxygen functions as shown in **25** to **26.** The question then arises: can one distinguish between the two groups, or is



either one, alkoxy or hydroxy, eliminated with equal ease? For the cis compounds **8** and **9,** no clear-cut answer is forthcoming from an examination of models. In the case of the trans compound, however, there should be a mechanistic distinction between the two γ-position oxygen groups. As shown in **27,** only the bond linking the ring oxygen to the B-ring lies perpendicular to the plane of the enone system. Only through the cleavage of this bond can overlap between the developing p orbital at C-6 and the rest of the unsaturated unit be achieved. The conversion of the trans compound **15** to **16** should then occur via the intermediacy of the enol–enolate **28.** The ulti-

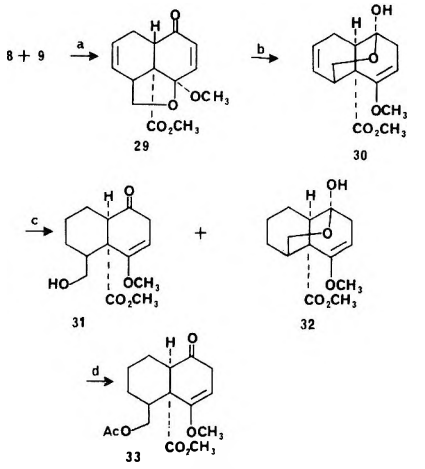


mate production of the keto hemiacetal **16** should result from ketonization of **28** followed by addition of the hydroxyl function to the regenerated C-6 carbonyl.

On the basis of the foregoing argument, a solution to the problem of hemiketal opening seemed readily at hand. Substitution of an alkoxy group for the hydroxy function of **15** should preclude the formation of a ketal product, since the intermediate stage would not be an *enol*–enolate but rather an *enol ether*–enolate.[17] The following sequence was then carried out to test these predictions.

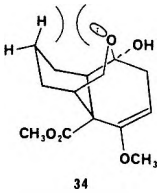
Treatment of the initial Diels–Alder adduct mixture **8** and **9** with methanol and toluenesulfonic acid afforded the trans-fused methyl ketal **29,** mp 106–107 °C (Scheme IV). The latter was then subjected to reduction with zinc in acetic acid. Somewhat surprisingly, the reduction in this case was extremely sluggish in comparison to others reported here. Stirring for 12 h was found necessary to effect saturation of the enone double bond. As anticipated, however, the principal

Scheme IV



[a] CH_3OH, H^+; [b] Zn, HOAc; [c] H_2, Pd; [d] Ac_2O, pyridine.

product was indeed a methyl enol ether[18] but no ketonic carbonyl group appeared in the spectra of the product. Instead, the product was again a hemiketal, in this instance the cis-fused six-membered one **30**, mp 143–145 °C, obtained in 64% yield. Although we had not previously encountered any ring-junction isomerization during short-term zinc reductions, apparently the time required for the reduction of **29** is sufficiently lengthy to allow the epimerization of the initially formed trans product to occur. The Gordian knot of this hemiketal proved simpler to cut than in the case of the five-membered one, however. We anticipated that the stability of the new hemiketal ring ought to be sharply reduced by saturation of the ring A double bond. Such a transformation leads to a 3,3,1-bicyclo system, e.g., **34**, which can relieve conformational interactions by opening of the heterocyclic ring. In the event, catalytic reduction of **30** afforded a product which proved to be a mixture of the keto enol ether **31** and the corresponding hemiketal **32**. Complete opening of the hemiketal ring was then accomplished by treatment of the mixture with acetic anhydride–pyridine to afford the diketo acetate **33**.



The Diels–Alder approach to the synthesis of ajugarin I discussed above has at present accomplished our initial goal; rapid construction of the decalin ring system with functionality strategically located for introduction of the remaining structural features of the natural product. Further transformations and alternative strategies will be discussed in forthcoming publications.

Experimental Section

Melting points were determined on an Arthur A. Thomas uni-melt apparatus. All melting and boiling points are uncorrected. Infrared spectra were determined on a Perkin-Elmer 257 grating infrared spectrometer, and Nuclear Magnetic Resonance (NMR) spectra were recorded using a Varian EM-360 spectrometer. Chemical shifts are reported in parts per million (δ) relative to Me_4Si (0.0 ppm) as an internal standard. ^{13}C spectra were recorded on a Varian Associates CFT-20 instrument. Mass spectra were determined either with a Varian Associates M-66 cycloidal mass spectrometer or a Finnigan Model 4000 GC–MS instrument. Microanalyses were performed by Atlantic Microlab Inc., Atlanta, Ga., and precise mass measurements were obtained with the M-66 mass spectrometer.

Diels–Alder Reaction of Carbomethoxy-*p*-benzoquinone and 1-Hydroxymethylbutadiene. Preparation of 8 and 9. To a stirred solution of 1.28 g (7.6 mmol) of carbomethoxy-*p*-benzoquinone in 6 mL of dry benzene at 0 °C was added dropwise, via a syringe, 0.68 g (8.1 mmol) of 2,4-pentadien-1-ol.[19] The reaction mixture was allowed to warm to room temperature and stirred under nitrogen for 2 h, during which a solid was precipitated. The solid was filtered and washed with cold benzene. Recrystallization from benzene afforded a white crystalline solid: 1.44 g (74.3%), mp 108–114 °C; IR ($CHCl_3$) 1740, 1680 cm^{-1}; NMR ($CDCl_3$) δ 1.78–4.43 (m, 7 H), 3.69, 3.71 (2 s, 3 H), 5.76 (m, 2 H), 6.01–6.72 (m, 2 H).

Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.45; H, 5.66.

Preparation of the Dihydro Cis Adduct 10. To a stirred solution of 5.05 g (20.2 mmol) of **8** and **9** in 50 mL of glacial acetic acid was added 10.0 g of zinc dust in small portions. The reaction mixture was allowed to stir at room temperature for 10 min. The mixture was poured into 200 mL of ice water. The zinc was removed by filtration and the filtrate was washed with chloroform. The aqueous layer was extracted four times with chloroform, and the combined chloroform extracts were washed with 10% aqueous sodium bicarbonate and dried over anhydrous magnesium sulfate. Removal of the solvent gave 4.70 g (93%) of a white solid, mp 140–142 °C. An analytical sample was prepared by recrystallization from benzene: IR ($CHCl_3$) 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.49–2.92 (m, 6 H), 3.12–3.62 (m, 4 H), 4.08–4.48 (m, 2 H), 5.67 (m, 2 H), 3.78 (s, 3 H); ^{13}C NMR δ 210.2, 171.9, 125.3, 123.0, 106.0, 72.4, 60.4, 53.1, 45.5, 38.5, 35.3, 31.2, 20.3.

Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.89; H, 6.41. Found: C, 61.84; H, 6.39.

Catalytic Reduction of 10. Preparation of the Cis Hemiacetal 11. A solution of 3.0 g (11.9 mmol) of **10** in 25 mL of ethanol was hydrogenated under atmospheric pressure using 10% palladium on charcoal as catalyst. Hydrogen uptake ceased after 1 h. The catalyst was filtered through a Celite cake, and the solvent was removed on the rotory evaporator to give a white solid, 2.9 g (96%), mp 142–144.5 °C. An analytical sample was prepared by crystallization from benzene: IR ($CHCl_3$) 1720 cm^{-1}; NMR ($CDCl_3$) δ 0.79–1.71 (m, 5 H), 1.91–2.86 (m, 5 H), 3.19–3.52 (m, 3 H), 3.65 (s, 1 H), 3.78 (s, 3 H), 3.88–4.18 (m, 1 H); ^{13}C NMR δ 211.5, 172.5, 105.9, 69.6, 60.5, 52.8, 45.9, 36.9, 35.7, 30.4, 21.5, 16.1.

Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.15. Found: C, 61.24; H, 7.20.

Formation of Enol Ether Ketal 12. A mixture of **11** [2.0 g (7.8 mmol) in 25 mL of dry benzene], 0.438 mL (7.8 mmol) of ethylene glycol, and a catalytic amount of *p*-toluenesulfonic acid monohydrate was refluxed in a nitrogen atmosphere under a Dean–Stark trap. Separation of the water began immediately. Refluxing was continued for 4 h. The mixture was cooled, washed with 10% aqueous sodium bicarbonate, and dried over anhydrous magnesium sulfate. Removal of the solvent gave a yellow oil: 2.1 g (95%); IR ($CHCl_3$) 1720 cm^{-1}; NMR ($CDCl_3$) δ 0.75–2.0 (m, 6 H), 2.11–2.72 (m, 3 H), 2.30 (dd, 1 H, J = 4, 8 Hz), 3.77–4.16 (m, 2 H), 3.67 (s, 3 H), 3.84 (m, 4 H), 4.76 (t, 1 H); ^{13}C NMR 175.6, 151.7, 110.0, 91.9, 73.6, 64.3, 64.0, 54.5, 52.4, 42.6, 41.3, 31.7, 27.8, 23.7, 22.6; MS *m/e* 280.

Anal. Calcd for $C_{15}H_{20}O_5$: 280.13098. Found: *m/e* 280.13056.

Isomerization of the Diels–Alder Adduct. Formation of 15. To a stirred solution of 0.48 g (1.92 mmol) of **8** and **9** in 10 mL of methanol was added a few milligrams of diazabicyclononane (DABCO). The reaction mixture was allowed to stir at room temperature for 48 h. The solvent was concentrated on the rotory evaporator and the residual brownish oil was taken up in 50 mL of methylene chloride, washed with 3 N HCl, 10% aqueous sodium bicarbonate, and finally with brine solution. It was then dried over anhydrous magnesium sulfate. Removal of the solvent gave 0.40 g of a light-yellow semisolid, which was recrystallized from benzene to give a white crystalline material: 0.295 g (61.5%); mp 142–145 °C; IR ($CHCl_3$) 1730, 1695 cm^{-1}; NMR ($CDCl_3$) δ 1.83–2.37 (m, 2 H), 2.81 (dd, 1 H, J = 4, 7 Hz), 3.63 (s, 3 H), 3.82 (m, 2 H), 4.45 (m, 2 H), 5.74 (m, 2 H), 6.28 (AB q, 2 H, J = 10 Hz); ^{13}C NMR δ 196.6, 169.9, 141.6, 129.2, 127.1, 124.5, 101.5, 73.5, 62.2, 52.7, 43.7, 40.6, 21.7.

Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.29; H, 5.64.

Zinc Reduction of 15. Preparation of 16. A solution of 0.180 g (0.42 mmol) of **15** in 4 mL of glacial acetic acid was reduced with 0.36 g of zinc dust as previously described for the reduction of **8** and **9**. Evaporation of the solvent gave a clear oil which solidified upon standing: 0.173 g (95%); mp 116–118 °C; IR ($CHCl_3$) 1728 cm^{-1}; NMR ($CDCl_3$) δ 1.73–2.79 (m, 4 H), 2.42 (s, 4 H), 3.58–3.76 (m, 2 H), 3.62 (s, 3 H), 3.94–4.77 (m, 2 H), 5.67 (m, 2 H).

Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.89; H, 6.41. Found: C, 61.85; H, 6.43.

Catalytic Reduction of 16. Preparation of Trans Hemiketal 17. A solution of 82 mg (0.32 mmol) of **16** in 4 mL of ethyl acetate was

hydrogenated with 10% palladium/charcoal as previously described for the hydrogenation of **10**. Removal of the solvent gave 80 mL (97%) of a white solid: mp 153–155 °C; IR ($CHCl_3$); NMR ($CDCl_3$) 0.80–2.32 (m, 7 H), 2.42 (br s, 4 H), 3.09–3.55 (m, 1 H), 3.68 (s, 3 H), 3.78–4.38 (m, 2 H).

Anal. Calcd for $C_{13}H_{18}O_5$: 254.11621. Found: *m/e* 254.11538.

Diels–Alder Reaction of Carbomethoxy-*p*-benzoquinone with 1-Chloromethylbutadiene. To a stirred solution of 1.2 g (7.14 mmol) of carbomethoxy-*p*-benzoquinone in 8 mL of benzene was added dropwise 1.0 g (9.8 mmol) of 2,4-pentadienyl chloride.[20] The reaction mixture was stirred at room temperature overnight, during which time the color of the solution changed from orange to yellow. Removal of the solvent and the excess diene gave a yellow oil which solidified upon standing. The solid was recrystallized from an ether–hexane mixture to give a light-yellow crystalline solid: 1.51 g (79%); mp 99.5–101 °C; IR ($CHCl_3$) 1700, 1740 cm^{-1}; NMR ($CDCl_3$) δ 2.35 (m, 2 H), 2.97 (m, 1 H), 3.74 (s, 3 H), 3.45–4.07 (m, 3 H), 5.76 (m, 2 H), 6.60 (d, 2 H, J = 3 Hz); ^{13}C NMR δ 197.3, 194.1, 170.3, 140.4, 137.8, 125.9, 124.5, 62.5, 53.6, 50.1, 44.8, 43.6, 25.3.

Anal. Calcd for $C_{13}H_{13}O_4Cl$: C, 58.11; H, 4.88. Found: C, 58.15; H, 4.91.

Zinc Reduction of the Chloromethyl Adduct. A solution of 0.53 g (1.79 mmol) of the chloromethyl adduct in 8 mL of glacial acetic acid was reduced with 1.0 g of zinc dust as previously described for the reduction of **8** and **9**. Removal of the solvent gave a white solid: 0.48 g (91%); mp 121–124 °C. An analytical sample was prepared by recrystallization from ether–hexane: IR ($CHCl_3$) 1720 cm^{-1}; NMR ($CDCl_3$) δ 2.02–3.07 (m, 2 H), 3.17–4.16 (m, 3 H), 3.79 (s, 3 H), 5.74 (m, 2 H).

Anal. Calcd for $C_{13}H_{15}O_4Cl$: C, 57.68; H, 5.58. Found: C, 57.64; H, 5.60.

Preparation of 23. A solution of 0.177 g (0.66 mmol) of the above zinc reduction product in 8 mL of ethyl acetate was hydrogenated with 10% palladium/charcoal as previously reported for the hydrogenation of **10**. Removal of the solvent gave a white solid, 0.178 g (97%). An analytical sample was prepared by crystallization from chloroform–hexane: mp 123–125 °C; IR ($CHCl_3$) 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.19–2.28 (m, 7 H), 2.44–3.11 (m, 5 H), 3.77 (s, 3 H), 3.40–4.23 (m, 2 H).

Anal. Calcd for $C_{13}H_{17}O_4Cl$: C, 57.25; H, 6.28. Found: C, 57.15; H, 6.29.

Formation of Keto Enol Ether 24. Ketone **23** [0.150 g (0.55 mmol)] was dissolved in 6 mL of dry benzene in a 10-mL round-bottom three-neck flask equipped with septum, nitrogen inlet, and a refluxing condenser. Diazabicyclononene (0.1 g) was added via syringe. The solution became brown. The reaction mixture was heated in an oil bath to 50–60 °C for 4 h. It was then cooled to room temperature, poured into ice, and neutralized with cold dilute sulfuric acid. The neutral solution was extracted twice with benzene. The combined yellow benzene extracts were washed with water and 10% sodium bicarbonate solution and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a yellow-brown oil which was kugelrohr distilled to give a light-yellow oil: IR ($CHCl_3$) 1730, 1700, 1640 cm^{-1}; NMR ($CDCl_3$) 0.94–2.15 (m, 6 H), 2.46–2.84 (m, 2 H), 2.88 (d, 2 H, J = 4 Hz), 3.62 (s, 3 H), 4.26 (dd, 1 H, J = 4 Hz), 4.97 (t, 1 H); MS *m/e* 236 (M^+).

The above oil was dissolved in 3 mL of a THF–H_2O–HCl mixture and allowed to stir overnight. Workup afforded hemiketal **11**.

Preparation of Ketal 18. To a solution of 0.40 g (1.58 mmol) of **10** in 10 mL of methanol was added a few milligrams of *p*-toluenesulfonic acid monohydrate. The reaction was stirred at room temperature for 2 days. Workup was carried out as described for the preparation of **12**. Removal of the solvent gave a white oily solid. Recrystallization from an ether–hexane mixture gave 0.295 g of white crystalline solid: mp 91–92.5 °C (70.2%); IR ($CHCl_3$) 1740 cm^{-1}; NMR ($CDCl_3$) δ 1.68–2.80 (m, 7 H), 3.22 (s, 3 H), 3.62 (s, 3 H), 3.54–4.31 (m, 3 H), 5.71 (m, 2 H); ^{13}C NMR δ 207.2, 169.9, 126.6, 126.0, 106.0, 71.1, 62.5, 52.1, 48.6, 46.0, 40.6, 36.17, 28.3, 21.7.

Anal. Calcd for $C_{14}H_8O_5$: C, 63.63; H, 6.10. Found: C, 63.70; H, 6.14.

Preparation of Saturated Ketal 19. A solution of 1.2 g (4.5 mmol) of **18** in 15 mL of ethanol was hydrogenated with 10% palladium/charcoal as previously described for the hydrogenation of **10**. Removal of the solvent gave a white solid: 1.19 g (98%); mp 70–73 °C. An analytical sample was obtained by crystallization from an ether–hexane mixture: IR ($CHCl_3$) 1730 cm^{-1}; NMR ($CDCl_3$) δ 0.61–2.08 (m, 7 H), 2.08–2.60 (m, 5 H), 3.16 (s, 3 H), 3.26–4.21 (m, 2 H), 3.59 (s, 3 H).

Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.79; H, 7.56.

Methylation of Ketal 19. Following the procedure of House,[21] 0.41 mL (0.926 mmol) of 2.29 M *n*-butyllithium and a few milligrams of triphenylmethane were dissolved in 5 mL of dry 1,2-dimethoxyethane (dried over lithium aluminum hydride) under nitrogen. The reaction mixture was cooled to −20 °C and 0.129 mL (0.926 mmol) of diisopropylamine was added dropwise via syringe. Ketal **19** [0.250 g (0.926 mmol)] in 2.5 mL of 1,2-dimethoxyethane was added dropwise. The resultant pink solution was allowed to warm to room temperature, and then 0.42 mL (7.3 equiv) of methyl iodide was added. The reaction was stirred at room temperature for 15 min, during which a precipitate was formed. Three milliliters of dilute hydrochloric acid was added and the resultant yellow solution was extracted twice with ether. The combined ether extracts were washed with a 10% aqueous sodium bicarbonate solution and then with brine and dried over anhydrous magnesium sulfate. Removal of the solvent gave a thick yellow oil, 0.216 g. The oil was chromatographed on 35 g of silica gel. Elution with an ethyl acetate–hexane mixture gave 33 mg of the cis isomer as a clear oil: IR ($CHCl_3$) 1722 cm^{-1}; NMR ($CDCl_3$) 0.92–3.07 (m, 9 H), 1.19 (d, 3 H, J = 6.5 Hz), 3.20 (s, 3 H), 3.25–4.03 (m, 4 H), 3.77 (s, 3 H).

Further elution gave the trans isomer, 95 mg, as a white solid: mp 76–80 °C; total yield 49.21%; IR ($CHCl_3$) 1722 cm^{-1}; NMR ($CDCl_3$) δ 0.86–3.05 (m, 10 H), 1.19 (d, 3 H, J = 6.5 Hz), 3.24 (s, 3 H), 3.35–4.22 (m, 3 H), 3.65 (s, 3 H).

Anal. Calcd for $C_{15}H_{22}O_5$: *m/e* 282.14683. Found: *m/e* 282.14511.

Preparation of Ketal 29. To a solution of 2.0 g (8 mmol) of **8** and **9** in 20 mL of absolute methanol was added a few milligrams of *p*-toluenesulfonic acid monohydrate. The reaction was stirred at room temperature for 3.5 h. The solvent was concentrated on the rotory evaporator and the residue was taken up in 30 mL of chloroform, washed with 10% aqueous sodium bicarbonate solution, and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a white oily solid. The solid was recrystallized from a chloroform–hexane mixture to give 0.82 g of white crystalline material: mp 106–107 °C. The mother liquor was concentrated and chromatographed on silica gel. Elution with ethyl acetate–hexane gave an additional 0.43 g (59%): IR ($CHCl_3$) 1685, 1740 cm^{-1}; NMR ($CDCl_3$) δ 2.0–2.36 (m, 2 H), 2.57 (dd, 1 H, J = 6, 8 Hz), 3.27 (s, 3 H), 3.58 (s, 3 H), 3.45–4.33 (m, 3 H), 5.88 (m, 2 H), 6.43 (AB q, 2 H).

Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.70; H, 6.14.

Formation of Hemiketal Enol Ether 30. To a stirred solution of 1.5 g (5.68 mmol) of **19** in 20 mL of glacial acetic acid was added 3.0 g of zinc dust in small portions. The reaction mixture was stirred at room temperature under nitrogen for 12 h. It was then poured into a solution of 5% aqueous sodium acetate. The zinc was filtered and washed with chloroform. The aqueous layer was extracted three times with chloroform. The combined chloroform extracts were washed with 10% aqueous sodium bicarbonate solution and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave an oily solid. The solid was recrystallized from a chloroform–hexane mixture to give a white crystalline material: 0.87 g, mp 143–145 °C. The mother liquor was concentrated on the rotory evaporator and yielded, after recrystallization, an additional 95 mg of product (63.8%): IR ($CHCl_3$) 1735, 1670 cm^{-1}; NMR ($CDCl_3$) 2.07–2.84 (m, 6 H), 3.37–4.20 (m, 3 H), 3.45 (s, 3 H), 3.65 (s, 3 H), 4.73 (t, 1 H), 5.72 (m, 2 H).

Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81. Found: C, 63.07; H, 6.84.

Formation of Ketone–Hemiketal Mixtures 31 and 32. A solution of 1.0 g (3.8 mmol) of **30** in 25 mL of ethanol was hydrogenated with 10% palladium/charcoal as previously reported for the hydrogenation of **10**. Evaporation of the solvent gave a light yellow oil (1.04 g) which partially solidified upon standing: IR ($CHCl_3$) 1730, 1670 cm^{-1}; NMR ($CDCl_3$) 3.41, 3.50 (2 s, 3 H), 3.63, 3.68 (2 s, 3 H), 4.70 (m, 1 H).

Preparation of Keto Acetate 33. A mixture of 91 mg (0.34 mmol) of **31** and **32** in 0.5 mL of dry pyridine and 0.086 g (0.85 mmol) of acetic anhydride, under nitrogen, was allowed to stir at room temperature for 2 h, during which time the solution became reddish orange. Sodium bicarbonate (2 mL of 10% solution) was added to destroy excess acetic anhydride. The reaction mixture was added into water and extracted twice with 10 mL of ether. The ether extracts were washed with 5% acetic acid, 10% sodium bicarbonate and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave 79 mg of an orange oil. The oil was purified by preperative thin-layer chromatography to give a light-yellow oil: IR ($CHCl_3$) 1730, 1670; NMR ($CDCl_3$) 1.19–2.54 (m, 7 H), 2.01 (s, 3 H), 2.80–3.16 (m, 1 H), 2.90 (d, 2 H, J = 4 Hz), 3.56 (s, 3 H), 3.69 (s, 3 H), 4.04 (m, 2 H).

Anal. Calcd for $C_{16}H_{22}O_6$: 310.14152. Found: *m/e* 310.14432.

Acknowledgment. This research was supported by a grant from the Public Health Service (ES-01615-01). We thank Dr. Donald Vanderveer of the Georgia Institute of Technology for

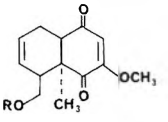
aid in obtaining X-ray measurements and Dr. Walter Dean of this department for help in solution of the structures. We also thank the National Science Foundation for a Departmental Instrument Grant in support of the purchase of a Finnigan Model 4000 GC–MS data system.

Registry No.—**1**, 62640-05-5; **5**, 4949-20-6; **6**, 3958-79-0; **8**, 66515-72-8; **9**, 66515-73-9; **10**, 66515-74-0; **11**, 66515-75-1; **12**, 66515-76-2; **15**, 66538-02-1; **16**, 66538-03-2; **17**, 66538-04-3; **18**, 66515-77-3; **19**, 66515-78-4; **20**, 66515-79-5; **21**, 66538-05-4; **23**, 66515-80-8; **24**, 66515-81-9; **29**, 66515-82-0; **30**, 66551-68-6; **31**, 66515-83-1; **32**, 66515-84-2; **33**, 66515-85-3; 2,4-pentadienyl chloride, 40596-30-3; 4a-α-carbomethoxy-5β-chloromethyl-4a,5,8,8a-β-tetrahydronaphthalene-1,4-dione, 66515-86-4; 4a-α-carbomethoxy-5β-chloromethyl-2,3,4a,5,8,8a-β-hexahydronaphthalene-1,4-dione, 66515-87-5.

Supplementary Material Available. Tables listing atom parameters, thermal parameters, bond distances, and bond angles for compounds **10** and **11** (12 pages). Ordering information is given on any current masthead page.

References and Notes

(1) I. Kubo, Y.-W. Lee, V. Balogh-Nair, K. Nakanishi, and A. Chapya, *J. Chem. Soc., Chem. Commun.*, 949 (1976).
(2) K. Nakanishi, T. Goto, S. Ito, S. Natori, and S. Nozoe, Ed., "Natural Products Chemistry", Vol. 1, Academic Press, New York, N.Y., 1974, p 208. For recent examples, see, W. Herz, A.-M. Pilotti, A.-C. Soderholm, I. Shuhama, and W. Vichnewski, *J. Org. Chem.* **42**, 3913 (1977).
(3) (a) K. Munakata in "Control of Insect Behavior by Natural Products", Academic Press, New York, N.Y., 1970, pp 179–187. (b) N. Kato, S. Shibayama, and K. Munakata, *J. Chem. Soc. D* 1632 (1971). (c) S. Hosozawa, N. Kato, K. Munakata, and Y.-L. Chen, *Agric. Biol. Chem.*, **38**, 1045 (1974). (d) S. Hosozawa, N. Kato, and K. Munakata, *Agric. Biol. Chem.*, **38**, 823 (1974). (e) S. Hosozawa, N. Kato, and K. Munakata, **Tetrahedron Lett.**, 3753 (1974).
(4) (a) W. Nudenberg, A. Gaddis, and L. Butz, *J. Org. Chem.*, **8**, 500 (1943). (b) J. Cason, *Org. React.*, **4**, 354.
(5) (a) J. Sauer, *Angew. Chem., Int. Ed. Engl.*, **6**, 16 (1967). (b) Z. Stojanac, R. Dickinson, N. Stojanac, R. Waznow, and Z. Valenta, *Can. J. Chem.*, **53**, 616 (1975).
(6) O. Eisenstein, J. Lefour, N. Anh, and R. Hudson, *Tetrahedron*, **33**, 523 (1977), and references therein.
(7) (a) M. F. Ansell, B. W. Nash, and D. A. Wilson, *J. Chem. Soc.*, 3012 (1963). (b) M. F. Ansell and A. H. Clements, *J. Chem. Soc. C*, 270 (1971).
(8) This Diels–Alder combination yields the "ortho" product exclusively and quantitatively. Unpublished results of this laboratory.
(9) In our experience, Diels–Alder reactions with carbomethoxy-*p*-benzoquinone are best carried out at room temperature. Elevated temperatures lead to lower yields of less pure products.
(10) M. F. Ansell, J. W. Lown, D. W. Turner, and D. A. Wilson, *J. Chem. Soc.*, 3036 (1963).
(11) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972.
(12) The cis compound **11** is also produced as the major product in the hydrolysis of enol ether ketal **12**, as well as when either **11** or **17** is treated with DABCO.
(13) Our assignment of stereochemistry to the methyl group of **22** is tentative. Since isomerization of the ring junction occurs in the hydrolysis of **20** to **22**, we assume that epimerization also occurs at C-8 to produce the more stable equatorial isomer.
(14) It has been reported recently [J.-L. Gras, *Tetrahedron Lett.*, 4117 (1977)] that 3-methoxy-2,4-toloquinone reacts with **5** to give adduct i (R = H) and that the latter is converted to its tetrahydropyranyl ether ii (R = THP) with dihydropyran at 0 °C. We have also found that the mixture of adducts **8** and **9** also form a THP derivative under these conditions. Unfortunately, this diketo ether has not proven synthetically useful. We would also suggest that Gras' adduct is almost certainly the hemiketal compound equivalent to **8** rather than the free hydroxymethyl material.



i R = H
ii R = THP

(15) Structure **12** is formally a Bredt's rule violation. The outer 11-membered ring is sufficiently large, however, to easily accommodate a trans double bond: (a) J. Marshall and H. Faubi, *J. Am. Chem. Soc.*, **92**, 948 (1970); (b) J. R. Weisman and W. A. Pletcher, *J. Am. Chem. Soc.*, **92**, 956 (1970).
(16) H. Uberwasser, K. Heusler, J. Kalvoda, Ch. Meystre, P. Wieland, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **46**, 344 (1963).
(17) Ketalization could of course occur by protonation of the enol ether double bond and addition of the hydroxymethyl oxygen to the resulting cation.
(18) The NMR spectrum of the crude product from zinc reduction of **30** reveals the presence of a small amount of the alternative enol ether **25**.
(19) S. Oida and E. Ohki, *Chem. Pharm. Bull.*, 990 (1969).
(20) L. Crombie, S. H. Harper, and D. Thompson, *J. Chem. Soc.*, 2906 (1951).
(21) H. O. House, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **36**, 2361 (1971).

Synthesis of the New Nucleoside Antibiotic 1-(2-Deoxy-β-D-ribofuranosyl)-5,6-dihydro-5-methyl-*s*-triazine-2,4(1*H*,3*H*)-dione[1]

Harvey Skulnick

The Upjohn Company, Experimental Chemistry Research, Kalamazoo, Michigan 49001

Received June 28, 1977.

1-(2-Deoxy-β-D-ribofuranosyl)-5,6-dihydro-5-methyl-*s*-triazine-2,4(1*H*,3*H*)-dione, "DHAdT" (I), a new nucleoside with both antiviral and antibacterial activity, has been synthesized along with its ribosyl analogue via the silyl ether modification of the Hilbert–Johnson reaction. Condensation of the mono- or disilyl-5,6-dihydro-5-methyl-*s*-triazine-2,4(1*H*,3*H*)-diones (V and VI) with 3,5-ditoluoyl-2-deoxy-D-ribofuranosyl chloride (VII) gave the protected nucleosides VIII and IX which, after removal of the protecting groups, afforded "DHAdT" (I) and its α anomer X. Condensation of V with tribenzoylribofuranosyl bromide (XI) or acetate (XII) gave the N_3 riboside. When V was condensed with tetraacetyl ribose (XIII), the N_1 and N_3 isomers were isolated. The ribose analogue was devoid of both antiviral and antibacterial activity.

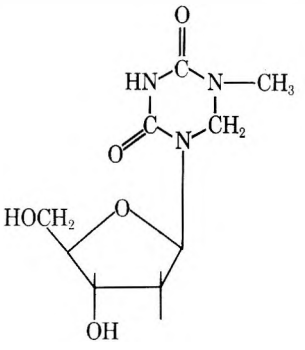
Bannister and DeBoer recently reported the isolation of a nucleoside antibiotic, 1-(2-deoxy-β-D-ribofuranosyl)-5,6-dihydro-*s*-triazine-2,4(1*H*,3*H*)-dione, I (DHAdT), from the culture *Streptomyces platensis* var. *clarensis*.[2] This same culture produces the nucleoside 1-*N*-methylpseudouridine, a compound whose isolation was reported by Argoudelis and Mizsak[3] and whose synthesis was recently reported by Fox et al.[4]

DHAdT exhibited in vitro activity against a variety of DNA viruses, including herpes simplex type 1, herpes simplex type 2, varicella zoster, and vaccinia, and gram-negative bacteria, although modest activity was observed vs. *Streptococcus hemolyticus* bacteria and poor activity vs. *Diplococcus pneumoniae*.[5] Thymidine and deoxyuridine completely reversed the antiviral activity, while deoxycytidine was partially effective.

0022-3263/78/1943-3188$01.00/0

DHAdT was active, in vivo, when administered PO, SQ, and IP; however, to date topical activity has not been demonstrated. Administered SQ, the nucleoside was active both prophylactically and therapeutically in mice innoculated IV with herpes simplex virus.[6]

This paper details the synthesis of the new nucleoside I, DHAdT, and its riboside analogue via the silyl ether modification of the Hilbert–Johnson condensation. This is the first reported application, to my knowledge, of the silyl ether procedure to the synthesis of a 5,6-dihydro nucleoside.



I
5,6-dihydro-5-azathymidine
(DHAdT)

The initial objective is the synthesis of the silyltriazine V. In 1961 Piskala and Gut reported the synthesis of 5-*N*-methyl-5,6-dihydro-*s*-triazine-2,4(1*H*,3*H*)-dione (IV) via the ring closure of *N*-methylbiuret with ethyl formate to yield III, followed by the reduction of the *N*-methyl-*s*-triazine with Raney Nickel (W2) or 5% Rh/C.[7]

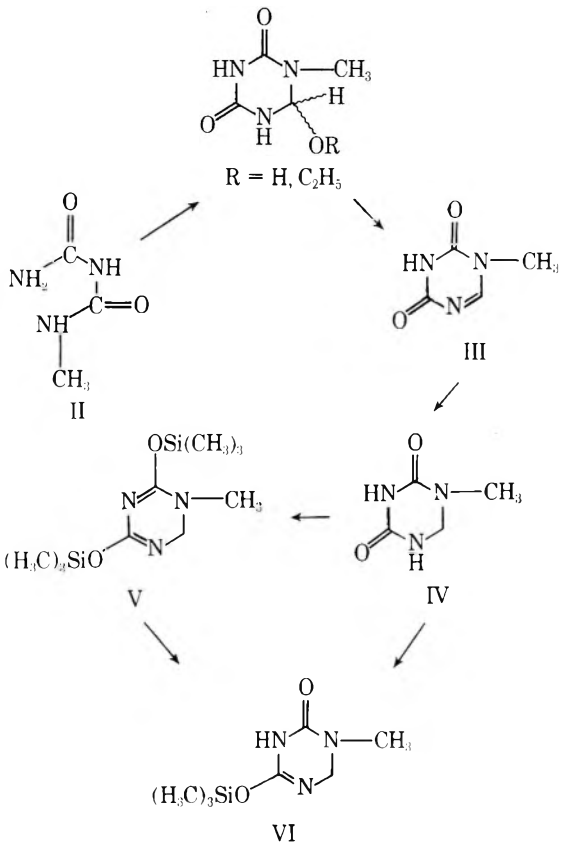
We found that the *N*-methyltriazine III is recovered as an ethanol or water adduct which can be reduced directly to IV. Alternatively, this adduct can be converted to triazine III by azeotroping from benzene with *p*-toluenesulfonic acid added. Silylation of the dihydro-*s*-triazinone IV with refluxing hexamethyldisilazane gave 2,4-bis(trimethylsilyloxy)triazine (V) as an oil. This disilyl base slowly hydrolyzed on standing to a crystalline monosilyltriazine whose ^{1}H NMR is consistent with the assigned structure VI.

The ^{1}H NMR signal observed for the methylene of IV appears at 4.30 ppm (Me_2SO) as a doublet. Irradiation of the N_1–H at 7.60 ppm reduced the methylene to a singlet, consistent with the assigned isomer, IV. The ^{1}H NMR of V has a singlet at 4.30 ppm ($CDCl_3$) for the methylene. When V hydrolyzed to the monosilyl triazine VI with the appearance of an N–H at 7.25 ppm ($CDCl_3$), the methylene remained a singlet, consistent with hydrolysis of the 4-*O*-trimethylsilyl group. The monosilyl triazine VI can also be synthesized directly using bis(trimethylsilyl)trifluoroacetamide in pyridine at 25 °C for 18 h.

The plan to prepare nucleoside I involved the condensation of the silylated triazine with the appropriate sugar. Although there is no reported synthesis of a nucleoside from a monosilylated triazine or pyrimidine, the synthesis of *s*-triazine nucleosides from their disilyl bases has been reported previously. In 1970 Winkley and Robins described the synthesis of 5-azacytidine and related derivatives employing direct glycosidation of a bissilyl-1,3,5-triazine ring.[8] The use of $SnCl_4$ as a Friedel–Crafts catalyst in Hilbert–Johnson type reactions is exemplified in the syntheses of 5-azacytidine[9] and *as*-triazine nucleosides by Vorbrüggen and co-workers.[10] There is, however, no reported synthesis of a dihydro (nonaromatic) triazine ring nucleoside via an acid-catalyzed condensation.

The only other previous *s*-triazine nucleoside synthesis was that reported by A. Piskala and F. Sǒrm via the orthoformate cyclization of 1-peracetylglycosyl-4-methylisobiuret to give the corresponding 4-methoxy-5-azauracil nucleosides.[11]

Scheme I



Condensation of the mono- or disilylated dihydro-*s*-triazines (V and VI) with 3,5-di-o-toluoyl-D-ribofuranosyl chloride in an acetonitrile/ethylene dichloride mixture using anhydrous $SnCl_4$ as Lewis acid catalyst[12] gave a 1:1 mixture of α and β anomers of the 3′,5′-ditoluate esters of DHAdT (VIII and IX). The assignment of isomers was determined by ^{1}H NMR wherein the β isomer exhibited the characteristic triplet for the anomeric proton and the α isomer the characteristic quartet (see Experimental Section).

The site of glycosidation was determined to be N_1 based on a comparison of the synthesized nucleoside with the known DHAdT isolated from microbial sources. The structure of DHAdT was determined by B. Bannister to be a β-N_1 nucleoside.[13] X-ray analysis of the nucleoside confirmed its structure.[14]

The condensation reaction was carried out under a variety of conditions as shown in Table I. On a 1-mmol scale, the best yields of DHAdT (based on bioassay vs. Kp)[19] were obtained in the more polar solvents such as acetonitrile and nitromethane. However, nitromethane was eliminated as a possible solvent due to a difficulty in controlling reaction rates.

When the reaction scale was increased to 0.1 M using a 1:2 mM ratio of sugar/base, 1.3 mM $SnCl_4$ in CH_3CN at −25 °C for 18 h, the reaction time increased markedly (7–10 days) and yields of the β-nucleoside isomer decreased to 1–2%. In addition, the ratio of α/β anomers increased to 15:1. Making the reaction mixture homogeneous by first dissolving the 3,5-di-o-toluoyl-D-ribofuranosyl chloride in ethylene dichloride, adding this solution to the acetonitrile/$SnCl_4$/silyl triazine solution at −25 °C, and then warming to +25 °C brought the α/β ratio back to 1:1 and overall yields of the dihydro nucleosides to 70%. A 25–30% yield of the desired β-nucleoside isomer can be directly crystallized out. Following the reaction progress by TLC indicates that the kinetics involve initial α-anomer formation at −25 °C followed by slow formation of the β-anomer at +25 °C. In addition, the reaction could now be warmed to 40–50 °C without any noticeable decomposition,

Table I

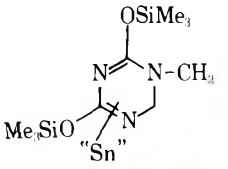
mM sugar/ mM base[a]	catalyst, mM $SnCl_4$	solvent	temp, °C	time	α/β	DHAdT yield,[23] %
1:1	0.7	$C_2H_4Cl_2$	5	18 h		0
1:2	0.7	$C_2H_4Cl_2$	5	18 h	4:1	2.85
2:1	0.7	$C_2H_4Cl_2$	5	18 h		<0.1
1:1	0.7	$C_2H_4Cl_2$	−25	18 h		0
1:2	0.7	$C_2H_4Cl_2$	−25	18 h	4:1	2.14
2:1	0.7	$C_2H_4Cl_2$	−25	18 h		0
1:1	0.7	CH_3CN	5	18 h		0
1:2	0.7	CH_3CN	5	18 h	1:1	9.1
1:1	0.7	CH_3CN	−25	18 h	1:1	8.9
1:2	0.7	CH_3CN	−25	18 h	1:1	19.0
2:1	0.7	CH_3CN	−25	18 h	1:1	12.0
1:1	0.35	CH_3CN	−25	18 h	1:1	12.8
1:2	0.35	CH_3CN	−25	18 h	1:1	8.8
2:1	0.35	CH_3CN	−25	18 h	1:1	12.2
1:1	1.3	CH_3CN	−25	18 h	1:1	14.4
1:2	1.3	CH_3CN	−25	18 h	1:1	24.0
2:1	1.3	CH_3CN	−25	18 h	1:1	14.9
1:2	0.9	CH_3NO_2	−25	5 min	1:1	29.0
1:2	0.9	CH_3NO_2	−25	18 h		<5.0

[a] Reactions based on 1 mM base.

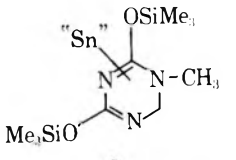
in contrast to the rapid decomposition of the sugar or nucleoside in a $SnCl_4$/acetonitrile mixture at 25 °C.

Niedballa and Vorbrüggen have recently reported on the $SnCl_4$-mediated reaction of protected 1-*O*-acyl sugars with silylated uracils.[15] Their results strongly suggest the formation of intermediate $SnCl_4$–uracil complexes which undergo ribosilylation upon addition of excess catalyst.

Our results with the disilylated triazine and the deoxyribofuranosyl bromide, as seen in Table I, exhibit analogous features which invite similar interpretations. Since there is (1) a higher rate of reaction in more polar solvents and higher catalyst concentrations, and (2) a "stability" upon warming the reaction, an initial $SnCl_4$–triazine complex such as **1** and **2** could exist, similar to that proposed by Niedballa and Vorbrüggen. As evidenced from Table I, the more stable the



1

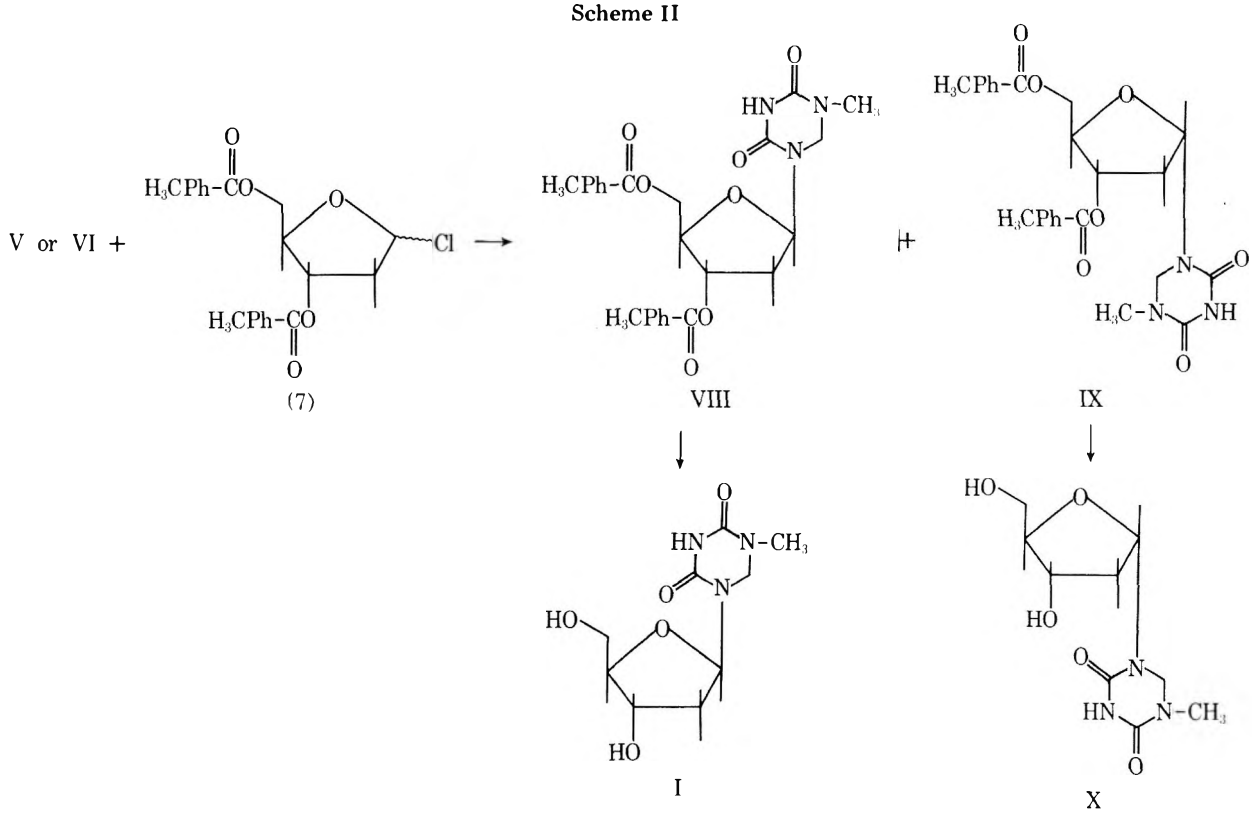


2

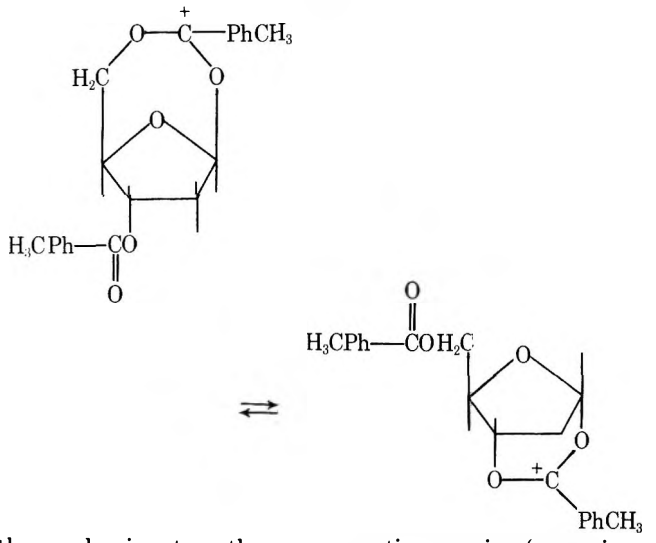
complex (favored by less polar solvents and minimal catalyst), the slower the rate of reaction. Conversely, more polar solvents or simultaneous mixing of catalyst, sugar, and triazine favor a more rapid rate of reaction/decomposition. The same rationalization is applicable to the monosilylated triazine.

The exclusive formation of the N_1-deoxynucleoside under the reaction conditions, in contrast to the ribosylation reaction of Niedballa and Vorbrüggen, suggests that complex **1** is either

Scheme II



Scheme III



the predominant or the more reactive species (assuming equilibria occurs). This coincides with expectation, since (1) the N_1 has only one α-electron withdrawing group whereas N_3 has two, (2) Niedballa and Vorbrüggen find N_1 predominates, and (3) N_1/N_3 reactivities in the ribosilylation of the disilyltriazines are greater than 1.

Sörm and co-workers[16] proposed a transannular participation effect of the 5-substituent of the α-chloro sugar, as shown in Scheme III, to rationalize the formation of α-nucleosides from the α-chloro sugar (the α configuration was initially suggested by Fletcher[17] and Zinner[18]).

If one assumes that the tin–dihydro-*s*-triazine complex reacts with the carbonium ion formed via transannular displacement of the ditoluoyl sugar halide, then the α anomer, that formed via the 5,1 carbonium ion, would be the kinetic product, and the β-anomer formed from the 3,1 carbonium ion would the thermodynamic product of the reaction.

There is little evidence to suggest that the α-chloro sugar at −25 °C is reacting directly with the silylated base via S_N2 displacement, since the initial product formed is the α anomer as opposed to the β.

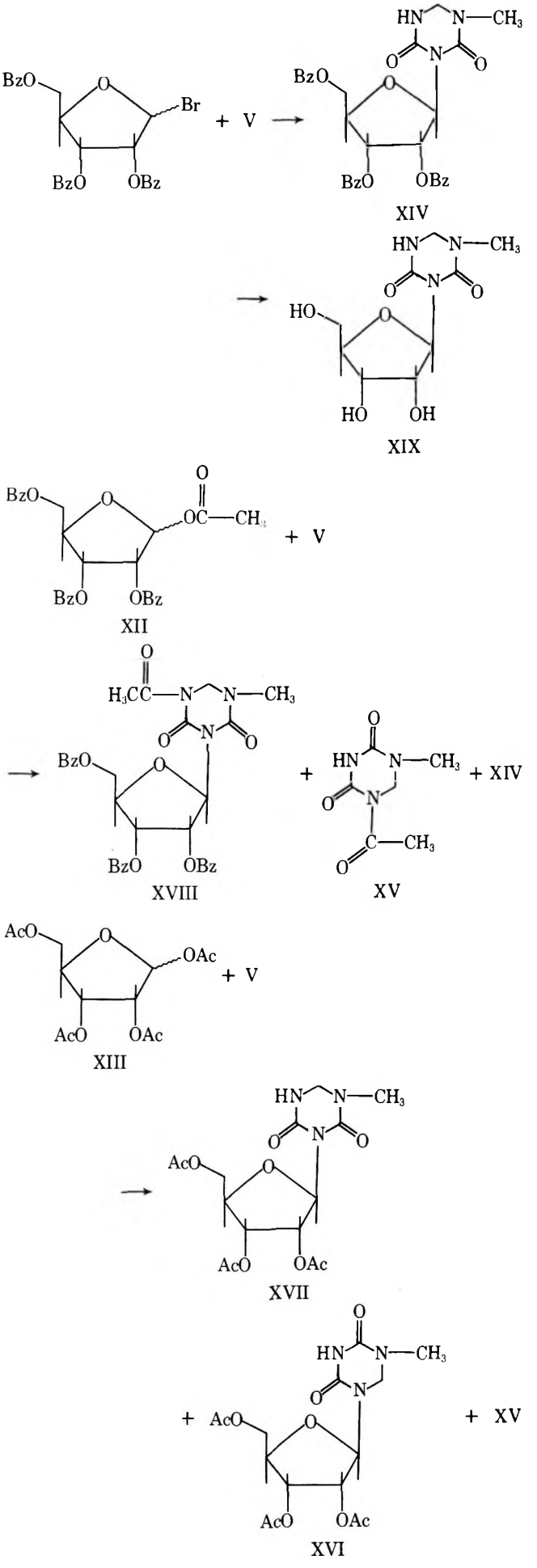
The condensation reaction can also be carried out with mercuric bromide as catalyst in the presence of molecular sieves. Acetonitrile is the solvent of choice. Yields are considerably lower (ca. 5%), although the β isomer predominates over the α. When molecular sieves are omitted, only the α anomer is isolated. These results are similar to those reported by Szabolcs involving the condensation of 5-alkyluracils with protected 2′-deoxyribofuranosyl chlorides in the presence of mercuric bromide and molecular sieves.[19]

Deprotection of VIII and IX with 25% sodium methoxide in methanol gave the unprotected nucleosides I and X. The synthetic antibiotic by physical and biological methods was identical to material obtained from the microbial source.

A greater than 70% yield of thymidine (α/β = 1:4.5) was obtained when the bis(silyl ether) of thymine was reacted with 3,5-di-*o*-toluoylribofuranosyl chloride in a manner identical to that which gave best yields of I.

The yields and α/β ratios compare favorably with those reported previously for the synthesis of thymidine via the Hilbert–Johnson reaction.[1,2] M. Prystas and F. Sorm reported yields of 39–74% of nucleoside with a 3.6–5.7:1 α/β ratio, while M. Kotick et al. had ratios of 1:3.2 but total nucleoside yields of only 34–36%. In the preparation of 5-ethyl-2-deoxyuridine via the silyl ether modification of the Hilbert–Johnson reaction (using $SnCl_4$ as catalyst), Niedballa and Vorbruggen always found a nearly constant ratio of anomers (α/β = 1) which could not be influenced by variation of the reaction conditions.[3]

Scheme IV



The condensation with 2,3,5-tribenzoyl-D-ribofuranosyl acetate or bromide to give the riboside analogue of DHAdT was markedly different from the deoxy series. A variety of products was obtained, depending upon solvent, sugar leaving group, and the sugar protecting group.

Only the N_3 isomers XIV and XVIII were isolated when the tribenzoyl sugars XI or XII were used in the condensation. When the protecting groups on the sugar were changed to acetyl (XIII), both the N_3 (XVII) and N_1 (XVI) isomers were obtained.

Isomeric and anomeric assignments were made on the basis of proton NMR spectra. Only one anomer was obtained in the condensation reaction between the tribenzoyl ribose and the silylated triazine. The coupling constant of 1.5 Hz for the anomeric proton at XIV was consistent with the coupling constants of β-ribofuranosyl nucleosides.[20] The coupling constant of 5 Hz obtained from the triacetyl nucleoside (XVI) was too large to make a definite assignment of β configuration. However, it was close to the coupling of the unprotected β-N_3 isomer (XIX) (4 Hz), and coupled with the knowledge that, in the presence of a Lewis acid acylated ribofuranosyl sugars in condensation with silylated pyrimidines yield mainly β-nucleosides,[21] the β configuration was assigned.

The assignment of N_1 vs. N_3 was made on the basis of coupling between the NH and methylene in the nucleoside *s*-triazine. In the acetyl sugar condensations a pair of isomers were obtained. In the benzoyl case only one isomer was found. In each case the assigned N_3 isomer exhibited a doublet for the methylene coupled to the triazine NH, and the assigned N_1 isomer showed a singlet for the methylene. Irradiation of the NH in the coupled spectra collapsed the methylene doublet to a singlet. The assignments were consistent with ^1H NMR data obtained from both the N_1 acetyl nucleoside (XVIII) and the N_1 acetyl base (XV), where no coupling was possible and whose methylene, as expected, appeared as singlets.

Why a change in protecting groups for benzoate to acetate should give some N_1 isomer rather than all N_3 is unclear. This is further contrasted with the fact that no N_3 isomer was ever isolated in the deoxyriboside condensations.

The acetyltriazine XV was a minor product in these reactions. However, when acetonitrile was used as solvent in the $SnCl_4$-catalyzed condensation of XII with V, only XV (identical to an authentic sample prepared via the acylation of 5,6-dihydro-5-methyl-*s*-triazine-2,4(1*H*,3*H*)-dione[22]) was isolated.

Neither the N_3 nor the N_1 ribofuranosyl nucleosides exhibited activity in any of the assays in which DHAdT was active.

Experimental Section

General. All solvents employed were reagent grade. ^1H NMR spectra were recorded on Varian A-60A and XL-100 instruments. Infrared spectra were recorded on a Digilab Model 140 spectrophotometer. Melting points were determined on a Thomas-Hoover melting-point apparatus and are uncorrected. Silica gel 60 (0.063–0.200 mm) and plates precoated with silica gel 60F-254 (both from E. Merck) were used for column and thin-layer chromatography, respectively.

1-(2-Deoxy-3,5-di-*o*-toluoyl-β-D-ribofuranosyl)-5,6-dihydro-5-methyl-*s*-triazine-2,4(1*H*,3*H*)-dione (VIII) and 1-(2-Deoxy-3,5-di-*o*-toluoyl-α-D-ribofuranosyl)-5,6-dihydro-5-methyl-*s*-triazine-2,4(1*H*,3*H*)-dione (IX). A reaction mixture consisting of 1.9 g (0.015 M) of 5,6-dihydro-5-methyl-*s*-triazine-2,4(1*H*,3*H*)-dione, 50 mL of hexamethyldisilazane and 2 mg of ammonium sulfate is heated at reflux under N_2 atmosphere for 48 h. The solution is then cooled to 25 °C and the excess hexamethyldisilazane is removed by evaporation under reduced pressure; the resulting bis(trimethylsilyl)-*s*-triazine (V) is used immediately. Under N_2, a solution consisting of 13.6 g (0.05 M) of 2,4-bis(trimethylsilyloxy)-5,6-dihydro-5-methyl-*s*-triazine (V) and 625 mL of acetonitrile (Burdick and Jackson Laboratories, Inc.) is chilled to −24 °C and 3.75 mL of fuming anhydrous stannic chloride is added. This solution is stirred for 5 min (at this point all $SnCl_4$ is in solution) before a 25 °C solution consisting of 9.7 g (0.025 M) of 2-deoxy-3,5-ditoluoyl-D-ribofuranosyl chloride in 100 mL of reagent grade ethylene dichloride is added. This reaction mixture is stirred at −20 °C for 5 min before being warmed to 25 °C. Stirring is continued as the solution gradually becomes a dark green. TLC (1:1 acetone–cyclohexane) shows the initial appearance of the α anomer followed by the slow appearance of the β anomer. After 3–5 h, the ratio of α/β becomes 1:1 with very little unreacted sugar left. The reaction mixture is decomposed by the addition of 100 mL of saturated aqueous $NaHCO_3$ and stirred for 1 h and chloroform is added until the aqueous phase separates. The organic phase is recovered, washed with aqueous $NaHCO_3$ and water, and dried over anhydrous $MgSO_4$. The organic solution is filtered and evaporated to dryness to give a foamy residue. This residue is dissolved in 50 mL of ethyl acetate and, after seeding, is cooled to 5 °C for 48 h (occasionally agitated). The solids are collected to give 3.46 g (28.8%) of VIII. An analytical sample is prepared by recrystallizing from ethyl acetate to give pure 1-(2-deoxy-3,5-di-o-toluoyl-β-D-ribofuranosyl)-5,6-dihydro-5-methyl-*s*-triazine-2,4(1*H*,3*H*)-dione (VIII): mp 184–185 °C; $[\alpha]^{25}_D$ −46° (c 1.087, $CHCl_3$); UV (ethanol) λ end absorption, 241 (ϵ 31 800), 269 (2250), 281 (1300) nm; IR 3200, 3080, 1730, 1710, 1610, 1575, 1520, 1275, 1265, 1250, 1180, 1110, 1100, 755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.43 (s, 3 H, arom CH_3), 2.68 (s, 3 H, N-CH_3), 4.90–4.25 (m, 5 H, 5′-CH_2, 4′-H, ring CH_2), 5.8–5.5 (m, 1 H, 5.8–5.5 (m, 1 H, 3′-H), 6.60–6.28 (t, $J_{1,2}$ = 8 Hz, 1 H, 1′-H), 7.5–7.2 (m, 2 H, arom), 8.1–7.8 (m, 2 H, arom).

Anal. Calcd for $C_{25}H_{27}N_3O_7$: C, 62.36; H, 5.65; N, 8.73. Found: C, 62.22; H, 5.50; N, 8.74.

Chromatographing the mother liquors over 500 g of silica gel using 1:3 acetone–cyclohexane as eluent gave IX as an amorphous foam which could be crystallized from acetone–SSB to give pure IX: mp 145.5–146.5 °C; $[\alpha]^{25}_D$ +4° (c 0.7440, $CHCl_3$); UV (ethanol) λ end absorption, 241 (ϵ 31 250), 269 (2250), 281 (1300) nm; IR 3200, 3060, 1725, 1690, 1610, 1580, 1520, 1275, 1180, 1095, 1020, 755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.40 (s, 3 H, arom CH_3) 2.88 (s, 3 H, N-CH_3), 4.80–4.40 (m, 5 H, 5′-CH_2, 4′-H, ring CH_2), 5.64–5.46 (m, 1 H, 3′-H), 6.5–6.32 (q, $J_{1'-2'\beta}$ = 3.5 Hz, $J_{1'-2'\alpha}$ = 8 Hz, 1 H, 1′-H).

Anal. Calcd for $C_{25}H_{27}N_3O_7$: C, 62.36; H, 5.65; N, 8.73. Found: C, 62.22; H, 5.50; N, 8.74.

1-(2-Deoxy-3,5-di-*o*-toluoyl-β-D-ribofuranosyl)-5,6-dihydro-5-methyl-*s*-triazine-2,4(1*H*,3*H*)-dione (VIII) and 1-(2-Deoxy-3,5-di-*o*-toluoyl-α-D-ribofuranosyl)-5,6-dihydro-5-methyl-*s*-triazine-2,4(1*H*,3*H*)-dione (IX) from the Monosilyltriazine (VI). To 1.28 g (0.010 M) of 5,6-dihydro-5-methyl-*s*-triazine-2,4(1*H*,3*H*)-dione was added 40.0 mL of reagent-grade pyridine and 4.0 mL of BSTFA (Regis Chemical Co.). The reaction was allowed to stir at ambient temperature for 18 h and then evaporated to dryness under reduced pressure. The crude monosilyl triazine (VI) was azeotroped under reduced pressure twice with dry acetonitrile. The monosilyltriazine, isolated as a white powder, was used immediately in the condensation reaction.

To 0.1 M VI, under a N_2 atmosphere, was added 1250 mL of acetonitrile. The reaction mixture was cooled to −24 °C and 7.50 mL of fuming $SnCl_4$ was added. After stirring at −24 °C for 5 min to complete solution, 19.4 g (0.050 M) of 3,5-ditoluoyl-2-deoxy-D-ribofuranosyl chloride in 200 mL of ethylene chloride was added. The reaction is run exactly as described for the synthesis of VIII and IX from the disilyltriazine V above. Yield of VIII, identical to that obtained above, was 5.6 g (23.3%), mp 183–185 °C.

1-(2-Deoxy-β-D-ribofuranosyl)-5,6-dihydro-5-methyl-*s*-triazine-2,4(1*H*,3*H*)-dione, DHAdT (I). To 7.85 g (0.016 M) of 1-(2-deoxy-3,5-di-*o*-toluoyl-β-D-ribofuranosyl)-5,6-dihydro-5-methyl-*s*-triazine-2,4(1*H*,3*H*)-dione (VIII) is added 160 mL of methanol and 0.8 mL of a 25% solution of $NaOCH_3/CH_3OH$. The reaction is stirred at 25 °C for 18 h, a few chips of CO_2 are added, and stirring is continued for 10 min. Silica gel (40 g) is added and the methanol is removed by evaporation under reduced pressure. The residual powder thus obtained is transferred to a column of 150 g of silica gel, and the column is developed with 5% methanol in chloroform. Fractions containing the desired material were combined to give 4.05 g (97.2%) of crude I. An analytical sample is prepared by dissolving 1.0 g in 4 mL of hot methanol and adding 25 mL of ethyl acetate. There is thus obtained 0.79 g of pure I: mp 142–143 °C; $[\alpha]^{25}_D$ −6° (c 0.9792, H_2O); IR 3440, 3340, 1695, 1683, 1510, 1483, 1440, 1396, 1243, 1060, 1011, 985, 943, 792, 755 cm^{-1}; ^1H NMR (D_2O) δ 2.43–2.13 (m, 2 H, 2′α 2′β-H), 3.0 (s, 3 H, NCH_3), 4.08–3.66 (m, 3 H, 4′-H, 5′-CH_2), 4.53–4.3 (m, 1 H, 3′-H), 4.66 (s, 2 H, ring CH_2), 6.36–6.05 (t, J = 7 Hz, 1 H, 1′-H); ^1H NMR (Me_2SO) δ 2.25–1.71 (m, 2 H, 2′α–2′β-H), 2.83 (s, 3 H, NCH_3), 3.70–3.36 (m, 4 H, 5′-CH_2, 4′-H, NH), 4.33–3.96 (m, 1 H, 3′-H),

4.46 (s, 2 H, ring CH_2), 4.88–4.71 (t, 1 H, 5′-OH), 5.13–5.06 (d, 1-H, 3′-OH), 6.15–5.91 (t, J = 7 Hz, 1 H, 1′-H).

Anal. Calcd for $C_9H_{15}N_3O_5$: C, 44.07; H, 6.16; N, 17.13. Found: C, 44.25; H, 6.28; N, 17.20.

1-(2-Deoxy-α-D-ribofuranosyl)-5,6-dihydro-5-methyl-*s*-triazine-2,4(1*H*,3*H*)-dione (X). To 1.13 g of 1-(3,5-ditoluoyl-2-deoxy-α-D-ribofuranosyl)-5,6-dihydro-5-methyl-*s*-triazine-2,4(1*H*,3*H*)-dione (IX) (2.3 mM) is added 10.0 mL of methanol and three drops of 25% CH_3ONa/CH_3OH. The reaction mixture is stirred at 25 °C for 18 h, whereupon a few chips of CO_2 are added. The mixture is evaporated to dryness and the residue separated between 50 mL of $CHCl_3$ and 50 mL of H_2O. The aqueous layer is washed with 4 × 20 mL of $CHCl_3$ and evaporated to dryness. The residue is dissolved in 5 mL of methanol, 5 g of silica gel is added, and the mixture is evaporated to a white powder under vacuum. This powder is chromatographed on 50 g of silica gel eluting with 20% $CH_3OH/CHCl_3$ to give 389 mg of crude X (69%). X is recrystallized from CH_3OH/Et_2O to give 279 mg of analytically pure 1-(2-deoxy-α-D-ribofuranosyl)-5,6-dihydro-5-methyl-*s*-triazine-2,4(1*H*,3*H*)-dione (X): mp 174–176 °C; $[\alpha]^{25}_D$ +54° (c 0.4320, H_2O); IR 3460, 3360, 3320, 3180, 3060, 1705, 1680, 1520, 1270, 1080, 1020 cm^{-1}.

Anal. Calcd for $C_9H_{15}N_3O_5$: C, 44.07; H, 6.16; N, 17.13. Found: C, 44.33; H, 6.20; N, 16.98.

3-(2,3,5-Tribenzoyl-β-D-ribofuranosyl)-5-methyl-5,6-dihydro-*s*-triazine-2,4(1*H*,3*H*)-dione (XIV) from the Acetyl Sugar (XII). To 5.0 g (10 mM) of tribenzoyl-D-ribofuranosyl acetate in 100 mL of analytical grade benzene is added a solution of 10 mM 2,4-bis(trimethylsilyloxy)-5-methyl-5,6-dihydro-*s*-triazine (V) in 25 mL of AR benzene. Anhydrous $SnCl_4$ (≃3.55 g ≃ 1.6 mL ≃ 13.5 mm) is injected into the reaction, and the mixture is allowed to stir at 25 °C for 18 h.

Saturated aqueous $NaHCO_3$ (5 mL) is added and the reaction is allowed to stir for 30 min. An additional 15 mL of saturated aqueous $NaHCO_3$ is added and stirred for an additional 30 min. Benzene is added, the layers are separated, and the organic phase is washed with 2 × 50 mL of saturated aqueous $NaHCO_3$ and saturated NaCl (aq), and then dried over anhydrous Na_2SO_4. The benzene solution is evaporated to dryness to give crude title compound as an amber gum (R_f 0.25 in 8:12:1 ethyl acetate–hexane–CH_3OH). The crude XIV is chromatographed on 400 g of silica gel and eluted with 8:12:1 ethyl acetate–hexane–CH_3OH, taking 25.0-mL fractions. Fractions 110–128 are combined to give 740 mg of XIV (a crude solid), recrystallization of which from acetone–hexane (1:3) gave 510 mg of pure 3-(2,3,5-tribenzoyl-β-D-ribofuranosyl)-5-methyl-5,6-dihydro-*s*-triazine-2,4(1*H*,3*H*)-dione (XIV): mp 203–203.5 °C; IR 3260, 1745, 1725, 1710, 1670, 1600, 1585, 1485, 1410, 1315, 1290, 1275, 1250, 1135, 1115, 1060, 1025, 985, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.5–4.4 (d, 2 H, NCH_2N), 4.8–4.55 (m, 3 H, 5′-CH_2/β; 4′-H), 6.25–6.15 (m, 2 H, 2′-H, 3′-H), 6.33–6.32 (d, 1 H, J = 1.5 Hz, 1′-H), 7.2 (br, 1 H, NH), irradiation at δ 7.2 causes the methylene to collapse to a singlet.

Anal. Calcd for $C_{30}H_{27}N_3O_9$: C, 62.82; H, 4.74; N, 7.33. Found: C, 62.88; H, 4.95; N, 7.18.

3-(2,3,5-Tribenzoyl-β-D-ribofuranosyl)-5-methyl-5,6-dihydro-*s*-triazine-2,4-dione (XIV) from the Bromo Sugar (XI). To 2.5 g (5 mM) of 2,3,5-tribenzoyl-D-ribofuranosyl acetate is added 50 mL of ethylene dichloride. After cooling to 0 °C, HBr is added over a period of 20 min. The solution is allowed to stand at 0 °C for 60 min, followed by warming to +25 °C over a period of 30 min. The solution is evaporated under vacuum to dryness (temp bath = 35 °C max), and the resulting gum is azeotroped with toluene and then held under vacuum (0.5 μm) for 30 min.

The resulting 2,3,5-tribenzoyl-D-ribofuranosyl bromide in 30 mL of ethylene dichloride is added to 1.75 g (6.4 mM) of 2,4-bis(trimethylsilyloxy)-5,6-dihydro-5-methyl-*s*-triazine (V). To the stirred solution is injected 2.2 g (1.0 mL ≃ 8.4 mM) of anhydrous $SnCl_4$. The reaction is allowed to stir at ambient temperature for 48 h following which 20 mL of saturated $NaHCO_3$ (aq) is added and is stirred for an additional 30 min. The layers are separated and the organic layer is washed with 2 × 20 mL of $NaHCO_3$ (aq) and H_2O saturated NaCl (aq) and dried over Na_2SO_4 (anhydrous). The organic phase is concentrated to dryness to yield 2.4 g of crude title compound. Chromatography on 150 g of silica gel, using ethyl acetate –hexane–CH_3OH (8:12:1) as eluent [R_f 0.25 in ethyl acetate–hexane–CH_3OH (8:12:1)], yielded the pure title compound [600 mg (21%), mp 200–202 °C]. This material is identical to that obtained previously.

3-(2,3,5-Tribenzoyl-β-D-ribofuranosyl)-1-acetyl-5,6-dihydro-5-methyl-*s*-triazine-2,4(1*H*,3*H*)-dione (XVIII) from the Acetyl Sugar (XII). To 6.25 g of tribenzoyl-D-ribofuranosyl acetate in 300 mL of CH_3CN is added 25 mM 2,4-bis(trimethylsilyloxy)-5-methyl-5,6-dihydro-*s*-triazine in 100 mL of CH_3CN. Next, $SnCl_4$ (2.0 mL ≃ 4.4 g ≃ 17 mM) is added and the solution is allowed to stir at ambient temperature for 94 h. While stirring, 50 mL of a saturated $NaHCO_3$ (aq) solution is added and the stirring is continued for 30 min, whereupon enough $CHCl_3$ is added to bring the aqueous layer to the top. The layers are separated, and the organic layer is washed successively with saturated $NaHCO_3$ and H_2O and dried over Na_2SO_4. The $CHCl_3$ solution is filtered and evaporated to dryness to yield 7.6 g of a mixture of XVIII and XIV as an amber gum.

Chromatography of 1 kg of silica gel, with 1:2 acetone–cyclohexane, gives 0.71 g of XIV (R_f 0.55, 1:1 acetone–cyclohexane) identical by H^1 NMR to that obtained previously. Fractions with R_f 0.80 were combined to give 2.32 g (41%) of XVIII as an amorphous foam: IR 3060, 1720, 1605, 1585, 1495, 1315, 1270, 1200, 1180, 1120, 1095, 1070, 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.45 (s, 3 H, NC(=O)CH_3), 3.05 (s, 3 H, NCH_3), 4.90–4.45 (m, 3-H, 4′-H, 5′-α/βCH_2), 5.0 (s, 2-H, ring CH_2), 6.35–6.10 (m, 3-H, 1′-, 2′-, 3′-H).

Anal. Calcd for $C_{32}H_{29}N_3O_{10}$: C, 62.33; H, 4.90; N, 6.81. Found: C, 62.44; H, 4.69; N, 6.51.

3-(β-D-Ribofuranosyl)-5,6-dihydro-5-methyl-*s*-triazine-2,4(1*H*,3*H*)-dione (XIX). To 200 mg of XIV (0.35 mM) is added 15 mL of a 0 °C saturated solution of NH_3/CH_3OH. The solution is stoppered and stored in a sealed tube at 5°C for 120 h. The reaction mixture is evaporated to dryness. The residue is tritiated with $CHCl_2$ and separated between $CHCl_3$ and H_2O. The aqueous layer is washed four times with $CHCl_3$ and lyophilized to give XIX as an amorphous foam: wt 73 mg (80%); ^1H NMR (D_2O) δ 2.95 (s, 3 H, NCH_3), 4.05–3.6 (s, 3 H, 5′-CH_2, 4′-H), 4.5 (s, 2 H, NCH_2N), 5.85–5.7 (d, 1 H, $J_{1'2'}$ = 4 Hz 1′-H); $(Me_4Si)_4$ *m/e* 549, calcd for $C_{21}H_{47}Si_4N_3O_6$, 549.2542; found 549.2562.

1-(2,3,5-Triacetyl-β-D-ribofuranosyl)-5-methyl-5,6-dihydro-*s*-triazine-2,4-dione (XVI) and 1-Acetyl-5,6-dihydro-5-methyl-*s*-triazine-2,4(1*H*,3*H*)-dione (XV). To 2.4 g (7.5 mM) of 1,2,3,5-tetraacetylribofuranose is added 10 mM 2,4-bis(trimethylsilyl)-5-methyl-5,6-dihydro-*s*-triazine (V) in 50 mL of ethylene dichloride and 1.0 mL (2.2 g ≃ 8.4 mM) of $SnCl_4$ is injected. The mixture is stirred at 25 °C for 72 h, 20 mL of saturated aqueous $NaHCO_3$ is added, and the mixture is stirred at ambient temperature for 30 min. An additional 50 mL of $C_2H_4Cl_2$ is added and the layers are separated. The organic layer is washed with saturated aqueous $NaHCO_3$ (20 mL), H_2O (20 mL), and saturated NaCl (20 mL), dried over Na_2SO_4 (anhydrous), and evaporated to dryness to yield 1.2 g of crude XVI as an amorphous foam.

All of XVI is chromatographed on 125 g of base-washed (washed with dilute NH_4OH followed by drying at 60 °C for 18 h) silica gel. The column is eluted with ethyl acetate and, taking 10.0-mL fractions, fractions 32–44 are combined (R_f 0.55 in ethyl acetate) to yield 105 mg of XV (3.6%): ^1H NMR ($CDCl_3$) δ 2.55 (s, 3 H, $COCH_3$), 3.0 (s, 3 H, NCH_3), 5.0 (s, 2 H, NCH_2N), 8.8 (m, 1 H, NH). Fractions 62–82 are combined to yield 120 mg (4.1%) of XVI as a white foam (R_f 0.45 in ethyl acetate): IR 3480, 3230, 3080, 1745, 1705, 1510, 1225, 1100, 1045, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.25–2.0 (m, 9 H, CCH_3), 3.0 (s, 3 H, NCH_3), 4.35–4.2 (m, 3 H, 5′-CH_2, 4′-H), 4.5 (s, 2 H, ring CH_2), 5.96–5.90 (d, J = 6 Hz, 1 H, 1′-H), 8.15 (s, 1 H, NH). There is no change in the ^1H NMR when δ 8.15 is irradiated. Fractions 110–122 were combined to yield a gum whose structure has been assigned the N_3 isomer: ^1H NMR ($CDCl_3$) δ 2.1 (m, 9 H, $COCH_3$), 3.0 (s, 3 H, NCH_3), 4.5–4.2 (m, 3 H, 4′-H, 5′-CH_2), 4.6 (m, 2 H, NCH_2N), 5.65 (m, 1 H, 3′-H), 5.85 (m, 1 H, 2′-H), 6.1 (d, J = 5 Hz, 1 H, 1′-H), 7.0 (br, 1 H, NH). When NH at δ 7.0 is irradiated, δ 4.6 collapses to a singlet.

Anal. Calcd for $C_{15}H_{21}N_3O_9$: C, 46.51; H, 5.47; N, 10.85. Found: C, 46.23; H, 5.62; N, 8.00.

Acknowledgments. The author thanks Mr. S. A. Mizsak and Mr. T. A. Scahill for their aid in the interpretation of the ^1H NMR spectra, and Drs. T. Brodasky, B. Bannister, and L. Dolak and Mr. R. Birkenmeyer of our Infectious Diseases section for their helpful consultations.

Registry No.—I, 57350-36-4; IV, 64332-47-4; V, 66515-67-1; VI, 66515-68-2; VII, 3601-89-6; VIII, 66515-69-3; IX, 66515-70-6; X, 66515-71-7; XI, 22860-91-9; XII, 14215-97-5; XIII, 28708-32-9; XIV, 66515-62-6; XV, 66515-63-7; XVI, 66515-64-8; XVII, 66515-65-9; XVIII, 66515-66-0; XIX, 64332-50-9.

References and Notes

(1) Presented in part at the 172nd National Meeting of the American Chemical Society, San Francisco, Calif., 1976, Abstr CARB 43.
(2) C. DeBoer, B. Bannister, A. Dietz, J. E. Gray, and C. Lewis, American Society for Microbiology, Atlantic City, N.J., 1976.
(3) A. D. Argoudelis and S. Mizsak, *J. Antibiot.*, **29**, 818 (1976).

(4) V. Reichman, K. Hirota, C. K. Chu, K. A. Watanabe, J. J. Fox, *J. Antibiot.*, **30**, 129 (1977).
(5) C. DeBoer and B. Bannister, U.S. Patent 3 907 643 and 3 907 779.
(6) H. Renis, B. Court, and E. Edison, American Society of Microbiology, Atlantic City, N.J., 1976.
(7) A. Piskala and J. Gut, *Collect. Czech. Chem. Commun.*, **26**, 2519 (1961).
(8) M. W. Winkley and R. K. Robins, *J. Org. Chem.*, **35**, 491 (1970).
(9) H. Vorbrüggen and U. Niedballa, *Tetrahedron Lett.*, *41*, 3571 (1970).
(10) U. Niedballa and H. Vorbrüggen, *J. Org. Chem.*, **39**, 3654 (1974).
(11) A. Piskala and F. Sörm, *Collect. Czech. Chem. Commun.*, **29**, 2060 (1964).
(12) U. Niedballa and H. Vorbrüggen, *Angew. Chem.*, **9**, 461 (1970).
(13) B. Bannister, 10th International Symposium on the Chemistry of Natural Products, Dunedia, New Zealand, Aug., 1976, Abstr C-28.
(14) D. Duchamp, B. Bannister, and C. Chidester, unpublished data.
(15) U. Niedballa and H. Vorbrüggen, *J. Org. Chem.*, **41**, 2084 (1976).
(16) M. Prystas, J. Farkas, and F. Sörm, *Collect. Czech. Chem. Commun.*, **30**, 3123 (1965).
(17) A. K. Bhattacharya, R. K. Ness, and H. G. Fletcher, Jr., *J. Org. Chem.*, **28**, 428 (1963).
(18) H. Zinner and M. Pfeyer, *Chem. Ber.*, **94**, 2792 (1961).
(19) A. Szabolcs, *J. Carbohydr., Nucleosides, Nucleotides*, **2(3)**, 197 (1975).
(20) W. Zorbach and R. Tipson, "Synthetic Procedures in Nucleic Acid Chemistry", Vol. 2, Wiley, New York, N.Y., 1973.
(21) K. A. Watanabe, D. H. Hollenberg, and J. J. Fox, *J. Carbohydr., Nucleosides, Nucleotides*, **1**, 1 (1974).
(22) A. Piskala and J. Gut, *Collect. Czech. Chem. Commun.*, **27**, 1562 (1962).
(23) Yields were determined by making a 1 mg/mL (H_2O) solution of the crude, hydrolyzed (25% CH_3ONa/CH_3OH) reaction mixture, saturating a 12.7 mm disk (No. 740-S, Schlercher and Schuell Inc.) with this solution, assaying against *Klebsiella pneumonia*, and comparing the results to those obtained with known concentrations of the antibiotic. The α anomer was shown to be devoid of any antibacterial activity.

C_{15} Halogenated Compounds from the Hawaiian Marine Alga *Laurencia nidifica*. Maneonenes and Isomaneonenes

Sigmund M. Waraszkiewicz, Hao H. Sun, and Karen L. Erickson*

Jeppson Laboratory, Clark University, Worcester, Massachusetts 01610

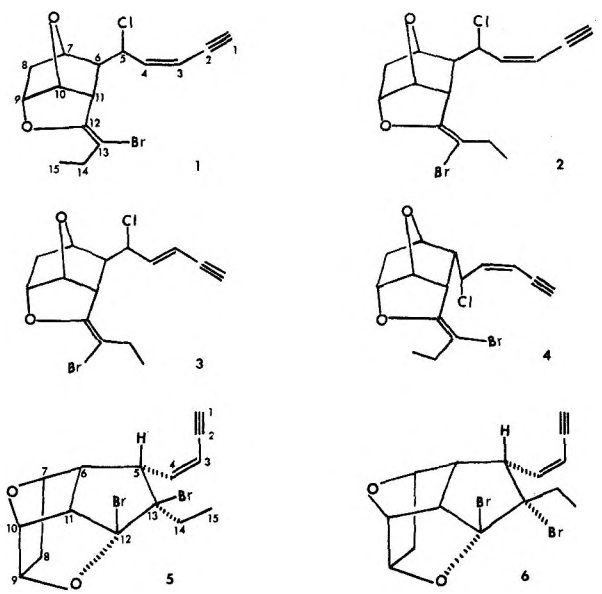
Janet Finer and Jon Clardy*

Ames Laboratory-USERDA and Department of Chemistry, Iowa State University, Ames, Iowa 50011

Received September 30, 1977

Six C_{15} nonterpenoid halo ethers from a green variety of the Hawaiian marine alga *Laurencia nidifica* have been isolated and characterized by chemical and spectroscopic methods. The maneonenes (1–4) have one carbocyclic ring and the isomaneonenes (5 and 6) possess two carbocyclic rings, an unusual feature for C_{15} nonterpenoid ethers of *Laurencia*. The structure of isomaneonene-B is confirmed by X-ray analysis.

Marine algae of the genus *Laurencia* have been extensively investigated in recent years and a variety of terpenoid and nonterpenoid metabolites have been isolated and characterized.[1] The Hawaiian alga *Laurencia nidifica* has been divided into two pink varieties, one elaborating laurinterol, aplysin, and pacifenol[2] and the second elaborating nidifidiene, nidificene,[2] nidifidienol,[3] and nidifocene,[4] and a green variety, containing sesquiterpenoid alcohols[5] and halogenated nonterpenoid C_{15} compounds, the maneonenes **1–4** and the isomaneonenes **5** and **6**.[6–8] This paper describes the details of the structural work on the latter two groups of compounds together with X-ray confirmation of structure for isomaneonene-B.



Collections of the alga were made in January and June 1975 and January 1976 at Diamond Head and Black Point reefs on the island of Oahu, Hawaii. The alga is bright green in color and grows in patches on the reef where the wave action is substantial. Although its color and habitat are different from other varieties of *L. nidifica*, this alga has been classified as the same species.[9]

Ether extracts of the air-dried alga were chromatographed on silica gel columns. The benzene fraction afforded the *cis*-maneonenes **1**, **2**, and **4** and benzene–ether fractions gave *trans*-maneonene-B (**3**) together with the isomaneonenes **5** and **6**. *cis*-Maneonene-B (**2**) was consistently the major component, but amounts of the other compounds varied, apparently with the season; *trans*-maneonene-B (**3**) was found only in the January 1976 collection. Separation of the isomers was achieved by repeated thin layer chromatography on silica gel with multiple developments (Scheme I).

High resolution mass spectroscopy established the formula of $C_{15}H_{16}BrClO_2$ for the maneonenes **1–4**. All of the spectral and chemical data suggested that these four compounds were very closely related, consequently the component of greatest abundance, *cis*-maneonene-B (**2**), and its isomer, *cis*-maneonene-A (**1**), were investigated first. These two compounds differ only in the configuration of the C-12 double bond.

cis-Maneonene-A displays an acetylenic C–H stretch (3310 cm^{-1}) in the IR spectrum. The UV (225 nm) and ^1H and ^{13}C NMR spectra (Table I, C_1, C_3, and C_4) established the *cis*-enyne portion of the C-5 side chain. Downfield absorptions in the ^{13}C NMR (δ 58.3) and in the ^1H NMR spectra (δ 5.08) were ascribed to a halogen-bearing carbon with one proton attached. This proton is coupled by 10.5 Hz to the C-4 vinylic

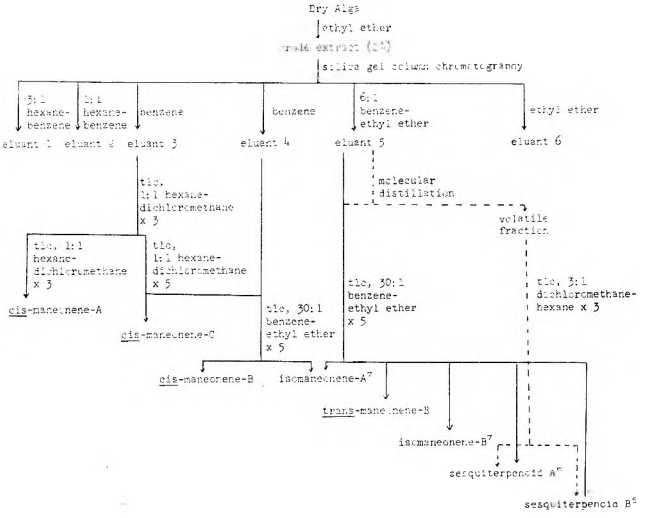
0022-3263/78/1943-3194$01.00/0

Table I. ^{13}C [a] and ^{1}H [b] NMR Data for *cis*-Maneonene-A (1)

Carbon no.	^{13}C δ	^{1}H δ	Multiplicity, J (Hz)
1	84.8	2.67	d, $J_{1,3}$ = 2.3
3	111.9	5.36	dd, $J_{1,3}$ = 2.3, $J_{3,4}$ = 10.5
4	142.0	6.05	t, $J_{3,4}$ = $J_{4,5}$ = 10.5
5	58.3	5.08	t, $J_{4,5}$ = $J_{5,6}$ = 10.5
6	58.3	1.89	dd, $J_{5,6}$ = 10.5, $J_{6,11}$ = 1.5
7	78.3	4.62	d, $J_{7,8exo}$ = 5
8	38.6	1.34 (exo) 0.96 (endo)	td, $J_{8exo,8endo}$ = 14, $J_{7,8exo}$ = 5, $J_{8exo,9}$ = 8 d, $J_{8exo,8endo}$ = 14
9	80.4	4.06	dd, $J_{8exo,9}$ = 8, $J_{9,10}$ = 5
10	82.2	4.34	t, $J_{9,10}$ = $J_{10,11}$ = 5
11	46.1	2.75	dd, $J_{10,11}$ = 5, $J_{6,11}$ = 1.5
14	26.7	2.47 2.51	sextet, $J_{14,14}$ = 14, $J_{14,15}$ = 7 sextet, $J_{14,14}$ = 14, $J_{14,15}$ = 7
15	13.0	1.06	t, $J_{14,15}$ = 7

[a] Proton decoupled values (ppm downfield from Me_4Si) in C_6D_6. [b] 270 MHz values (ppm downfield from Me_4Si) in C_6D_6.

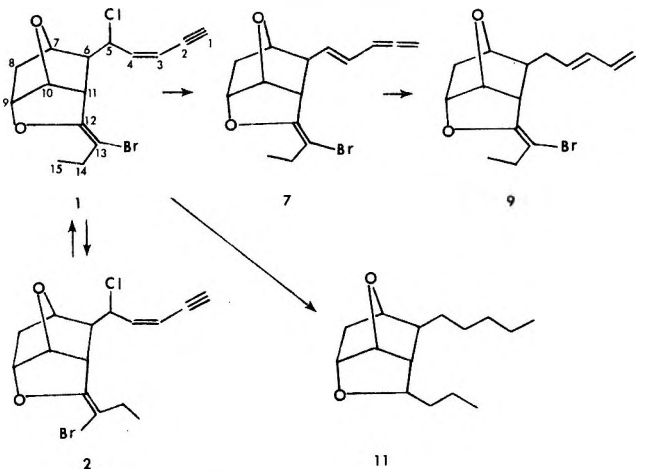
Scheme I



proton (and to a second neighboring proton by the same amount) indicating that this halogen-bearing carbon is C-5. The presence of halogen at this position is unusual in these systems, and additional evidence was sought to verify its placement. This was forthcoming when *cis*-maneonene-A was treated with bis(ethylenediamine)chromium(II)[10] in an attempt to remove halogen from the molecule. The product of this reaction (**7**) had retained bromine but not chlorine, and the enyne grouping was converted into a terminal allene conjugated with a double bond at C-4. The IR spectrum of this allenic material displays strong bands at 1940 (C=C=C) and 860 cm^{-1} (C=C=CH_2) and the UV spectrum (227 nm) demonstrates the conjugated nature of the allene grouping. ^{13}C NMR data were unavailable for **7** but were obtained for its C-12 double bond isomer, **8**, derived from *cis*-maneonene-B (**2**) (Scheme III), and they fully confirmed the presence of a conjugated allene moiety with the terminal allenic carbon signal appearing at δ 76.6 and the C-3 allenic carbon signal at δ 93.4. The stereochemistry of the olefinic bond could not be ascertained with certainty, but a strong absorption in the 970-cm^{-1} region of the IR spectrum suggests that it is trans. The other functionalities in the parent molecule (vida infra) were unaffected by the chromous reagent.

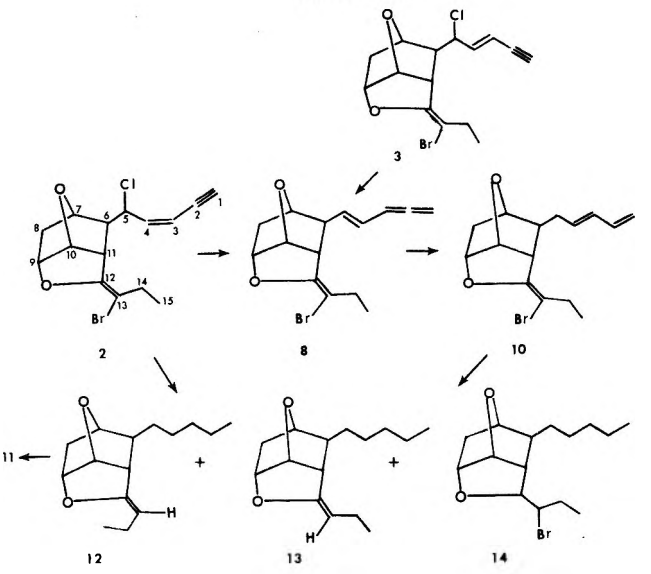
Allenes **7** and **8** could be further reduced with chromous sulfate to conjugated dienes **9** and **10** (Schemes II and III), which could also be obtained by direct reduction of **1** and **2** with chromous sulfate. Whereas amine-complexed chromous ion does not reduce multiple bonds,[11] other chromous reagents do. Thus, triple bonds may be reduced to trans double bonds[11]

Scheme II



and enynes[12] and enallenes[13] to conjugated dienes. The conversion of the 5-halo-3-en-1-yne system into a conjugated 4-en-1-allene by bis(ethylenediamine)chromium(II) would be expected to proceed analogously to the well-known allylic halide reductions with this reagent.[14] Although we are unaware of any reports in the literature on the conversion of such haloenynes into conjugated allenes by chromous reagents, lithium aluminum hydride has been used to effect such conversions.[15]

Scheme III



The remaining functionalities in *cis*-maneonene-A were assigned from IR and NMR analysis. A vinyl ether stretch (1685 cm^{-1}) and strong C–O bands (1100, 1040 cm^{-1}) are evident in the IR spectrum. Since there are no hydroxyl or carbonyl absorptions, the two oxygens of **1** were assumed to be involved as ether links. This was verified by the ^{13}C NMR spectrum which shows three oxygen-bearing carbons[16] and the ^1H NMR spectrum which shows three downfield methines (Table I). The assignment of these methine absorptions to the oxygen-bearing carbons was confirmed by specific hydrogen–carbon decoupling experiments. The fourth oxygen-bearing carbon would then be quaternary.

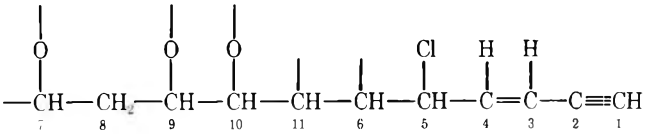
The ^{13}C NMR spectrum established the presence of 12 hydrogen-bearing carbons, only two of which were in the olefinic region. The three quaternary centers are accounted for by the internal acetylenic carbon and the vinyl carbons of the double bond bearing the ether function. The other substituents on this tetrasubstituted double bond can be shown to be an ethyl group and the bromine atom. Thus, the bromine must be at a quaternary center since there are no additional halomethine resonances in the ^1H NMR spectrum. Placement of the ethyl group also follows from the ^1H NMR spectrum. The ethyl resonances appear as a triplet at δ 1.06 (J = 7 Hz) and two doublets of quartets (J = 7, 14 Hz) at 2.47 and 2.51 indicating that the methylene hydrogens are nonequivalent and coupled only to each other and the methyl protons. This, plus their chemical shift values, establish the ethyl group as vinylic.

When *cis*-maneonene-A was catalytically hydrogenated, a saturated product, $C_{15}H_{26}O_2$ (**11**, Scheme II), was obtained confirming four sites of unsaturation and therefore three rings in the molecule. The specific ^{13}C and ^1H NMR absorptions of this saturated product show that the four oxygen methine groups are unchanged. The mass spectrum shows that both halogens were replaced by hydrogens. Facile loss of a pentyl and a propyl, but not an ethyl, group on electron impact supports the presence of C_5 and C_3 side chains. The C_5 side chain arises from the original chloroenyne group. The C_3 side chain must arise from the ethyl end of the molecule and can be accounted for only if the original bromine is attached to the vinyl carbon bearing the ethyl group as shown in **1**.

Further confirmation of this assignment comes from the sodium–ammonia reduction of *cis*-maneonene-B, the C-12 double bond isomer of *cis*-maneonene-A. The mixture of products obtained in this reaction was catalytically hydrogenated to give two isomeric vinyl ethers (**12** and **13**) and a saturated ether (**14**) which retained the bromine (Scheme III). The same product mixture was obtained when the diene from chromous sulfate treatment (**10**) was subjected to sodium–ammonia followed by catalytic hydrogenation (Scheme III(/ The bromo compound (**14**) displays a bromomethine at δ 3.52 in the ^1H NMR spectrum as a complex multiplet. Four oxygen methines are also evident with no hydroxyl absorption in the IR spectrum, again indicating that none of the ether bonds had broken. When passed through the gas chromatograph, this bromide eliminated HBr and gave one of the vinyl ethers (**12**) obtained directly in the reduction sequence. This vinyl ether was hydrogenated to the same saturated ether (**11**) obtained on hydrogenation of *cis*-maneonene-A (Scheme II). The trisubstituted vinyl ether functionality for **12** and **13** was assigned on the basis of IR (1700 cm^{-1} for **12** and 1695 cm^{-1} for **13**), ^1H NMR (δ 4.31 for **12** and 4.88 for **13**), and ^{13}C NMR (δ 95.6 for **13**) spectra. The fact that the vinyl hydrogen in these two vinyl ethers is vicinally coupled (t, J = 7 Hz) to the methylene protons of the ethyl group confirmed its placement and that of the original bromine at C-13.

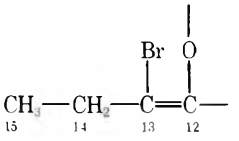
The assignment of the Z configuration to vinyl ether **12** and the E configuration to vinyl ether **13** was made by comparing the influence of the oxygen atom on the chemical shifts of the vinyl hydrogen and the ethyl hydrogens. The vinyl hydrogen in **13** is cis to the oxygen function and occurs 0.57 ppm further downfield than the vinyl hydrogen in **12**. Similarly, the ethyl group in **12** is cis to the oxygen, and these protons are more deshielded than in **13**.

Thirteen of the fifteen carbon atoms and thirteen of the sixteen hydrogen atoms of *cis*-maneonene-A have now been defined; the remaining two carbons and three hydrogens were ascribed to a CH and a CH_2 group. A doublet (J = 14 Hz) centered at δ 0.96 in the ^1H NMR spectrum supports the presence of a geminally coupled pair of methylene hydrogens. Specific hydrogen–carbon decoupling experiments permitted the assignment of proton methine absorptions with oxygen-bearing carbons and with the chlorine-bearing carbon. Proton–proton decoupling experiments gave the following proton sequence:[17]

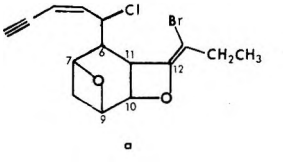


Thus, irradiation of the choromethine at δ 5.08 (C-5) affected not only the C-4 olefinic proton at 6.05 but also collapsed the doublet of doublets at 1.89 (C-6) to a broad singlet. Irradiation in the δ 2.7–2.8-region collapsed the olefinic doublet of doublets at 5.36 (C-3) and the doublet of doublets at 1.89 (C-6) each to doublets and effected a change in the absorption of the oxygen methine at 4.34 (C-10). Two protons are being irradiated in this region, the acetylenic proton at C-1, which is coupled to the olefinic proton at C-3, and the methine at C-11, which is coupled to the protons at C-6 and C-10. Irradiation of the oxygen methine at δ 4.06 (C-9) collapsed the oxygen methine at 4.34 (C-10) to a doublet and also changed the appearance of the multiplet at 1.34 ($C\text{-}8_{exo}$). Irradiation of this latter absorption likewise effected a change in the δ 4.06 (C-9) absorption and collapsed the oxygen methine doublet at 4.62 (C-7) and the doublet at 0.96 ($C\text{-}8_{endo}$) each to singlets. Finally irradiation of the oxygen methine at δ 4.62 (C-7) collapsed the multiplet at 1.34 ($C\text{-}8_{exo}$) to a doublet of doublets.

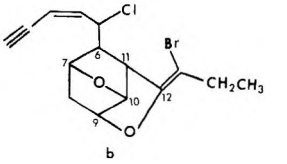
The butenyl unit



must be attached to the main chain and three rings must be formed to complete the structure of *cis*-maneonene-A. Two of these rings are oxide rings, and the third must be carbocyclic. Attachment of C-12 at C-7 would necessitate an additional bond between C-6 and C-11, and this is not tenable as there are only two double bonds in the molecule. Attachment at C-11 with bonding between C-6 and C-7 and ether closures gives three possible structures, two of which are shown below (a and b); the third possibility would contain an epoxide



a



b

moiety for which there is no evidence. Attachment of C-12 at C-6 with bonding between C-7 and C-11 and ether closures leads to three additional structures based on a branched C_{15} chain. These are considered highly unlikely on biogenetic grounds as C_{15} nonterpenoids of *Laurencia* are most probably fatty acid derived. Furthermore, an examination of the mo-

Table II. ^{13}C [a] and ^{1}H [b] NMR Data for *cis*-Maneonene-B (2)

Carbon no.	^{13}C δ	^{1}H δ	Multiplicity, J (Hz)
1	85.4	2.86	d, $J_{1,3}$ = 2.3
3	111.9	5.35	dd, $J_{1,3}$ = 2.3, $J_{3,4}$ = 10.5
4	141.0	5.75	t, $J_{3,4}$ = $J_{4,5}$ = 10.5
5	58.3	4.96	t, $J_{4,5}$ = $J_{5,6}$ = 10.5
6	58.3	1.83	dd, $J_{5,6}$ = 10.5, $J_{6,11}$ = 1.5
7	78.1	4.60	br d, $J_{7,8exo}$ = 5
8	38.7	1.30	m
9	79.4	4.25	m
10	82.8	4.60	t, $J_{9,10}$ = $J_{10,11}$ = 5
11	43.7	2.68	br d, $J_{10,11}$ = 5
14	29.2	2.32	q, $J_{14,15}$ = 7
15	13.8	1.07	t, $J_{14,15}$ = 7

[a] Proton decoupled values (ppm downfield from Me_4Si in C_6D_6. [b] 60 MHz values (ppm downfield from Me_4Si) in C_6D_6.

Table III. ^{13}C [a] and ^{1}H [b] NMR Data for *trans*-Maneonene-B (3)

Carbon no.	^{13}C δ	^{1}H δ	Multiplicity, J (Hz)
1	79.1	2.76	d, $J_{1,3}$ = 2
3	113.3	5.43	dd, $J_{1,3}$ = 2, $J_{3,4}$ = 15.5
4	142.2	6.05	dd, $J_{3,4}$ = 15.5, $J_{4,5}$ = 9
5	63.8	3.90	dd, $J_{4,5}$ = 9, $J_{5,6}$ = 11
6	58.2	1.62	dd, $J_{5,6}$ = 11, $J_{6,11}$ = 2
7	78.0	3.87	d, $J_{7,8exo}$ = 5
8	39.0	~1.4	m
9	80.7	4.27	dd, $J_{8exo,9}$ = 6, $J_{9,10}$ = 5
10	82.6	4.57	t, $J_{9,10}$ = $J_{10,11}$ = 5
11	45.1	2.87	dd, $J_{10,11}$ = 5, $J_{6,11}$ = 2
14	29.3	2.7	m
15	14.2	1.23	t, $J_{14,15}$ = 7

[a] Proton decoupled values (ppm downfield from Me_4Si) in C_6D_6. [b] 60 MHz values (ppm downfield from Me_4Si) in C_6D_6.

lecular models of all six of these structures clearly shows that only one is in agreement with the ^{1}H NMR spectra, that of b. This skeletal structure gives an excellent fit for all of the maneonenes. Thus, in *cis*-maneonene-A, represented by structure **1**, $J_{6endo,7}$ = $J_{7,8endo}$ = $J_{8endo,9exo}$ = 0, in agreement with the literature for similar compounds[18] where these dihedral angles are 90°. The 30° angle between H-9 and H-10 and between H-10 and H-11 gives a satisfactory fit for the 5 Hz coupling constant observed as does the 0° angle between $H\text{-}8_{exo}$ and H-9 where J = 8 Hz. The $J_{6endo,11exo}$ is small (1.5 Hz) in agreement with their dihedral angle which is not far from 90°. This C-6, C-11 bond is unprecedented in these metabolites but is clearly necessary in order to accommodate the decoupling data. The H–H coupling constants around the carbocyclic ring for the other maneonenes (Tables II–IV) are also in excellent agreement with their predicted values.[18]

That the C-12 double bond is of the *E* configuration in *cis*-maneonene-A (**1**) is shown by comparison with its isomer, *cis*-maneonene-B (**2**). These two materials are interconvertible by treatment with catalytic amounts of acid. Starting with either isomer, a roughly equivalent mixture of both persists at equilibrium. As expected from the dipole alignments, **2** is the more polar material. The spectral characteristics of both compounds are essentially identical except in the region influenced by the substituents on the C-12 double bond. In the ^{1}H NMR spectrum, H-4 is 0.3 ppm further downfield in **1** than it is in **2**, a consequence of the deshielding effect of the bromine on this hydrogen in **1**. Similarly in **1**, the C-14 protons are 0.2 ppm further downfield than those in **2**, reflecting the influence of the cis oxygen atom in **1**.

trans-Maneonene-B (**3**) was shown to have a *trans*-enyne function by UV and ^{1}H NMR analysis. The two olefinic protons are coupled to each other by 15.5 Hz. The C-3 proton is also coupled to the acetylenic hydrogen (2 Hz), and the C-4 proton is further coupled to the C-5 halomethine (9 Hz) in analogy with *cis*-maneonene-A and *cis*-maneonene-B (Table III). In the IR spectrum a band at 955 cm^{-1} supports the trans-disubstituted double bond moiety. Treatment of *trans*-maneonene-B with bis(ethylenediamine)chromium(II) gave the same allene (**8**) as that derived from **2** (Scheme III) and established the structure of the molecule as **3**.

The spectral properties of *cis*-maneonene-C (**4**) and its conversion into a conjugated allene (**15**, Scheme IV) on treatment with bis(ethylenediamine)chromium(II) indicated that it has the same chloroenyne side chain as **1** and **2**. Catalytic reduction of *cis*-maneonene-C afforded compound **16** with the vinyl ether group intact as well as the other three ether bonds. Sodium–ammonia reduction of this vinyl bromo ether gave a new vinyl ether **17** in which the vinyl bromide had been replaced by a hydrogen which is vicinally coupled to the methylene protons of the ethyl group (Scheme IV). The chemical shift of this new vinyl hydrogen (δ 4.19) suggests that it is trans to the oxygen group (compare to δ 4.31 for **12** and δ 4.88 for **13**).

Specific-hydrogen decoupling in the ^{13} NMR spectrum and proton–proton decoupling experiments confirmed that *cis*-maneonene-C has the same proton and heteroatom sequence and therefore the same carbon skeleton as **1–3**. The most obvious difference in the spectral properties between *cis*-ma-

Table IV. ^{13}C [a] and ^{1}H [b] NMR Data for *cis*-Maneonene-C (4)

Carbon no.	^{13}C δ	^{1}H δ	Multiplicity, J (Hz)
1	85.3	2.83	d, $J_{1,3}$ = 2.3
3	109.9	5.15	dd, $J_{1,3}$ = 2.3, $J_{3,4}$ = 10.5
4	141.9	5.56	t, $J_{3,4}$ = $J_{4,5}$ = 10.5
5	54.5	5.01	t, $J_{4,5}$ = $J_{5,6}$ = 10.5
6	54.0	2.61	m, $J_{5,6}$ = 10.5, $J_{6,7}$ = 4.5, $J_{6,11}$ = 9.5
7	77.9	3.98	t, $J_{6,7}$ = $J_{7,8exo}$ = 4.5
8	36.4	1.42 (exo)	td, $J_{8exo,8endo}$ = 14, $J_{7,8exo}$ = 4.5, $J_{8exo,9}$ = 7
		1.90 (endo)	d, $J_{8exo,8endo}$ = 14
9	81.2	4.31	dd, $J_{8exo,9}$ = 7, $J_{9,10}$ = 5
10	83.5	4.65	t, $J_{9,10}$ = $J_{10,11}$ = 5
11	45.0	3.52	dd, $J_{10,11}$ = 5, $J_{6,11}$ = 9.5
14	27.9	2.61	m, $J_{14,14}$ = 14, $J_{14,15}$ = 7
		2.97	sextet, $J_{14,14}$ = $J_{14,15}$ = 7
15	13.6	1.35	t, $J_{14,15}$ = 7

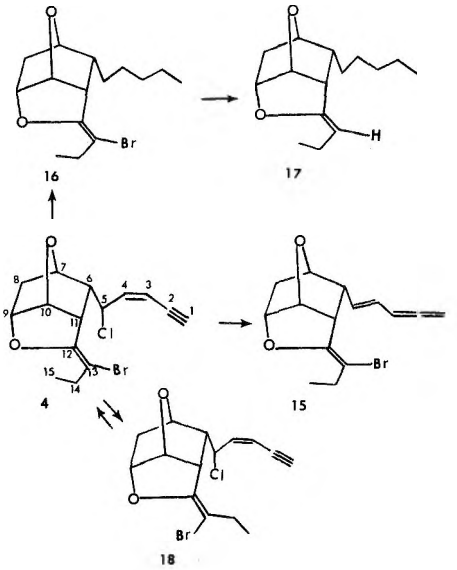
[a] Proton decoupled values (ppm downfield from Me_4Si) in C_6D_6. [b] 270 MHz values (ppm downfield from Me_4Si) in C_6D_6.

Table V. ^{13}C [a] and ^{1}H [b] NMR Data for Isomaneonene-A (5)

Carbon no.	^{13}C δ	^{1}H δ	Multiplicity, J (Hz)
1	84.7	2.72	d, $J_{1,3} = 2$
2	79.5[c]		
3	109.2	4.98	dd, $J_{1,3} = 2$, $J_{3,4} = 10.5$
4	144.5	5.66	dd, $J_{3,4} = 10.5$, $J_{4,5} = 8$
5	49.7	4.33	dd, $J_{4,5} = 8$, $J_{5,6} = 10$
6	50.5	3.38	sextet, $J_{5,6} = J_{6,11} = 10$, $J_{6,7} = 5$
7	77.6	4.19	t, $J_{6,7} = J_{7,8exo} = 5$
8	41.4	1.15 (exo) 1.59 (endo)	dt, $J_{7\,8exo} = J_{8exo,9} = 5$, $J_{8exo,8endo} = 13$ d, $J_{8exo,8endo} = 13$
9	83.3	4.31	t, $J_{8exo,9} = J_{9,10} = 5$
10	82.9	5.02	t, $J_{9,10} = J_{10,11} = 5$
11	63.1	3.88	dd, $J_{10,11} = 5$, $J_{6,11} = 10$
12	110.6[c]		
13	89.7[c]		
14	26.8	2.08 2.33	sextet, $J_{14,14} = 14$, $J_{14,15} = 7$ sextet, $J_{14,14} = 14$, $J_{14,15} = 7$
15	10.0	1.06	t, $J_{14,15} = 7$

[a] Proton decoupled values (ppm downfield from Me_4Si) in $CDCl_3$. [b] 270 MHz values (ppm downfield from Me_4Si) in C_6D_6. [c] Quaternary carbon.

Scheme IV



neonene-C and its isomers is the coupling of H-6 with its neighbors on the carbocyclic ring. Thus, whereas $J_{6,7} = 0$ in **1–3**, in *cis*-maneonene-C $J_{6,7} = 4.5$ Hz. Similarly, $J_{6,11} = 1.5$ Hz in **1** and **2** and 2 Hz in **3**, while in *cis*-maneonene-C $J_{6,11} = 9.5$ Hz. These *J* values for *cis*-maneonene-C are in excellent agreement with the literature for couplings of an exo H-6 to a bridgehead H-7, and an exo H-6 to an exo H-11,[18] and again confirm the C-6, C-11 bond. *cis*-Maneonene-C is then the C-6 epimer of **1** or **2**.

Catalytic amounts of acid equilibrated *cis*-maneonene-C with its C-12 double bond isomer (**18**, Scheme IV). Since the H-4 and the H-14 protons of *cis*-maneonene-C absorb further downfield than the same protons in its isomer, *cis*-maneonene-C was assigned the *E* configuration at the C-12 double bond and its isomer the *Z* configuration. *cis*-Maneonene-C is then represented by structure **4**.

The maneonenes are unique in structure for C_{15} nonterpenoids from *Laurencia* and *Aplysia* species. Although a number of these materials have been described, only one recently reported example, panacene, contains a carbocyclic ring (C-8, C-13 juncture).[19] The maneonenes contain one carbocyclic ring by virtue of the C-6, C-11 bond. Also occurring with them are the isomaneonenes which contain this same carbocyclic ring and an additional one as well.

Isomaneonene-A (**5**) and isomaneonene-B (**6**) were obtained from the benzene and benzene–ether eluants of the chromatography of the crude algal extract (Scheme I). Both compounds analyzed for $C_{15}H_{16}Br_2O_2$ by high resolution and field desorption mass spectroscopy. Their UV (229, 228 nm), IR (3300, 2970 cm^{-1}), and ^{13}C and ^{1}H NMR spectra (Tables V and VI) indicated the presence of a conjugated *cis*-enyne group.

The IR spectrum of isomaneonene-A shows no hydroxyl, carbonyl, or vinyl ether absorption. Strong bands in the 1000–1100-cm^{-1} region indicate the presence of ether functions. The ^{13}C NMR spectrum shows three oxygen-bearing carbons which could be correlated with three oxygen methine absorptions in the ^{1}H NMR spectrum (Table V) by specific hydrogen–carbon decoupling experiments. The fourth oxygen-bearing carbon, having no associated proton absorption, must be quaternary.

The ^{13}C NMR spectrum established that 3 of the 15 carbon atoms of isomaneonene-A are quaternary. One of these quaternary centers is the internal acetylenic carbon and the other two bear the second oxygen atom, both bromines, and an ethyl group. The placement of the ethyl group follows from the ^{1}H NMR spectrum. A three-proton triplet ($J = 7$ Hz) at δ 1.06 and two doublets of quartets ($J = 7$, 14 Hz) at 2.08 and 2.33 show that the methylene protons of the ethyl group are magnetically nonequivalent and are coupled only to each other and the adjacent methyl protons. The attachment of the two bromine atoms and the fourth oxygen link to the remaining quaternary centers is indicated by the deshielded chemical shift values for these carbons (δ 110.6 and 89.7). Catalytic hydrogenation of either isomaneonene-A or isomaneonene-B afforded a saturated ether with all oxygen bonds intact but with both bromines replaced by hydrogens (**19**, Scheme V). This ether has four oxygen methines rather than three as found in the original compound. A new oxygen methine can arise from reductive debromination of a quaternary carbon bearing an oxygen and a bromine but not from one bearing two bromines.

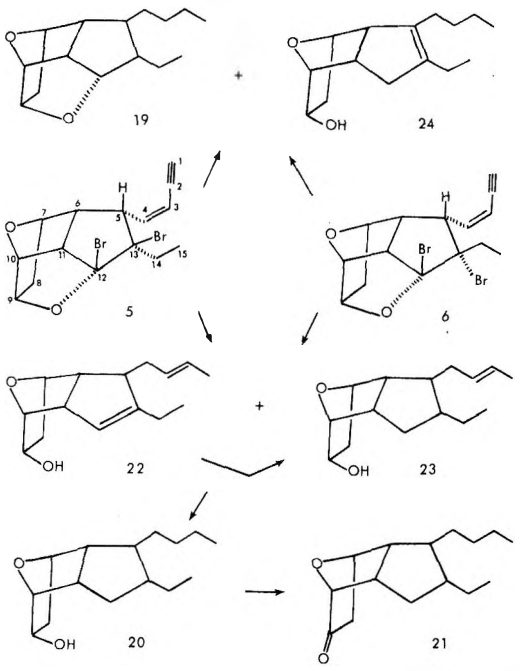
The quaternary ether linkage of isomaneonene-A was cleaved under dissolving metal reduction conditions. Treatment with sodium in ammonia followed by catalytic hydrogenation gave a saturated ether alcohol (**20**, Scheme V) again with both bromines replaced by hydrogens. The mass spectrum of this alcohol shows the loss of butyl (from the original enyne side chain) and ethyl fragments. The loss of an ethyl rather than a propyl group fixes this substituent at the qua-

Table VI. ^{13}C [a] and ^{1}H [b] NMR Data for Isomaneonene-B (6)

Carbon no.	^{13}C δ	^{1}H δ	Multiplicity, J (Hz)
1	83.5	2.72	d, $J_{1,3} = 2$
2	79.9[c]		
3	108.7	5.08	dd, $J_{1,3} = 2$, $J_{3,4} = 10.5$
4	146.9	6.34	dd, $J_{3,4} = 10.5$, $J_{4,5} = 9$
5	43.2	3.53	t, $J_{4,5} = J_{5,6} = 9$
6	50.0	2.75	sextet, $J_{5,6} = 9$, $J_{6,7} = 5$, $J_{6,11} = 10$
7	77.6	4.08	t, $J_{6,7} = J_{7,8exo} = 5$
8	41.1	1.15 (exo) 1.67 (endo)	dt, $J_{7,8exo} = J_{8exo,9} = 5$, $J_{8exo,8endo} = 13$ d, $J_{8exo,8endo} = 13$
9	81.4	4.25	t, $J_{8exo,9} = J_{9,10} = 5$
10	84.6	5.03	t, $J_{9,10} = J_{10,11} = 5$
11	58.7	2.96	dd, $J_{10,11} = 5$, $J_{6,11} = 10$
12	109.5[c]		
13	85.2[c]		
14	38.0	1.30 2.36	sextet, $J_{14,14} = 14$, $J_{14,15} = 7$ sextet, $J_{14,14} = 14$, $J_{14,15} = 7$
15	10.6	0.95	t, $J_{14,15} = 7$

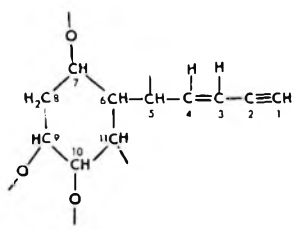
[a] Proton decoupled values (ppm downfield from Me_4Si) in $CDCl_3$. [b] 270 MHz values (ppm downfield from Me_4Si) in C_6D_6. [c] Quaternary carbon.

Scheme V



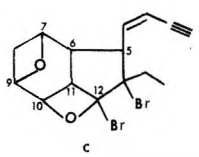
ternary carbon bearing the single bromine and completes the assignment of C-12 through C-15 as shown in **5**.

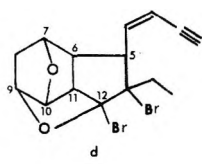
Twelve of the fifteen carbon atoms and twelve of the sixteen hydrogen atoms of isomaneone-A have now been defined. The remaining groups must be a methylene and two methines as the one methyl carbon and the three quaternary carbons have already been assigned. A geminally coupled pair of hydrogens is evident from the ^{1}H NMR spectrum where a doublet (J = 13 Hz) appears at δ 1.59. The two methine protons and the second hydrogen of the methylene group are also shown in the ^{1}H NMR spectrum (Table V, C-6, C-11, and C-8_{exo}). Proton–proton decoupling experiments established the proton sequence as:[17]



Irradiation at δ 4.98 (C-3) collapsed the doublet at 2.72 (C-1) to a singlet and the doublet of doublets at 5.66 (C-4) to a doublet. Irradiation at δ 3.38 (C-6) effected changes in the signals at 4.33 (C-5), 4.19 (C-7), and 3.88 (C-11). The sextet at δ 3.38 (C-6) collapsed to a triplet upon irradiation of the 4.19 signal (C-7) and the doublet of triplets at 1.15 (C-8_{exo}) collapsed to a doublet of doublets. Irradiation of the latter (C-8_{exo}) converted the triplets at 4.19 (C-7) and 4.31 (C-9) each to doublets and the doublet at 1.59 (C-8_{endo}) to a singlet. Irradiation at δ 5.02 (C-10) collapsed the triplet at 4.31 (C-9) and the doublet of doublets at 3.88 (C-11) each to doublets.

The quaternary carbons bearing the ethyl, bromines, and one oxygen must be attached to the main chain through carbons 5 and 11. If the bromine, ethyl-bearing carbon is attached at C-5 and the bromine, oxygen-bearing carbon at C-11 followed by ether ring closures, two viable structures (c and d) are generated which are based on an unbranched C_{15} chain:


c


d

Since no epoxide moiety is evident in isomaneonene-A, the structure resulting from oxide ring closure between C-9 and C-10 is not considered possible. If the bromine, ethyl-bearing carbon is attached at C-11 and the bromine, oxygen-bearing carbon at C-5, three additional structures arise, these based on a branched C_{15} chain. As with the maneonenes, a branched carbon skeleton for these compounds is considered highly unlikely on biogenetic grounds. Moreover, molecular models of all isomers of these six structures show that only structure d will fit the spectroscopic data. Structure d is confirmed also on the basis of the following information. The secondary alcohol (**20**) obtained from the sodium and ammonia hydrogenation sequence (Scheme V), when treated with Jones reagent, afforded a ketone (**21**). Proton–proton decoupling experiments with this ketone showed that the oxygen-bearing methine at δ 4.39 (C-7) is coupled to two protons, one at 2.62 (C–6) and the other at 2.20 (C-8_{exo}); the other oxygen-bearing methine (δ 4.06, C-10) is coupled to a proton at 2.49 (C-11). The proton at δ 2.49 (C-11) and the proton at 2.62 (C-6) *are also coupled with each other as well as to additional protons other than the oxygen methines.* This data can only be accommodated by ketone **21** arising from **5** (Scheme V).

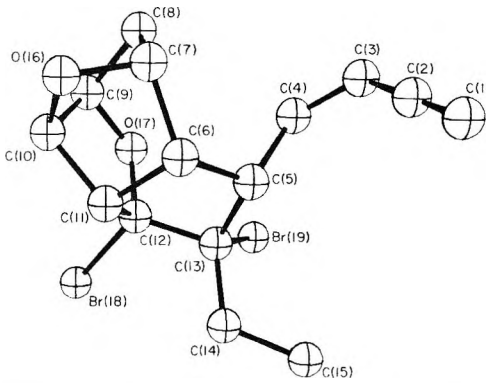


Figure 1. A computer generated perspective drawing from the crystal structure of isomaneonene-B (**6**).

An analysis of the H–H couplings in the ^{1}H NMR spectrum of isomaneonene-A shows an excellent agreement with the structure assigned. The coupling constants $J_{5,6}$ (10 Hz) and $J_{6,11}$ (10 Hz) indicate that H-6 is cis to H-5 and H-11. The dihedral angle between H-6 and H-7, H-9 and H-10, and H-10 and H-11 is approximately 30°, which gives a satisfactory fit for the observed coupling constant of 5 Hz.[18]

The different chemical environments of H-8_{exo} and H-8_{endo} give two absorptions, coupled to each other by 13 Hz. The dihedral angle between H-7 and H-8_{exo} and H-8_{exo} and H-9 is also approximately 30° to give rise to a 5 Hz coupling. $J_{7,8endo}$ and $J_{8endo,9}$ = 0 in agreement with their 90° dihedral angles (Table V).

Isomaneonene-B (**6**) is the C-13 isomer of isomaneonene-A. The distinction between them is made on the basis of their ^{1}H NMR spectra. In **5** the bromine atom on C-13 is cis to H-5 and trans to the enyne function and H-4, while the opposite situation obtains in **6.** The deshielding effect of this bromine is reflected in the chemical shift of H-5 where it occurs 0.80 ppm further downfield in **5** than in **6,** while H-4 is 0.68 ppm further downfield in **6** than in **5.** H-6 and H-11 also occur substantially further downfield when the C-13 bromine is cis to them (Table V).

Several olefinic intermediates were isolated in the reductions shown in Scheme V. In the sodium–ammonia reaction olefins **22** and **23** were the immediate products. No stereochemistry at the side chain junctures is implied by the formulas shown. Diene **22** analyzed for $C_{15}H_{22}O_2$ by mass spectroscopy. The presence of two nonconjugated double bonds was indicated by three olefinic protons and three olefinic carbons[16] in the ^{1}H and ^{13}C NMR spectra. Three oxygen methines and an OH stretch (IR 3540 cm^{-1}) indicated that one oxygen link remained intact, while the quaternary C–O linkage was reductively cleaved. Further treatment with sodium–ammonia converted diene **22** to the monoene **23.** Both compounds show strong absorption in the IR spectrum for a disubstituted trans double bond (960 cm^{-1}). The presence of only one ethyl group suggests the placement of this double bond as shown (Scheme V); this would be expected for a 1,4 reduction of the conjugated system. The trisubstituted double bond in **22** cannot be exo to the oxirane ring as the oxygen methine couplings, $J_{6,7}$ and $J_{10,11}$, are unchanged from the isomaneonenes themselves. It also cannot be exo to the five-membered carbocyclic ring as its IR signal (1630 cm^{-1}) occurs at too low a frequency. Both diene **22** and monoene **23** were catalytically reduced to the fully saturated alcohol ether **20.**

Direct hydrogenation of isomaneonene-A or isomaneonene-B afforded an olefinic product (**24**) as well as the fully saturated material (**19,** Scheme V). The olefin analyzes for $C_{15}H_{24}O_2$ by mass spectroscopy and its IR spectrum shows hydroxyl absorption (3570, 3430 cm^{-1}). Three oxygen methines are indicated by the ^{1}H NMR spectrum, again consistent with reductive cleavage of the quaternary ether link. The tetrasubstituted nature of the double bond is evident from the lack of vinylic proton absorption in the ^{1}H NMR spectrum. Proton–proton decoupling studies indicated that the H-6 and H-11 protons are still present, therefore this double bond must be between C-5 and C-13.

The complexity of the isomaneonene structures and their abundance of chiral centers (eight) made an X-ray study of these materials desirable. Accordingly a single-crystal X-ray diffraction experiment on isomaneonene-B was carried out. The computer-generated perspective drawing of the final model is shown in Figure 1. The indications of absolute stereochemistry given by the anomalous scattering of bromine were not decisive and the enantiomer shown was only marginally favored. The relative stereochemistry of isomaneonene-B is that predicted on chemical and spectral grounds. All bond distances and angles generally agree with accepted values.

Experimental Section

Melting points were determined on a Hoover Unimelt apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer 700 and 337 spectrophotometers in CCl_4. The ^{1}H NMR spectra were recorded with JEOL C-60H, Perkin-Elmer R-12, Perkin-Elmer R-20, Varian HA 100, JEOL-PFT-100, or Brucker 270 HX spectrometers, and the ^{13}C NMR spectra were determined on JEOL-PFT-100 or Varian CFT-20 spectrometers with C_6D_6 or $CDCl_3$ as solvents. Chemical shift values are reported as ppm downfield from Me_4Si at 60 MHz for protons and at 25 MHz for ^{13}C unless otherwise specified. Low resolution mass spectra were obtained on a Finnigan 1015 D GC–mass spectrometer and high resolution mass spectra on a CEC-21-110B spectrometer. Field desorption mass spectra were taken on a Varian CH 5/DF spectrometer. UV spectra were recorded with a Perkin-Elmer 202 spectrophotometer in 95% ethanol unless otherwise indicated. Optical rotations were measured in $CHCl_3$ on a Zeiss Type VDr Na polarimeter. Vapor phase chromatography was done with a Varian-Aerograph 90-P3 instrument. Brinkmann silica gel 60 (30–70 mesh) was used for column chromatography and Brinkmann silica gel HF-254 + 366, Type 60 (500 μm, activated 0.5 h at 100 °C), for TLC.

All solvents and chemicals were reagent grade.

Separation of the Maneonenes. The air-dried alga, 160 g, was ground to a fine powder with a Waring blender, covered with 400 mL of anhydrous ether, and allowed to stand with occasional shaking for 1 week. The ether was decanted and the extraction was repeated with 250 mL of fresh ether for an additional 7 days. The ether extracts were combined, concentrated, and centrifuged and the ether was removed to give 3.3 g (2%) of a green brown oil. This oil was dissolved in 5 mL of 3:1 hexane–benzene and applied to a 4-step glass column (2.50–0.75 cm) packed with 45 g of silica gel. Elution was begun with 3:1 hexane–benzene, and the following eluants were obtained: eluant 1, 3:1 hexane–benzene, 231 mg (7%); eluant 2, 1:1 hexane–benzene, 309 mg (9%); eluant 3, benzene, 329 mg (10%); eluant 4, benzene, 465 mg (14%); eluant 5, 6:1 benzene–ether, 426 mg (13%); eluant 6, ether, 561 mg (17%). The total recovery was 2.37 g (70%).

Isolation of *cis*-Maneonene-A (1), *cis*-Maneonene-B (2), and *cis*-Maneonene-C (4). Eluant 3 (150 mg) was dissolved in ether and spotted onto TLC plates so that each spot contained about 3 mg of material. The plates were developed twice in benzene, drying between developments, and the spots were scraped off and extracted with ether. After filtering and evaporating the ether, the following fractions were obtained: 1, R_f 0.63, 32 mg (21%); 2, R_f 0.50, 47 mg (31%); 3, R_f 0.09, 11 mg (8%).

Thirty milligrams of fraction 1 was spotted onto a TLC plate with ether so that each spot contained about 1.5 mg of material. The plate was developed three times in 1:1 dichloromethane–hexane, drying between developments. The spots were scraped off and extracted with ether. *cis*-Maneonene-A (**1**) was obtained as a colorless oil, R_f 0.47, 16 mg (0.02% of dry alga): $[\alpha]^{21}_D$ +39° (c 0.97); UV λ_{max}^{hexane} 225 nm (ε 14 900); IR ν_{max} 3310, 2960, 2940, 1685, 1455, 1430, 1185, 1160, 1100, 1040, 975, 905, and 865 cm^{-1}; NMR Table I; mass spectrum *m/e* 346 (3), 344 (9), 342 (8), 310 (8), 309 (36), 308 (8), 307 (36), 265 (6), 263 (11), 249 (5), 247 (5), 237 (5), 235 (5), 229 (5), 228 (17), 227 (14), 219 (3), 213 (5), 210 (5), 209 (8), 201 (9), 200 (9), 199 (28), 185 (28), 184 (42), 171 (28), 169 (22), 159 (23), 157 (30), 155 (23), 153 (20), 145 (20), 143 (28), 141 (34), 129 (55), 128 (45), 115 (52), 108 (50), 91 (55), 79 (50), 77 (81), 69 (100), 65 (48), 55 (41), 53 (41), 51 (42), 41 (84), 39 (66). High reso-

lution mass spectrum. Calcd for $C_{15}H_{16}Br^{79}Cl^{35}O_2$ (M^+): 342.0021. Found: 342.0026.

Forty-five milligrams of fraction 2 was dissolved in ether and spotted onto TLC plates so that each spot contained approximately 1 mg of material. The plates were developed five times in 1:1 dichloromethane–hexane, drying between developments, and the spots were scraped off and extracted with ether to give *cis*-maneonene-B (**2**), R_f 0.45 (19 mg), and *cis*-maneonene-C (**4**), R_f 0.57 (17 mg), as colorless oils. Additional amounts of both compounds were obtained from rechromatography of eluant 4 or the original column chromatography. Based on dry weight of alga, the total yield of **2** was 0.15% and that of **4** was 0.08%.

***cis*-Maneonene-B (2):** $[\alpha]^{21}_D$ −49° (c 3.60); UV λ_{max} 227 nm (ε 12 200); IR ν_{max} 3310, 2980, 2950, 2880, 1685, 1455, 1430, 1345, 1315, 1305, 1290, 1220, 1190, 1160, 1135, 1110, 1085, 1025, 975, 950, 895, 875, and 845 cm^{-1}; NMR Table II; mass spectrum identical to *cis*-maneonene-A (**1**). High resolution mass spectrum. Calcd for $C_{15}H_{16}Br^{79}Cl^{35}O_2$ (M^+): 342.0021. Found: 341.9990.

***cis*-Maneonene-C (4):** $[\alpha]^{21}_D$ +336° (*c* 1.46); UV λ_{max} 222 (ε 21 700); IR ν_{max} 3310, 2985, 2945, 2880, 1680, 1455, 1440, 1180, 1165, 1100, 1040, 985, 965, 955, 890, 870, and 850 cm^{-1}; NMR Table IV; mass spectrum *m/e* 346 (3), 344 (9), 342 (6), 310 (6), 309 (37), 308 (6), 307 (37), 266 (3), 265 (19), 264 (3), 263 (19), 228 (4), 227 (9), 221 (4), 219 (4), 203 (5), 202 (4), 201 (14), 200 (6), 199 (21), 189 (6), 187 (9), 185 (9), 183 (8), 181 (6), 171 (11), 169 (11), 159 (41), 143 (21), 141 (31), 129 (38), 128 (41), 123 (29), 122 (46), 121 (38), 115 (52), 108 (44), 107 (39), 91 (67), 81 (52), 79 (68), 77 (100), 69 (71), 65 (57), 53 (46), 51 (47), 41 (76), 39 (72). High resolution mass spectrum. Calcd for $C_{15}H_{16}Br^{79}Cl^{35}O_2$: 342.0021. Found: 342.0019.

Isolation of *trans*-Maneonene-B (3). Approximately 700 mg of eluant 5 from the original column chromatography was dissolved in ether and spotted onto TLC plates so that each plate contained 70 mg of material. The plates were developed five times in 30:1 benzene–ether, drying between developments, and the spots were scraped off and extracted with ether. After filtering and evaporation of the ether, the following compounds were obtained: isomaneonene-A (**5**) (R_f 0.86), *trans*-maneonene-B (**3**) (R_f 0.77), isomaneonene-B (**6**) (R_f 0.63), sesquiterpenoid A (R_f 0.57),[5] and sesquiterpenoid B (R_f 0.50).[5] *trans*-Maneonene-B (**3**) was repurified by the same TLC procedure to give a colorless oil (30 mg, 0.01% of dry alga): $[\alpha]^{21}_D$ −25° (*c* 0.397); UV λ_{max} 232 nm (ε 15 000); IR ν_{max} 3330, 3000, 2960, 2900, 1685, 1630, 1455, 1435, 1350, 1320, 1295, 1265, 1220, 1190, 1140, 1120, 1030, 955, 890, and 880 cm^{-1}; NMR Table III; mass spectrum *m/e* 346 (3), 344 (11), 342 (8), 309 (3), 307 (3), 265 (2), 263 (3), 249 (2), 247 (2), 237 (2), 235 (2), 228 (6), 227 (6), 201 (8), 199 (14), 189 (8), 187 (14), 185 (13), 184 (14), 181 (6), 171 (11), 169 (11), 165 (9), 159 (10), 157 (11), 155 (11), 153 (10), 149 (14), 141 (25), 129 (28), 128 (22), 121 (22), 115 (28), 109 (19), 108 (33), 107 (22), 99 (22), 97 (28), 95 (33), 91 (36), 85 (24), 83 (33), 81 (39), 79 (36), 77 (47), 71 (42), 69 (100), 57 (47), 55 (72), 53 (39), 51 (39), 41 (50), 39 (47). High resolution mass spectrum. Calcd for $C_{15}H_{16}Br^{79}Cl^{35}O_2$: 342.0021. Found: 341.9989.

Reaction of *cis*-Maneonene-A (1) with Bis(ethylenediamine)chromium(II) to Produce 7. Chromous sulfate solution was prepared by stirring an aqueous solution of 1.14 g of $Cr_2(SO_4)\cdot nH_2O$ with 0.65 g of activated powdered zinc in a nitrogen atmosphere overnight. The resultant blue solution was filtered under nitrogen and a 2.50-mL aliquot (0.5 mmol Cr^{2+}) was added to 1.25 mL of an aqueous solution of $enSO_4$ (1.0 mmol). This mixture was added to a degassed solution of 22 mg (0.048 mmol) of *cis*-maneonene-A (**1**) in 4 mL of DMF. Nitrogen was bubbled through the solution for 4 h; a precipitate formed during this time. Ten milliliters of water was added and the resulting suspension was extracted with three 10-mL portions of CCl_4. The extracts were dried over Na_2CO_3 and filtered and the CCl_4 was evaporated to give a yellow oil. This oil was dissolved in ether, spotted onto TLC plates, and developed twice in 1:1 dichloromethane–hexane, drying between runs. The spots were scraped off, extracted with ether, and filtered and the ether was evaporated to give 11 mg (50%) of **7** as a colorless oil, R_f 0.50: UV λ_{max} 220 nm (ε 24 200); IR ν_{max} 3000, 2955, 1940, 1685, 1460, 1440, 1350, 1320, 1290, 1260, 1195, 1170, 1125, 1100, 1055, 1035, 990, 975, 880, 860 cm^{-1}; ^1H NMR (C_6D_6) δ 1.0–1.3 (2 H, m), 1.12 (3 H, t, *J* = 7 Hz), 2.34 (2 H, m), 2.58 (2 H, q, *J* = 7 Hz), 2.98 (1 H, br d, *J* = 5 Hz), 3.94 (1 H, d, *J* = 4.5 Hz), 4.22 (1 H, br dd), 4.50 (1 H, t, *J* = 5 Hz), 4.70 (1 H, br s), 4.80 (1 H, br s), and 5.35–6.25 (3 H, several m); mass spectrum *m/e* 310 (15), 308 (15), 267 (1), 265 (1), 253 (1), 251 (1), 239 (1), 237 (1), 231 (6), 229 (13), 202 (28), 200 (28), 189 (14), 187 (23), 185 (14), 121 (52), 108 (77), 91 (48), 79 (83), 77 (100), 65 (34), 53 (43), 51 (32), 41 (55), 39 (63).

Reaction of 7 with $CrSO_4$ to Produce 9. A solution of 62 mg (0.20 mmol) of **7** in 15 mL of degassed DMF and 10 mL of an aqueous solution containing 2.0 mmol of $CrSO_4$ was stirred at 25 °C for 3 days under a nitrogen atmosphere. The solution was diluted with 50 mL of water and the resulting suspension was extracted with three 20-mL portions of CCl_4. The combined extracts were washed with water, dried over Na_2CO_3, filtered, and evaporated to give 51 mg (82%) of **9** as a yellow oil: IR ν_{max} 3080, 2990, 2950, 1690, 1640, 1460, 1435, 1380, 1350, 1320, 1295, 1260, 1195, 1165, 1100, 1040, 985, 950, 915, 875 cm^{-1}; ^1H NMR (C_6D_6) δ 1.09 (3 H, t, *J* = 7.5 Hz), 1.5–2.9 (5 H, several m), 2.58 (2 H, q, *J* = 7.5 Hz), 3.00 (1 H, br d, *J* = 5 Hz), 4.00 (1 H, d, *J* = 5 Hz), 4.28 (1 H, br dd, *J* = 7, 5 Hz), 4.58 (1 H, t, *J* = 5 Hz), and 4.9–5.8 (5 H, several m); mass spectrum *m/e* 312 (11), 310 (11), 244 (8), 242 (8), 231 (26), 229 (11), 215 (5), 213 (5), 203 (28), 202 (55), 201 (33), 200 (55), 189 (23), 187 (37), 185 (15), 121 (69), 110 (36), 108 (78), 95 (56), 91 (58), 81 (100), 79 (87), 77 (63), 69 (38), 68 (33), 67 (38), 65 (38), 57 (18), 55 (52), 53 (54), 51 (21), 43 (33), 41 (62), 39 (52).

Hydrogenation of *cis*-Maneonene-A (1) to Produce 11. A suspension of 76 mg (0.22 mmol) of *cis*-maneonene-A (**1**) and 16 mg of PtO_2 (previously reduced) in 15 mL of anhydrous ethanol was stirred for 2.25 h under an atmosphere of hydrogen. The catalyst was centrifuged and the ethanol was evaporated to give 60 mg of a tan oil. This oil was spotted onto TLC plates with ether, the plates were developed twice in 5:1 dichloromethane–ether, drying between runs, and the spots were scraped off and extracted with ether to give 9 mg (17%) of a colorless oil, R_f 0.64: IR ν_{max} 2950, 2860, 1465, 1430, 1380, 1280, 1245, 1200, 1155, 1130, 1055, 1025, 960, 890, and 835 cm^{-1}; ^1H NMR (C_6D_6) δ 0.93 (3 H, br t), 1.0–2.1 (br envelope), 3.78 (1 H, br m), 4.16 (1 H, br t, *J* = 4 Hz), 4.35 (1 H, br m), and 4.85 (1 H, br t, *J* = 5 Hz); ^{13}C NMR (C_6D_6) δ 14.4 (2), 20.3, 23.0, 27.5, 32.4, 34.8, 36.1, 42.3, 43.1, 51.0, 77.3, 78.5, 79.5, and 83.7; mass spectrum *m/e* 238 (10), 221 (2), 209 (1), 195 (100), 167 (10), 165 (22), 152 (18), 151 (27), 138 (18), 123 (24), 109 (17), 95 (28), 81 (31), 71 (24), 69 (20), 67 (28), 57 (20), 55 (37), 43 (36), 41 (34). High resolution mass spectrum. Calcd for $C_{15}H_{26}O_2$: 238.1933. Found: 238.1952.

Interconversion of *cis*-Maneonene-A (1) with *cis*-Maneonene-B (2). A solution of 20 mg of *cis*-maneonene-A (**1**) and one crystal of *p*-toluenesulfonic acid monohydrate in 1.0 mL of anhydrous benzene was heated at reflux for 4 h. The benzene was evaporated and the residue was dissolved in ether and spotted onto a TLC plate. The plate was developed in benzene, the spots were scraped off and extracted with ether, and the two major spots were identified as unreacted **1** and *cis*-maneonene-B (**2**) by comparison of their IR spectra with authentic compounds. The ratio of **1**:**2** was approximately 1:1. The same results were obtained by starting with *cis*-maneonene-B (**2**).

Reaction of *cis*-Maneonene-B (2) with $Cr(en)_2SO_4$ to Produce 8. This reaction was carried out in a manner identical to that with *cis*-maneonene-A (**1**) to give 10 mg (50%) of **8** as a colorless oil, R_f 0.56 (1:1 dichloromethane–hexane, three developments): IR ν_{max} 3010, 2970, 1940, 1690, 1460, 1440, 1355, 1325, 1290, 1270, 1200, 1175, 1150, 1120, 1100, 1070, 1060, 1035, 995, 980, 910, 895, and 860 cm^{-1}; ^1H NMR (C_6D_6) δ 1.07 (3 H, t, *J* = 7 Hz), 1.3 (2 H, m), 2.2 (1 H, m) 2.28 (2 H, q, *J* = 7 Hz), 2.54 (1 H, br d, *J* = 5 Hz), 3.93 (1 H, br d, *J* = 4 Hz), 4.26 (1 H, br dd), 4.60 (1 H, t, *J* = 5 Hz), 4.82 (2 H, m), and 5.84 (3 H, m); ^{13}C NMR (C_6D_6) δ 14.3, 29.7, 39.2, 48.1, 56.3, 76.6, 79.8, 80.8, 82.6, 93.4, 125.4, 133.2; mass spectrum *m/e* 310 (9), 308 (9), 231 (5), 229 (11), 203 (9), 202 (30), 201 (16), 200 (30), 189 (16), 187 (29), 185 (16), 121 (50), 108 (85), 107 (39), 91 (45), 79 (85), 77 (100), 69 (34), 67 (24), 65 (34), 57 (28), 55 (37), 53 (37), 51 (28), 43 (35), 41 (62), 39 (62).

Reaction of *cis*-Maneonene-B (2) with $CrSO_4$ to Produce 10. A solution of 80 mg (0.232 mmol) of *cis*-maneonene-B (**2**) in 20 mL of degassed DMF and 10 mL of an aqueous solution containing 2.0 mmol $CrSO_4$ was allowed to stand for 4 days at 25 °C under an atmosphere of nitrogen. The solution was diluted with 50 mL of water and the resulting suspension was extracted with three 20-mL portions of CCl_4. The combined extracts were washed with 25 mL of water, dried over Na_2CO_3, filtered, and evaporated to give 69 mg (96%) of **10** as a yellow oil: IR ν_{max} 3080, 2995, 2945, 1685, 1640, 1455, 1430, 1370, 1340, 1315, 1270, 1190, 1160, 1135, 1100, 1030, 980, 970, 910, 875, and 845 cm^{-1}; mass spectrum identical to that of **9**.

This same compound is produced when **8** is treated with $CrSO_4$.

Reaction of 10 with Na/NH_3 and H_2/Pt to Produce 14. To a solution of 70 mg (3 mg atom) of sodium in 20 mL of anhydrous ammonia at −78 °C was slowly added a solution of 69 mg (0.221 mmol) of **10** in 5 mL of anhydrous ether. The solution was stirred for 1 h under a nitrogen atmosphere. The reaction was quenched by slow addition of solid NH_4Cl until the blue color disappeared. Twenty milliliters of ether and 20 mL of water were added, and the layers were separated. The aqueous layer was extracted with an additional two 20-mL portions of ether. The combined ether extracts were washed with 25 mL of water, dried over Na_2CO_3, filtered, and evaporated to give 40 mg of a colorless oil, which was dissolved in ether and spotted

onto a TLC plate. The plate was developed four times in 1:1 hexane–ether, drying between developments, and the spots were scraped off and extracted with ether to give 14 mg (20%) of a colorless oil, R_f 0.50. ^{1}H NMR and GC–mass spectra showed this oil to be a mixture of at least two partially reduced unstable compounds. The mixture was therefore hydrogenated with 2 mg of PtO_2 (previously reduced) in 10 mL of anhydrous ethanol for 30 min. The catalyst was removed by centrifugation and the ethanol was evaporated to give a colorless oil which was dissolved in ether and spotted onto a TLC plate. The plate was developed four times in 9:1 hexane–ether, drying between runs, and the spots were scraped off and extracted with ether to give 5 mg (40%) of **14** as a colorless oil, R_f 0.41: IR ν_{max} 2960, 2885, 1475, 1385, 1330, 1295, 1265, 1220, 1165, 1125, 1075, 1025, 975, 910, and 855 cm^{-1}; ^{1}H NMR (C_6D_6) δ 0.95 (6 H, br t), 1.1–2.3 (br envelope), 3.50 (1 H, dd, J = 11, 6 Hz), 3.52 (1 H, m), 4.13 (1 H, br d, J = 4 Hz), 4.30 (1 H, br t, J = 6 Hz), and 5.38 (1 H, t, J = 5 Hz); mass spectrum m/e 236 (9) (M^+ − HBr), 221 (29), 177 (4), 165 (11), 137 (7), 123 (10), 109 (17), 107 (17), 97 (15), 95 (28), 93 (17), 91 (11), 85 (14), 83 (17), 81 (34), 79 (18), 77 (9), 71 (34), 69 (42), 67 (31), 57 (38), 55 (100), 53 (10), 43 (56), 41 (58), 39 (14).

This same product is obtained by allowing *cis*-maneonene-B (**2**) to react under the same conditions.

Reaction of *cis*-Maneonene-B (2) with Na/NH$_3$ and H$_2$/Pt to Produce 12 and 13. One-hundred milligrams (0.29 mmol) of *cis*-maneonene-B (**2**) was allowed to react with sodium in liquid ammonia under the same conditions as that for **10**. Fifty milligrams (56%) of the crude mixture of olefins was obtained. This was suspended in 15 mL of ethanol with 7 mg of PtO_2 (previously reduced) and stirred for 30 min under a hydrogen atmosphere. The catalyst was centrifuged and the ethanol was evaporated to give a colorless oil, which was spotted onto a TLC plate with ether. The plate was developed three times in 9:0.5:0.5 hexane–dichloromethane–ether, drying between runs, and the spots were scraped off and extracted with ether to give 10 mg (20%) of **12** as a colorless oil, R_f 0.40, and 10 mg (20%) of **13** also as a colorless oil, R_f 0.30.

12: IR ν_{max} 2950, 2875, 1700, 1460, 1360, 1320, 1295, 1275, 1165, 1060, 1040, 975, 945, 910, and 855 cm^{-1}; ^{1}H NMR (C_6D_6, 270 MHz) δ 0.88 (3 H, t, J = 7 Hz), 1.06 (3 H, t, J = 7 Hz), 1.1–1.3 (9 H, br envelope), 1.26 (1 H, d, J = 14 Hz), 1.51 (1 H, td, J = 5, 8, 14 Hz), 2.21 (1 H, d, J = 5 Hz), 2.31 (1 H, septet, J = 7, 14 Hz), 2.34 (1 H, sextet, J = 7, 14 Hz), 3.89 (1 H, d, J = 5 Hz), 4.30 (1 H, dd, J = 5, 8 Hz), 4.31 (1 H, t, J = 7 Hz), 4.62 (1 H, t, J = 5 Hz); mass spectrum m/e 236 (21), 221 (60), 207 (3), 203 (2), 193 (5), 177 (6), 165 (19), 153 (9), 151 (7), 149 (6), 147 (5), 137 (10), 135 (6), 133 (5), 123 (14), 111 (12), 109 (22), 107 (20), 97 (19), 95 (33), 93 (20), 91 (12), 85 (16), 83 (22), 81 (38), 79 (18), 71 (42), 69 (45), 67 (32), 54 (39), 45 (100), 43 (52), 41 (54).

13: IR ν_{max} 2950, 2875, 1695, 1460, 1375, 1360, 1315, 1290, 1265, 1165, 1125, 1100, 1030, 970, 940, 910, and 880 cm^{-1}; ^{1}H NMR (C_6D_6, 270 MHz) δ 0.88 (3 H, t, J = 7 Hz), 0.98 (3 H, t, J = 7 Hz), 1.1–1.3 (9 H, br envelope), 1.26 (1 H, d, J = 14 Hz), 1.51 (1 H, td, J = 5, 8, 14 Hz), 1.99 (2 H, quintet, J = 7 Hz), 2.40 (1 H, d, J = 5 Hz), 3.91 (1 H, d, J = 5 Hz), 4.27 (1 H, dd, J = 5, 8 Hz), 4.61 (1 H, t, J = 5 Hz), and 4.88 (1 H, t, J = 7 Hz); ^{13}C NMR (C_6D_6) δ 10.7, 12.5, 17.8, 19.5, 23.9, 28.6, 30.7, 36.2, 41.6, 49.6, 75.1, 76.3, 78.6, and 95.6; mass spectrum identical to that of **12**.

The same two products, **12** and **13**, are obtained from the reaction of **10** under the same conditions.

Dehydrobromination of 14 to Produce 12. A solution of **14** was injected onto a 0.25 in. × 10 ft GC column (20% SE-30 on 60/80 Chromosorb W, AW DMCS) at 200 °C and the single peak with a retention time of 7 min was collected. The IR and ^{1}H NMR spectra showed this compound to be identical to **12**.

Hydrogenation of 12 to Produce 11. A suspension of 5 mg of **12** and 1 mg of PtO_2 (previously reduced) in 10 mL of anhydrous ethanol was stirred for 1 h under a hydrogen atmosphere. The catalyst was removed by centrifugation and the ethanol was evaporated to give 5 mg of a colorless oil. The IR spectrum of this oil was identical to **11** obtained from the hydrogenation of *cis*-maneonene-A (**1**).

Reaction of *trans*-Maneonene-B (3) with Cr(en)$_2$SO$_4$ to Produce 8. The Cr(en)$_2$SO$_4$ solution was prepared by mixing 1.25 mL of a solution containing 0.25 mmol of $CrSO_4$ with 0.6 mL of a solution of $enSO_4$ (0.48 mmol) in water. This solution was added to a degassed solution of 8 mg (0.023 mmol) of *trans*-maneonene-B (**3**) in 2 mL of DMF. The reaction and the workup procedure were the same as that described for *cis*-maneonene-A (**1**). TLC purification of the crude product (1:1 dichloromethane–hexane, three developments) gave 4.5 mg (56%) of **8** as a colorless oil. This product was identical to that derived from *cis*-maneonene-B (**2**) as determined by a comparison of the IR, ^{1}H NMR, and mass spectra.

Reaction of *cis*-Maneonene-C (4) with Cr(en)$_2$SO$_4$ to Produce 15. A procedure identical to that used for *cis*-maneonene-A (**1**) gave 11 mg (42%) of **15** as a colorless oil, R_f 0.65 (1:1 dichloromethane–hexane, three developments): IR ν_{max} 3000, 2970, 2920, 1940, 1690, 1460, 1440, 1350, 1330, 1310, 1250, 1220, 1190, 1170, 1105, 1050, 990, 970, 930, 900, 885, and 855 cm^{-1}; ^{1}H NMR (C_6D_6) δ 1.10 (3 H, t, J =8 Hz), 1.43 (2 H, m), 2.58 (2 H, q, J = 8 Hz), 2.5–2.9 (1 H, m), 3.25 (1 H, dd, J = 5, 10 Hz), 4.02 (1 H, m), 4.26 (1 H, m), 4.58 (1 H, t, J = 5 Hz). 4.75 (2 H, m), and 5.83 (3 H, m); mass spectrum m/e 310 (8), 308 (10), 231 (6), 229 (14), 203 (10), 202 (35), 201 (17), 200 (35), 189 (18), 187 (31), 185 (18), 121 (52), 108 (81), 107 (42), 91 (54), 81 (35), 80 (35), 79 (77), 77 (100), 69 (29), 67 (25), 65 (38), 57 (23), 55 (28), 53 (44), 51 (32), 43 (30), 41 (58), 39 (62).

Hydrogenation of *cis*-Maneonene-C (4) to Produce 16. A suspension of 15 mg of *cis*-maneonene-C (**4**) and 2 mg of PtO_2 (previously reduced) in 10 mL of absolute ethanol was stirred for 20 min at 25 °C under an atmosphere of hydrogen. The catalyst was filtered and the ethanol was evaporated to give 9 mg of a yellow oil. The oil was spotted onto a TLC plate with ether and the plate was developed three times in 2:1 dichloromethane–hexane, drying between developments. The spots were scraped off and extracted with ether to give 3 mg (20%) of **16** as a colorless oil, R_f 0.55: IR ν_{max} 2985, 2950, 2885, 1690, 1460, 1435, 1380, 1345, 1330, 1250, 1185, 1165, 1105, 1045, 990, 925, 895, 880, and 860 cm^{-1}; ^{1}H NMR (C_6D_6) δ 1.02 (3 H, t, J = 7 Hz), 1.15 (3 H, t, J = 7 Hz), 1.0–2.0 (several m), 2.4–2.8 (m), 2.67 (2 H, q, J = 7 Hz), 3.27 (1 H, dd, J = 5, 10 Hz), 4.32 (1 H, m), 4.74 (1 H, t, J = 5 Hz), and 5.50 (1 H, br t, J = 5 Hz); ^{13}C NMR (C_6D_6) δ 13.6 (2), 26.8 (2), 28.2, 32.0, 35.2, 36.2, 45.2, 45.9, 79.0, 81.9, and 83.4; mass spectrum m/e 316 (20), 314 (20), 301 (2), 299 (2), 273 (1), 271 (1), 257 (1), 255 (1), 245 (1), 243 (1), 236 (5), 235 (25), 233 (3), 231 (3), 229 (3), 217 (7), 215 (3), 203 (3), 202 (4), 201 (3), 200 (4), 193 (47), 151 (62), 123 (87), 109 (51), 95 (43), 91 (37), 81 (71), 69 (67), 67 (55) 55 (63), 43 (69), 41 (100).

Reaction of 16 with Na/NH$_3$ to Produce 17. To a solution of 60 mg (2.6 mg-atom) of sodium in 20 mL of anhydrous ammonia at −78 °C was slowly added a solution of 53 mg (0.17 mmol) of **16** in 5 mL of anhydrous ether. The solution was stirred for 1 h under a nitrogen atmosphere. The workup procedure was the same as that for **12** and **13**. Thirty milligrams of a colorless oil was obtained which was chromatographed on TLC developing four times with 9:1 hexane–ether. The spots were scraped off and extracted with ether to give 6 mg (15%) of **17** as a colorless oil, R_f 0.58: IR ν_{max} 2975, 2890, 1700, 1465, 1370, 1335, 1280, 1255, 1210, 1190, 1170, 1055, 1000, 980, 960, 915, 900, 880, and 855 cm^{-1}; ^{1}H NMR (C_6D_6, 270 MHz) δ 0.87 (3 H, t, J = 7 Hz), 1.04 (3 H, t, J = 7 Hz), 1.1–1.6 (9 H, several m), 1.90 (2 H, br m), 2.29 (2 H br m), 2.50 (1 H, dd, J = 5, 9.5 Hz), 4.08 (1 H, t, J = 5 Hz), 4.19 (1 H, t, J = 7 Hz), 4.28 (1 H, br dd, J = 7.5 Hz), and 4.72 (1 H, br t, J = 5 Hz); ^{13}C NMR (C_6D_6) δ 15.2 (2), 18.7, 22.9, 27.1, 28.5, 32.3, 34.3, 45.0, 46.0, 78.9, 80.0, 83.4, and 101.6; mass spectrum m/e 236 (4), 221 (2), 193 (9), 153 (57), 124 (31), 123 (80), 111 (32), 109 (29), 95 (65), 81 (93), 71 (53), 69 (58), 67 (43), 57 (54), 55 (100), 43 (80), 41 (93).

Isomerization of *cis*-Maneonene-C (4) to Produce 18. A solution of 10 mg of *cis*-maneonene-C (**4**) and one crystal of *p*-toluenesulfonic acid monohydrate in 1.5 mL of benzene was heated at reflux for 4 h. The benzene was evaporated and the residue was dissolved in ether and spotted onto a TLC plate. The plate was developed twice in 1:1 dichloromethane–hexane and the spots were scraped off and extracted with ether to give 3 mg (30%) of unreacted *cis*-maneonene-C (**4**) and 3 mg (30%) of **18**, R_f 0.30: $[\alpha]^{21}_D$ +137° (c 0.60); IR ν_{max} 3300, 2970, 2920, 1680, 1450, 1345, 1320, 1260, 1245, 1215, 1200, 1180, 1160, 1125, 1040, 985, 965, 950, 880, and 825 cm^{-1}; ^{1}H NMR (C_6D_6, 270 MHz) δ 1.33 (3 H, t, J = 7 Hz), 1.42 (1 H, td, J = 5, 8, 14 Hz), 1.91 (1 H, d, J = 14 Hz), 2.43 (1 H, td, J = 5, 10, 10 Hz), 2.59 (1 H, sextet, J = 7, 14 Hz), 2.65 (1 H, sextet, J = 7, 14 Hz), 2.85 (1 H, d, J = 2 Hz), 2.92 (1 H, dd, J = 5. 10 Hz), 3.96 (1 H, t, J = 5 Hz), 4.30 (1 H, dd, J = 5, 8 Hz), 4.61 (1 H, t, J = 5 Hz), 5.00 (1 H, t, J = 10 Hz), 5.17 (1 H, dd, J = 2, 10 Hz), and 5.56 (1 H, t, J = 10 Hz); mass spectrum m/e 346 (1), 344 (3), 342 (2), 308 (8), 306 (8), 265 (7), 263 (7), 227 (4), 204 (4), 202 (7), 200 (11), 159 (17), 149 (13), 123 (21), 122 (21), 121 (21), 115 (17), 111 (21), 109 (28), 108 (19), 107 (19), 97 (40), 95 (43), 91 (30), 85 (30), 83 (43), 81 (62), 79 (34), 77 (45), 71 (55), 69 (83), 57 (100), 55 (77), 43 (74), 41 (87), 39 (47).

Isolation and Purification of Isomaneonene-A (5) and Isomaneonene-B (6). Approximately 730 mg of eluate 4 from column chromatography of the algal extract was dissolved in a small volume of anhydrous ether and spotted on TLC plates so that each plate contained 70 mg of material. The plates were developed five times in 30:1 benzene–ether, drying between developments, and the spots were scraped off and extracted with ether. After filtering and evaporation of the ether, *cis*-maneonene-B and isomaneonene-A were obtained. These two compounds were repurified by TLC developing

in 30:1 benzene–ether and approximately 86 mg of *cis*-maneonene-B, R_f 0.90, and 100 mg of isomaneonene-A, R_f 0.86 (0.04% of dry alga), were obtained.

Approximately 700 mg of eluate 5 from the column chromatography was dissolved in a small amount of anhydrous ether and spotted onto TLC plates so that each plate contained 70 mg of material. The plates were developed five times in 30:1 benzene–ether, drying between developments, and the spots were scraped off and extracted with ether. After filtering and evaporation of the ether, the following compounds were obtained: isomaneonene-A, isomaneonene-B, *trans*-maneonene-B, sesquiterpenoid A,[5] and sesquiterpenoid B.[5] All the compounds were repurified by TLC developing in 30:1 benzene–ether five times, and approximately 40 mg of isomaneonene-A, R_f 0.86 (0.015% of dry alga), 30 mg of *trans*-maneonene-B, R_f 0.77, 105 mg of isomaneonene-B, R_f 0.63 (0.04% of dry alga), 90 mg of sesquiterpenoid A,[5] R_f 0.57 (0.03% of dry alga), and 50 mg of sesquiterpenoid B,[5] R_f 0.50 (0.02% of dry alga), were obtained.

Isomaneonene-A (5): yellow crystals, mp 114.5–115.5 °C; $[\alpha]^{21}_D$ +106° (*c* 1.72); UV λ_{max} 229 nm (ϵ 14 500); IR ν_{max} 3300, 2970, 2940, 2870, 1680, 1460, 1440, 1380, 1320, 1290, 1150, 1130, 1110, 1090, 1070, 1050, 1030, 1010, 960, 890, 855, and 835 cm^{-1}; NMR Table V; mass spectrum *m/e* 390 (0.2), 388 (0.4), 386 (0.2), 309 (4), 307 (4), 265 (3), 263 (3), 228 (6), 227 (14), 202 (4), 201 (5), 200 (6), 199 (9), 189 (5), 187 (5), 185 (5), 184 (4), 183 (5), 181 (6), 171 (8), 169 (8), 159 (10), 157 (10), 155 (10), 149 (11), 141 (23), 131 (22), 129 (25), 123 (18), 121 (18), 115 (19), 111 (24), 109 (24), 97 (46), 95 (50), 91 (29), 85 (33), 83 (50), 81 (57), 79 (36), 77 (32), 71 (64), 69 (75), 67 (46), 57 (100), 55 (89), 43 (79), 41 (75). FD mass spectrum *m/e* 390 (32), 389 (10), 388 (100), 386 (53), and 58 (26). High resolution mass spectrum. Calcd for $C_{15}H_{16}O_2Br_2^{79}$ (M^+): 385.9517. Found: 385.9495.

Isomaneonene-B (6): white crystals; mp 136.5–137.0 °C; $[\alpha]^{21}_D$ +87° (c 0.83); UV λ_{max} 228 nm (ϵ 13 500); IR ν_{max} 3330, 2970, 2940, 2850, 1680, 1460, 1440, 1380, 1320, 1280, 1220, 1160, 1120, 1100, 1060, 1030, 1020, 1015, 960, 940, and 890 cm^{-1}; NMR Table VI; mass spectrum *m/e* 390 (2), 388 (4), 386 (2), 309 (36), 307 (36), 265 (14), 263 (11), 228 (21), 227 (34), 203 (15), 202 (21), 201 (18), 200 (34), 199 (29), 189 (10), 187 (13), 185 (13), 184 (8), 183 (10), 181 (7), 171 (13), 169 (11), 159 (18), 157 (16), 155 (16), 153 (11), 143 (18), 141 (32), 131 (27), 129 (39), 128 (40), 121 (24), 115 (51), 108 (28), 107 (47), 105 (25), 103 (24), 95 (21), 91 (60), 81 (43), 79 (84), 78 (52), 77 (100), 69 (35), 67 (35), 65 (60), 63 (30), 55 (38), 53 (48), 51 (51), 41 (78), 39 (85). High resolution mass spectrum. Calcd for $C_{15}H_{16}O_2Br_2^{79}$ (M^+): 385.9517. Found: 385.9532.

Catalytic Hydrogenation of Isomaneonene-A (5) to Produce 19 and 24. A suspension of 100 mg (0.258 mmol) of isomaneonene-A (**5**) and 40 mg of 5% Pd/C in approximately 10 mL of anhydrous ethanol was stirred for 5 h under an atmosphere of hydrogen. The catalyst was centrifuged and the supernatant was evaporated to give an oil. This oil was dissolved in a small volume of ether and spotted onto a TLC plate. The plate was developed twice in 5:1 dichloromethane–ether, drying between developments, and the spots were scraped off and extracted with ether to give 15 mg (25%) of **19**, R_f 0.60, and 11 mg (18%) of **24**, R_f 0.30.

19: colorless oil; IR ν_{max} 2950, 2870, 1460, 1435, 1375, 1350, 1290, 1160, 1120, 1080, 1050, 1035, 1015, 975, 925, and 850 cm^{-1}; ^1H NMR (270 MHz, C_6D_6) δ 0.91 (3 H, t, J = 7 Hz), 1.10 (3 H, t, J = 7 Hz), 1.14–1.40 (m), 1.64 (m), 2.03 (m), 2.61 (m), 4.23 (1 H, m), 4.30 (2 H, m) and 4.77 (1 H, t, J = 5 Hz); ^{13}C NMR (C_6D_6) δ 13.7, 14.4, 21.2, 23.4, 27.8, 32.7, 38.7, 40.5, 51.6, 52.3, 54.9, 76.6, 78.2, 83.6, and 85.4; mass spectrum *m/e* 236 (12), 221 (1), 218 (2), 208 (6), 207 (35), 193 (6), 192 (5), 189 (17), 179 (11), 163 (18), 151 (14), 149 (22), 139 (11), 137 (11), 135 (18), 133 (12), 125 (12), 124 (14), 123 (18), 121 (20), 111 (45), 109 (24), 108 (29), 107 (41), 95 (61), 83 (55), 81 (100), 79 (43), 69 (68), 67 (63), 57 (55), 55 (78), 43 (59), 41 (94).

24: colorless oil; IR ν_{max} 3570, 3430, 2950, 2930, 2850, 1460, 1440, 1370, 1210, 1120, 1090, 1075, 1010, 965, and 900 cm^{-1}; ^1H NMR (270 MHz, C_6D_6) δ 0.90 (3 H, t, J = 7 Hz), 1.00 (3 H, t, J = 7 Hz), 1.17–1.40 (m), 1.28 (1 H, dd, J = 12, 4 Hz), 1.58 (m), 1.89–2.20 (m), 2.87 (1 H, m), 3.05 (1 H, dd, J = 16, 2 Hz), 3.45 (1 H, m), 4.08 (1 H, t, J = 5 Hz), 4.23 (1 H, m), and 4.46 (1 H, t, J = 5 Hz); mass spectrum *m/e* 236 (13), 218 (3), 207 (5), 193 (7), 192 (7), 189 (13), 179 (10), 164 (10), 163 (40), 151 (8), 150 (8), 149 (10), 135 (13), 133 (11), 121 (30), 119 (13), 108 (28), 107 (70), 105 (25), 95 (25), 93 (32), 91 (40), 81 (25), 79 (50), 77 (25), 69 (25), 67 (25), 57 (100), 55 (48), 43 (40), and 41 (70).

The same products were obtained on catalytic hydrogenation of isomaneonene-B (**6**).

Sodiun Reduction of Isomaneonene-A (5) to Produce 22 and 23. To a solution of 70 mg (3 mg-atoms) of sodium in approximately 20 mL of anhydrous ammonia at −78 °C was slowly added a solution of 95 mg (0.245 mmol) of isomaneonene-A (**5**) in approximately 5 mL of anhydrous ether. The solution was stirred for 2 h under a nitrogen atmosphere. The reaction was quenched by slow addition of solid ammonium chloride until the blue color disappeared. Approximately 20 mL of ether and 20 mL of distilled water was added and the layers were allowed to separate. The aqueous layer was extracted with an additional two 20-mL portions of ether. The combined ether extracts were washed with 25 mL of distilled water, dried over anhydrous sodium carbonate, filtered, and evaporated to give 52 mg of a colorless oil which was dissolved in a small volume of ether and spotted onto a TLC plate. The plate was developed in 5:1 dichloromethane–ether to give 10 mg (17%) of **22**, R_f 0.35, and 15 mg (26%) of **23**, R_f 0.20, as colorless oils.

22: IR ν_{max} 3540, 2970, 2850, 1630, 1445, 1400, 1375, 1255, 1155, 1110, 1090, 1060, 1010, 960, 905, and 845 cm^{-1}; ^1H NMR (270 MHz, C_6D_6) δ 0.88 (3 H, t, J = 7 Hz), 1.31 (1 H, dd, J = 12, 4 Hz), 1.28–1.38 (m), 1.57 (m), 1.73 (m), 1.89 (m), 2.15 (m), 2.48 (1 H, m), 2.97 (1 H, sextet, J = 9, 9, 5 Hz), 3.19 (1 H, m), 4.31 (1 H, t, J = 5 Hz), 4.38 (1 H, m), 4.50 (1 H, t, J = 5 Hz), 5.31 (2 H, m), and 5.44 (1 H, m); ^{13}C NMR (C_6D_6)[16] δ 12.4, 18.0, 22.7, 31.8, 35.8, 45.8, 51.1, 52.2, 76.5, 80.2, 80.7, 123.3, 125.9, and 130.8; mass spectrum *m/e* 234 (2), 216 (1), 205 (3), 187 (3), 179 (8), 175 (8), 161 (26), 159 (8), 147 (4), 145 (16), 133 (34), 131 (15), 119 (79), 107 (62), 105 (47), 95 (26), 93 (26), 91 (56), 83 (19), 81 (27), 79 (44), 77 (27), 71 (22), 69 (29), 67 (25), 65 (14), 57 (38), 55 (100), 43 (38), 41 (55), 39 (38).

23: IR ν_{max} 3600, 3430, 2970, 2930, 2860, 1450, 1380, 1120, 1080, 965, 920, and 900 cm^{-1}; ^1H NMR (270 MHz, C_6D_6) δ 0.99 (3 H, t, J = 7 Hz), 0.90–1.14 (m), 1.40–1.72 (m), 1.90 (1 H, m), 2.04 (1 H, ddd, J = 13, 10, 6 Hz), 2.24 (1 H, m), 2.55 (1 H, dd, J = 13, 7 Hz), 2.72 (1 H, sextet, J = 10, 10, 5 Hz), 2.85 (1 H, sextet, J = 10, 10, 6 Hz), 4.05 (1 H, t, J = 5 Hz). 4.13 (1 H, dd, J = 10, 5 Hz), 4.46 (1 H, t, J = 6 Hz), and 5.41 (2 H, m); ^{13}C NMR (C_6D_6) δ 12.7, 24.6, 28.1, 31.3, 33.1, 35.3, 45.3, 46.8, 47.2, 52.9, 75.3, 79.6, 81.1, 125.1, and 131.5; mass spectrum *m/e* 236 (1), 218 (1) 207 (2), 205 (8), 203 (12), 193 (5), 189 (6), 181 (4), 177 (4), 163 (18), 145 (15), 137 (19), 135 (18), 133 (1), 121 (21), 119 (27), 109 (48), 107 (35), 97 (24), 95 (66), 93 (39), 91 (29), 83 (32), 81 (50), 79 (48), 77 (21), 71 (26), 69 (40), 67 (61), 57 (68), 55 (100), 43 (53), 41 (68).

Sodium Reduction of 22 to Produce 23. Approximately 17 mg (0.073 mmol) of **22** was allowed to react with sodium in liquid ammonia under conditions identical to those used for isomaneonene-A to give 15 mg (87%) of a colorless oil. Its IR, ^1H NMR, and mass spectra were identical to those of **23**.

Catalytic Hydrogenation of 23 to Produce 20. A suspension of 30 mg (0.127 mmol) of **23** and 40 mg of PtO_2 (previously reduced) in approximately 10 mL of anhydrous ethanol was stirred for 6 h under an atmosphere of hydrogen. The catalyst was centrifuged and the supernatant was evaporated to give 25 mg of an oil. This oil was dissolved in a small volume of ether and spotted onto a TLC plate. The plate was developed in 3:1 chloroform–ethyl acetate. The spots were scraped off and extracted with ether to give 16 mg (53%) of **20** as a colorless oil, R_f 0.37: IR ν_{max} 3610, 3430, 2960, 2930, 2850, 1455, 1375, 1210, 1100, 1075, 965, 915, and 895 cm^{-1}; ^1H NMR (270 MHz, C_6D_6) δ 0.89 (3 H, t, J = 7 Hz), 0.99 (3 H, t, J = 7 Hz), 1.19–1.39 (m), 1.48 (1 H, m), 1.58 (1 H, dd, J = 13, 4 Hz), 1.69 (1 H, m), 2.00 (1 H, ddd, J = 13, 10, 6 Hz), 2.16 (1 H, m), 2.53 (1 H, dd, J = 13, 7 Hz), 2.73 (1 H, sextet, J = 10, 10, 5 Hz), 2.82 (1 H, sextet, J = 10, 10, 6 Hz), 4.05 (1 H, t, J = 5 Hz), 4.10 (1 H, br m), and 4.39 (1 H, t, J = 6 Hz); ^{13}C NMR (C_6D_6) δ 13.0, 14.4, 23.3, 28.1, 29.2, 31.1, 31.9, 35.2, 45.3, 46.9, 47.0, 52.7, 73.5, 77.7, and 79.1; mass spectrum *m/e* 238 (1), 220 (3), 209 (1), 195 (4), 194 (3), 191 (5), 181 (3), 179 (4), 177 (6), 165 (8), 164 (7), 163 (10), 152 (9), 151 (10), 149 (12), 139 (9), 137 (13), 135 (12), 125 (12), 123 (16), 121 (13), 111 (19), 109 (31), 107 (17), 97 (37), 95 (57), 86 (26), 83 (52), 81 (55), 71 (47), 69 (77), 67 (51), 57 (100), 55 (94), 43 (77), 41 (81). High resolution mass spectrum. Calcd for $C_{15}H_{26}O_2$ (M^+): 238.1933. Found: 238.1950.

Reaction of Isomaneonene-B (6) with Na/NH_3 and H_2/Pt to Produce 20. Approximately 55 mg (0.142 mmol) of isomaneonene-B (**6**) was allowed to react with sodium in liquid ammonia under conditions identical to those used for isomaneonene-A (**5**) to give 34 mg of a mixture of **22** and **23**. A suspension of this mixture and 20 mg of PtO_2 (previously reduced) in approximately 15 mL of anhydrous ethanol was stirred for 3 h under an atmosphere of hydrogen. The catalyst was centrifuged and the supernatant was evaporated to give a colorless oil. The oil was dissolved in a small volume of ether and spotted onto a TLC plate. The plate was developed in 5:1 dichloromethane–ether, and the spots were scraped off and extracted with anhydrous ether to give 6.5 mg (19%) of a colorless oil. Its IR and ^1H NMR spectra were identical to those of **20**.

Oxidation of 20 to Produce 21. To a solution of 16 mg (0.067 mmol) of **20** in 5 mL of acetone was added drop by drop a solution of 11 mg (0.110 mmol) of chromium trioxide in 0.05 mL of concentrated

sulfuric acid and 0.5 mL of water. The suspension was stirred for 50 min at 25 °C and the acetone was decanted and evaporated to give an aqueous suspension which was mixed with 5 mL of ether, dried over anhydrous sodium sulfate, and filtered, and the ether was evaporated to give 14 mg of a brown oil. This was dissolved in a small volume of anhydrous ether and spotted onto a TLC plate so that each spot contained approximately 2 mg of material. The plate was developed twice in 1:2 hexane–dichloromethane, drying between developments, and the spots were scraped off and extracted with ether to give 10 mg (63%) of **21** as a colorless oil, R_f 0.45: IR ν_{max} 2960, 2940, 2870, 1760, 1460, 1410, 1380, 1300, 1140, 1070, 1000, and 910 cm^{-1}; ^1H NMR (270 MHz, C_6D_6) δ 0.81 (3 H, t, J = 7 Hz), 0.89 (3 H, br t, J = 7 Hz), 1.03–1.27 (m), 1.43 (1 H, br m), 1.73 (1 H, dd, J = 12, 6 Hz), 2.05 (1 H, d, J = 17 Hz), 2.20 (1 H, dd, J = 17, 5 Hz), 2.49 (1 H, sextet, J = 10, 10, 6 Hz), 2.62 (1 H, sextet, J = 10, 10, 5 Hz), 4.06 (1 H, d, J = 6 Hz), and 4.39 (1 H, t, J = 5 Hz); mass spectrum m/e 236 (2), 208 (7), 207 (1), 193 (7), 179 (17), 165 (7), 163 (7), 161 (8), 152 (10), 151 (27), 149 (11), 137 (14), 135 (17), 125 (13), 123 (43), 111 (17), 109 (47), 107 (17), 97 (40), 95 (80), 83 (77), 81 (62), 71 (43), 69 (73), 67 (57), 57 (73), 55 (100), 43 (67), 41 (87).

X-ray Crystallographic Analysis of Isomaneonene-B (6). A clear, pale yellow crystal of isomaneonene-B, approximately 0.3 × 0.2 × 0.1 mm, proved to be monoclinic with a = 6.122 (3) Å, b = 15.457 (6) Å, c = 8.425 (3) Å, β = 111.30°, and ρ_{calcd} = 1.74 g/cm^3 for two molecules in the unit cell. Systematic absences of $0k0$, $k = 2n + 1$, reflections identified the space group as $P2_1$. Unique reflections with $2\theta \leq 114.1°$ were measured on a Syntex $P2_1$ four-circle diffractometer using graphite monchromated Cu Kα radiation (λ 1.5418 Å) and 1° ω scans with a scan rate dependent on the intensity of the reflection. Three check reflections measured after every 50 reflections showed no decrease in intensity during data collection. Data were corrected for Lorentz, polarization, and background effects and 1028 out of 1050 reflections, about 98% of the data, had $F_o^2 \geq 3\sigma(F_o^2)$.

Both bromines were located by means of a Patterson synthesis and a bromine phased F_o synthesis served to reveal the remaining atoms.[20] Theoretical positions for the hydrogens were computed and included for full-matrix least-squares refinement of the structure. All nonhydrogen atoms were assigned anisotropic thermal parameters and hydrogens were assigned isotropic parameters.

Anomalous dispersion corrections for the bromines brought the standard crystallographic residual to 0.061 for both enantiomers and the weighted residual to 0.062 and 0.064 for the structure shown and its enantiomer, respectively.[21] The intensities of 11 pairs of the most enantiomorph sensitive reflections were carefully measured and five were consistent with the enantiomer chosen while for the remaining six the intensities of the hkl and $\overline{hkl}$ reflections did not differ by more than one standard deviation.

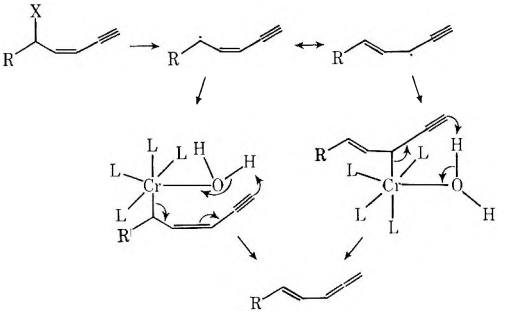
Acknowledgments. This work was supported by the National Institutes of Health (1 RO1 CA 16267). We are indebted to Drs. P. J. Scheuer and R. E. Moore, University of Hawaii, for the use of their laboratories during collecting trips, to Dr. M. R. Brennan, S. L., Dr. B. J. Burreson, M. Serraon, and D. Dalietos for assistance in collecting the alga, and to Mr. J. B. Keenaghan, Astra Pharmaceutical Products, Inc., for the low resolution mass spectra. We thank Dr. W. Anderson, Worcester Foundation for Experimental Biology, Dr. G. E. Wright, University of Massachusetts Medical School, and Dr. P. McMaster, Holy Cross College, for the use of their ^1H NMR spectrometers. The high resolution mass spectra were provided by the facility at MIT, Grant FR00317 (Principal Investigator K. Biemann), and the FD mass spectra by the facility at Michigan State University, Grant RR00480 (Principal Investigator C. C. Sweeley). The ^{13}C NMR spectra were recorded at the facility at the University of Connecticut Health Center, Grant RR0639 (Principal Investigator J. Glasel), and by Dr. M. Missakian, University of Rhode Island. The 270 MHz ^1H NMR spectra were obtained at the Yale facility, Grant 1-P07-PR00798 (Principal Investigator M. Saunders), and the MIT facility, NSF Contract C-670 (Principal Investigator L. Neuringer).

Registry No.—**1,** 61661-24-3; **2,** 61661-25-4; **3,** 61688-65-1; **4,** 62624-86-6; **5,** 62583-57-7; **6,** 62623-94-3; **7,** 61666-69-1; **8,** 61688-72-0; **9,** 66290-73-1; **10,** 66322-54-1; **11,** 61666-70-4; **12,** 61666-72-6; **13,** 61688-73-1; **14,** 61666-71-5; **15,** 66322-55-2; **16,** 66290-74-2; **17,** 66322-56-3; **18,** 62624-86-6; **19,** 62583-59-9; **20,** 62583-58-8; **21,** 62583,60-2; **22,** 66290-75-3; **23,** 66290-76-4; **24,** 66290-77-5.

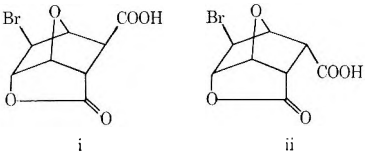
Supplementary Material Available: Fractional coordinates (Table VIII), bond distances (Table IX), and bond angles (Table X) (4 pages). Ordering information is given on any current masthead page.

References and Notes

(1) For a recent review see W. Fenical, *J. Phycol.*, **11,** 245 (1975).
(2) S. M. Waraszkiewicz and K. L. Erickson, *Tetrahedron Lett.*, 2003 (1974).
(3) S. M. Waraszkiewicz and K. L. Erickson, *Tetrahedron Lett.*, 281 (1975).
(4) S. M. Waraszkiewicz and K. L. Erickson, *Tetrahedron Lett.*, 1443 (1976); S. M. Waraszkiewicz, K. L. Erickson, J. Finer, and J. Clardy, *ibid.*, 2311 (1977).
(5) H. H. Sun, S. M. Waraszkiewicz, and K. L. Erickson, *Tetrahedron Lett.*, 585 (1976).
(6) S. M. Waraszkiewicz, H. H. Sun, and K. L. Erickson, *Tetrahedron Lett.*, 3021 (1976).
(7) H. H. Sun, S. M. Waraszkiewicz, and K. L. Erickson, *Tetrahedron Lett.*, 4227 (1976).
(8) The name maneonene is taken from the Hawaiian term for *Laurencia,* limu mane'one'o (ticklish seaweed after its peppery taste).
(9) Y. Saito, *Pac. Sci.*, **23,** 148 (1969).
(10) J. K. Kochi and P. E. Mocadlo, *J. Am. Chem. Soc.*, **88,** 4094 (1966).
(11) C/ E. Castro and R. D. Stephens, *J. Am. Chem. Soc.*, **86,** 4358 (1964).
(12) Ortho Pharmaceutical Corp., British Patent 740 851 (1955); *Chem. Abstr.* **51,** 479c (1957).
(13) W. Oroshnik, A. D. Mebane, and G. Karmas, *J. Am. Chem. Soc.*, **75,** 1050 (1953).
(14) J. R. Hanson, *Synthesis,* 1 (1974); C. E. Castro and W. C. Kray, Jr., *J. Am. Chem. Soc.*, **85,** 2768 (1963). The following scheme may be envisaged:



(15) J. K. Crandall, D. J. Keyton, and J. Kohne, *J. Org. Chem.*, **33,** 3655 (1968); T. L. Jacobs and R. D. Wilcox, *J. Am. Chem. Soc.*, **86,** 2240 (1964); J. P. Dulcere, M. Santelli, and M. Bertrand, *C. R. Hebd. Seances Acad. Sci.*, **271,** 585 (1970).
(16) Quaternary carbons were not recorded.
(17) The numbering system is in keeping with that used for other members of this class of compounds.
(18) (a) F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy", Academic Press, New York, N.Y., 1969. (b) D. Gagnaire and E. Payo-Subiza, *Bull. Chim. Soc. Fr.*, 2627 (1963). Compounds i and ii were chosen as models:



i ii

(19) R. Kinnel, A. J. Duggan, T. Eisner, J. Meinwald, and I. Miura, *Tetrahedron Lett.*, 3913 (1977).
(20) The following library of crystallographic programs was used: C. R. Hubbard, C. O. Quicksall, and R. A. Jacobson, "The Fast Fourier Algorithm and the Programs ALFF, ALFFDP, ALFFT and FRIEDEL", USAEC Report IS-2625, Iowa State University-Institute for Atomic Research, Ames, Iowa 1971; W. R. Busing, K. O. Martin, and H. A. Levy, "A Fortran Crystallographic Least Squares Program", USAEC Report ORNL-TM-305, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965; C. Johnson, "ORTEP, A Fortran Thermal-Ellipsoid Plot Program", U.S. Atomic Energy Commission Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965.
(21) W. C. Hamilton, *Acta Crystallogr.*, 502 (1965).

Synthesis of Compounds Structurally Related to Poison Ivy Urushiol. 7. 4-, 5-, and 6-(Piperidinomethyl)-3-*n*-pentadecylcatechols

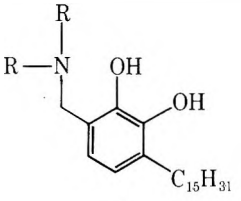
Gilbert P. Ng and Charles R. Dawson*

Department of Chemistry, Columbia University, New York, New York 10027

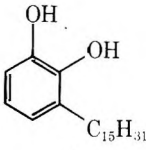
Received February 10, 1978

Derivatives of 3-*n*-pentadecylcatechol, the saturated component of poison ivy urushiol, which are substituted in the 6 position of the aromatic ring by various aminomethyl groups, have been found to be toleragens, the most potent being 6-(piperidinomethyl)-3-*n*-pentadecylcatechol (**24**). In order to examine the structural requirements of a toleragen, 4- and 5-(piperidinomethyl)-3-*n*-pentadecylcatechols (**11** and **21**) have been synthesized and isolated as their hydrochloride salts **13** and **23** along with the hydrochloride salt **25** of **24**. The syntheses include as the last step a novel coupled use of boron tribromide and piperidine to effect ether cleavage followed by ammonolysis. In the synthesis of the 5 isomer, an unusual exclusive para substitution of a phenol using the Mannich reaction has been exploited.

Recently, it has been observed that a number of substituted 6-aminomethyl analogues **1** of 3-*n*-pentadecylcatechol (3-PDC) **2** are potent toleragens for poison ivy.[1,2] This ob-



1



2

servation has inspired the present investigation, which is focused on the synthesis of structural isomers of 6-(piperidinomethyl)-3-*n*-pentadecylcatechol (**24**), the most promising toleragen of those observed. The objective has been to study the effect of the position of substitution on toleragenicity. The synthesis of 4- (**11**) and 5-(piperidinomethyl)-3-*n*-pentadecylcatechol (**21**) in the form of their hydrochloride salts **13** and **23**, respectively, has been achieved. For comparison, 6-(piperidinomethyl)-3-*n*-pentadecylcatechol (**24**) has been resynthesized in the form of its hydrochloride salt **25**.

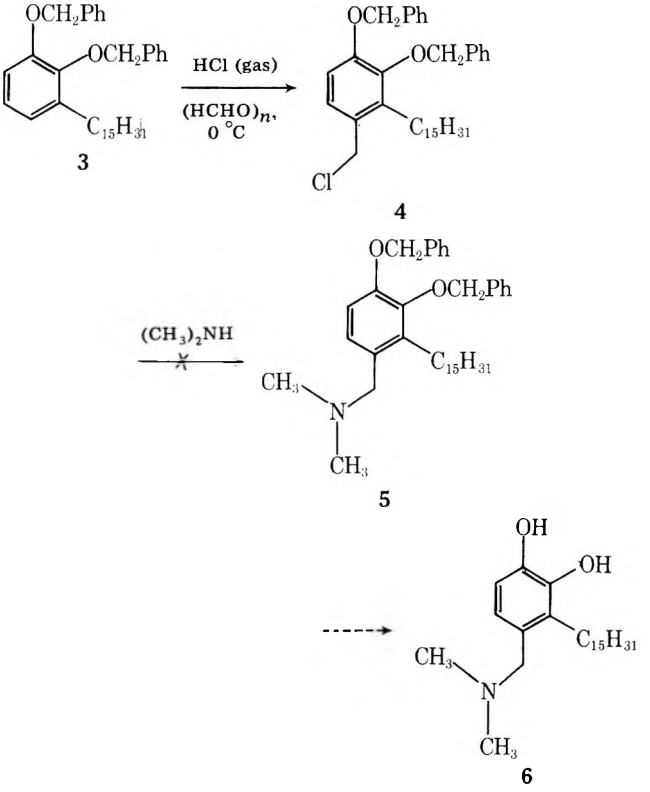
Results and Discussion

The 4 Isomer. The synthesis of 4-(*N*,*N*-dimethylamino)-methyl-3-*n*-pentadecylcatechol (**6**) was attempted (Scheme I) by Lerner[2] using the dibenzyl ether of 3-PDC. His failure to isolate a product in the ammonolysis step suggested a possible advantage of using a different protective group. In the present investigation, the methyl protective group was chosen as the alternative because of its stability to both acids and bases and because of the better availability of the starting material **8b** than **3**.

The optimum conditions for the introduction of only one chloromethyl group into a 3-alkylveratrole were studied using a readily available model compound, 3-*n*-decylveratrole (**8a**), which was prepared using an improvement of the Byck and Dawson[3] procedure (as described in the Experimental Section). Thus, 4-(chloromethyl)-3-*n*-decylveratrole (**9a**) was synthesized from **8a** in 73% yield. Under similar conditions, 4-(chloromethyl)-3-*n*-pentadecylveratrole (**9b**) was obtained from **8b**. The ammonolysis reaction was also found feasible when **9b** was converted to 4-(piperidinomethyl)-3-*n*-pentadecylveratrole (**10**) in 78% yield by reacting it at room temperature in toluene with an excess of piperidine for 24 h.

The unusually high temperature recommended for the cleavage of 3-alkylcatechol methyl ethers[4] posed a serious problem for the heat-sensitive benzylaminocatechols such as **11**. A solution to this problem was found in the use of boron tribromide,[5] an agent which has been found in the present

Scheme I

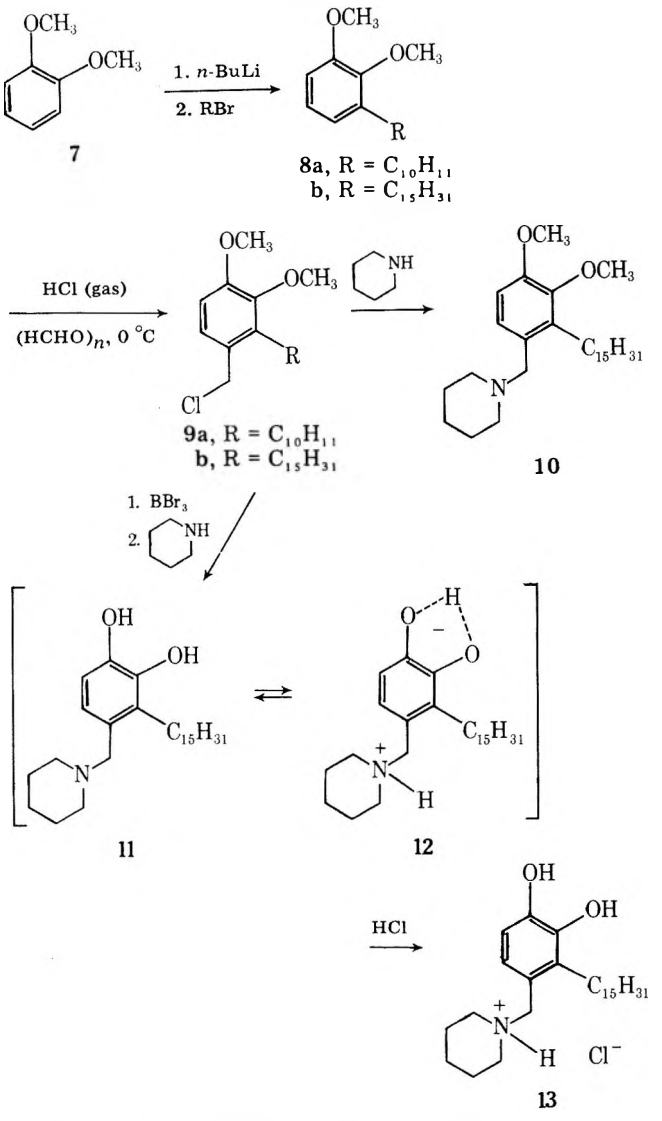


investigation to be extremely effective in the low-temperature cleavage of 3-alkylcatechol methyl ethers. For example, when **8b** was treated with boron tribromide, high-purity 3-PDC was obtained in 90% yield.[6] However, the cleavage reaction could not be done directly on **10** since in an exploratory experiment it was discovered that boron tribromide cleaved *N*-benzylpiperidine even at room temperature.

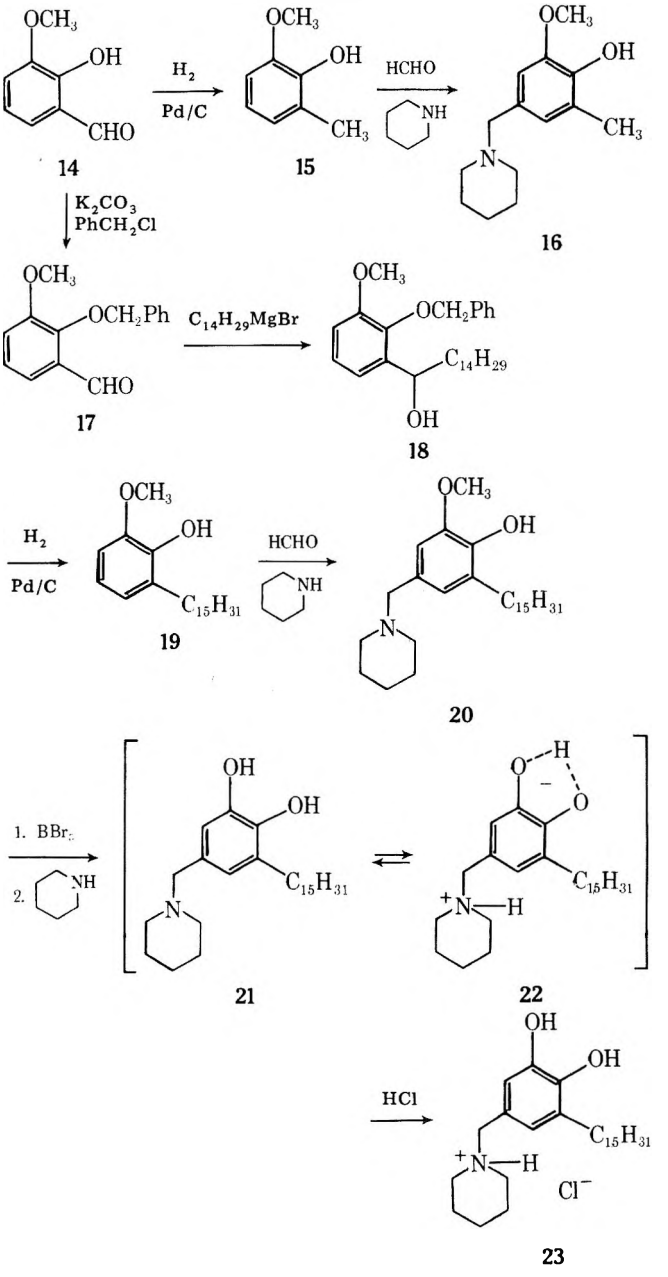
The final route by which **11** was synthesized is shown in Scheme II. The key step in this route was the use of boron tribromide and piperidine in the same step. In effect, the boron dibromide group (which remains attached to the phenolic oxygen atom after the first step of the cleavage reaction[5]) was exploited as a protective group against the strongly basic piperidine that was added for the ammonolysis. The isolation of the intermediate, 4-(chloromethyl)-3-*n*-pentadecylcatechol, was not attempted because it was reasoned that in the presence of the basic piperidine the unprotected chloromethylphenol would be under conditions equivalent to those used in the benzylation of 3-PDC.[7] Consequently, extensive polymeric benzylation would likely occur if the ether cleavage and the ammonolysis were carried out as two distinct steps.

0022-3263/78/1943-3205$01.00/0

Scheme II



Scheme III



Isolation of the product **11** was complicated by its high sensitivity to air oxidation and its heat-labile property.[6b] Conversion of **11** to its hydrochloride salt **13** provided a means to isolate a pure product. The hydrochloride salt **13** differs from many salts of amines in that it is insoluble in both water and ether, which made it rather simple to isolate. Recrystallization from hot acetone afforded an 89% yield of pure **13** from **9b**.

Repeated attempts to convert **13** to the free base **11** have failed, despite extreme precautionary measures under low temperature and anaerobic conditions. In every case,[6b] only a dark-brown resinous material was obtained. It appears that 4-(piperidinomethyl)-3-*n*-pentadecylcatechol (**11**) exists largely in the form of the zwitterion **12**. This dipolar ion, being both a benzylamine cation and a phenolate, is susceptible to polymerization via nucleophilic attack of the phenolate ion on the benzylic carbon (Figure 1) or on the trienone which could be formed from the expulsion of piperidine (Figure 2). Such polymerizations are enhanced when the systems are concentrated in an effort to isolate the product.

The 5 Isomer. The direct introduction of a functional group to the 5 position of the aromatic ring of 3-PDC exclusively is developed for the first time in the present investigation. The synthesis of 5-(piperidinomethyl)-3-*n*-pentadecylcatechol (**21**) is shown in Scheme III.

The conversion of *o*-vanillin (**14**) to 2-benzyloxy-3-methoxybenzaldehyde (**17**) was accomplished in nearly quantitative yield using the procedure of Merz and Pfäffle.[8] Reaction of **17** with myristyl Grignard reagent, followed directly by hydrogenolysis (compare[9]), gave 3-*n*-pentadecylguaiacol (**19**) in an overall yield of 67%. The crucial step in Scheme III is a special adaptation of the Mannich reaction. This reaction, which normally alkylates at room temperature ortho to the hydroxyl group, has been found in this investigation to result in para alkylation at reflux temperature when blocking groups are situated at both positions ortho to the hydroxyl group. The exploratory experiment using 3-methylguaiacol (**15**) clearly demonstrated that the Mannich reaction at higher temperature results in para alkylation when both of the ortho phenolic positions are occupied. When these conditions were applied to **19**, 5-(piperidinomethyl)-3-*n*-pentadecylguaiacol (**20**) was isolated in 79% yield.

The last step in this reaction sequence uses the same reaction as that for the preparation of **13**. In view of the polymerizing behavior of **11**, the hydrochloride salt **23** was isolated directly from the reaction mixture in 87% yield. Surprisingly, this salt **23** is only slightly soluble in water and is appreciably soluble in ether and benzene. It is also an excellent emulsifier, which caused some difficulties in its isolation. Fortunately, it can also be crystallized from hot acetone.

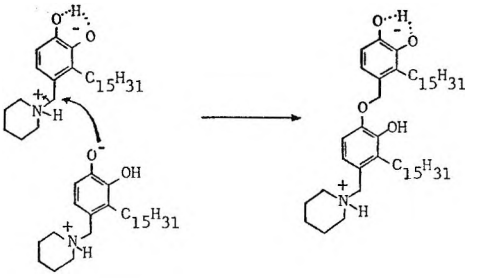


Figure 1. Polymerization via nucleophilic attack of the phenolate ion on the benzylic carbon.

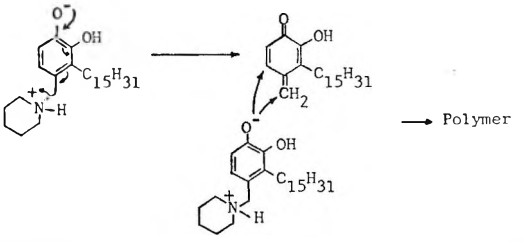
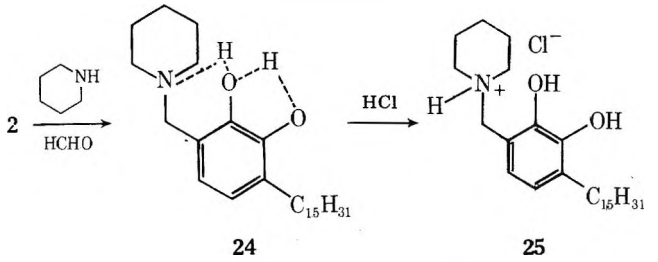


Figure 2. Polymerization via nucleophilic attack of the phenolate ion on the trienone.

Scheme IV



24 **25**

The 6 Isomer. The synthesis of 6-(piperidinomethyl)-3-*n*-pentadecylcatechol hydrochloride (**25**) (shown in Scheme IV) was accomplished simply by mixing the free base **24** with dilute hydrochloric acid. Synthesis of **24** was accomplished via an application of the Mannich reaction[10,11] to 3-PDC as reported by Lerner.[2]

Experimental Section

Melting points were taken in open capillary tubes using a Thomas-Hoover capillary melting-point apparatus and are uncorrected. The IR spectra were recorded on a Jasco IRA-1 diffraction grating IR spectrophotometer and were measured in CCl_4 solution unless otherwise specified. The NMR spectra were obtained with a Varian T-60 spectrometer using CCl_4 as solvent, unless otherwise indicated. Chemical shifts, δ, are expressed in ppm relative to internal tetramethylsilane. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill. Mass spectra were obtained on a Finnigan 3300 quadrapole mass spectrometer. Anhydrous $MgSO_4$ was used as the drying agent. Air-free water was prepared by purging distilled water with nitrogen. Additional information about the experimental observations is given in the thesis of G. P. Ng.[6b]

3-*n*-Decylveratrole (8a). To a solution of 104 g (0.750 mol) of veratrole (**7**) in 440 mL of tetrahydrofuran (THF) at 0 °C under a nitrogen atmosphere was added, with stirring, 367 mL (0.500 mol) of a solution of 1.36 M *n*-butyllithium[12] in anhydrous ether during 30 min. The mixture was stirred at 0 °C for 2 h. A solution of 55.3 g (0.250 mol) of 1-bromodecane[13] in 55 mL of THF was then added. The mixture was refluxed for 4 h, cooled to room temperature, and then hydrolyzed with 300 mL of 10% HCl. The layers were separated. The aqueous layer was extracted with ether. The combined organic solution was washed with 10% aqueous NaOH and brine. The solution was dried and the solvents were evaporated. Vacuum distillation yielded 51.0 g (73%) of **8a** as a colorless liquid: bp 139–140 °C (0.50 mm); NMR δ 6.67 (m, 3 H), 3.75 (s, 6 H), 2.58 (t, 2 H), 1.25 (s, 16 H), 0.90 (t, 3 H); IR no –OH peak.

4-(Chloromethyl)-3-*n*-decylveratrole (9a). A mixture of 15.9 g (0.0570 mol) of **8a**, 64 mL of benzene, 64 mL of glacial acetic acid, and 10.3 g (0.340 mol) of paraformaldehyde[13] was cooled to 0 °C. Dry HCl gas was passed into the mixture rapidly with stirring. When the mixture had become clear, the reaction was continued for 2 h at 0 °C. Then the mixture was poured onto ice and diluted with ether. The layers were separated, and the organic layer was washed with water, saturated aqueous bicarbonate, and brine. After the solution was dried, the solvents were evaporated, leaving a red oily liquid. Vacuum distillation of this liquid yielded 13.6 g (73%) of **9a** as a colorless liquid: bp 167–170 °C (0.50 mm); NMR δ 6.77 (q, 2 H), 4.50 (s, 2 H), 3.77 (s, 6 H), 2.65 (t, 2 H), 1.25 (s, 16 H), 0.90 (t, 3 H); IR no –OH peak.

4-(Chloromethyl)-3-*n*-pentadecylveratrole (9b). Using a mixture of 20.9 g (0.0600 mol) of **8b**, 85 mL of benzene, 85 mL of glacial acetic acid, and 10.0 g (0.333 mol) of paraformaldehyde, a procedure similar to that used for **9a** was followed. The faint yellow oil obtained after the workup solidified on standing. Recrystallization from hexanes yielded in several crops 18.6 g (78%) of **9b** as a white amorphous powder: mp 47.0–49.0 °C; NMR δ 6.77 (q, 2 H), 4.47 (s, 2 H), 3.78 (s, 6 H), 2.60 (t, 2 H), 1.25 (s, 26 H), 0.90 (t, 3 H); IR no –OH peak.

4-(Piperidinomethyl)-3-*n*-pentadecylveratrole (10). To 118 mL (1.19 mol) of piperidine was added, with stirring, a solution of 15.0 g (0.0378 mol) of **9b** in 50 mL of toluene. A white precipitate of high melting point appeared within seconds. The mixture was stirred at room temperature for 24 h. It was then shaken with excess 10% aqueous NaOH. The aqueous layer was extracted with ether. The combined organic solution was washed with brine and then dried. After removal of the solvents, the yellow oily liquid was subjected to vacuum distillation to yield 13.2 g (78%) of **10** as a yellow oil: bp 217–218 °C (0.15 mm); NMR δ 6.65 (q, 2 H), 3.76 (s, 6 H), 3.24 (s, 2 H), 2.58 (t, 2 H), 2.25 (m, 4 H), 1.45 (br s, 6 H), 1.25 (s, 26 H), 0.90 (t, 3 H). The mass spectrum showed the M^+ peak at *m/e* 445.

The Boron Tribromide Cleavage of *N*-Benzylpiperidine. To a solution of 2.14 g (0.00854 mol) of boron tribromide[14] in 7.6 mL of methylene chloride at −77 °C was added a solution of 1.01 g (0.00574 mol) of a solution of *N*-benzylpiperidine (prepared according to Schotten[15]) in 20 mL of methylene chloride, with rapid stirring. The mixture was allowed to warm up to room temperature slowly over 24 h. The mixture was hydrolyzed with water, diluted with ether, and then shaken with excess 2 N HCl. The layers were separated. The ether layer was washed with 2 N HCl, dried, and distilled at 50 °C (15 mm). A yellow liquid identified as benzyl bromide was left. In a control experiment, where boron tribromide was replaced by methylene chloride, no residue remained after the evaporation of the solvents.

4-(Piperidinomethyl)-3-*n*-pentadecylcatechol Hydrochloride (13). To a solution of 20.0 g (0.0800 mol) of boron tribromide in 50 mL of benzene under a dry nitrogen atmosphere was added, with rapid stirring, a solution of 14.0 g (0.0350 mol) of **9b** in 300 mL of benzene during 30 min. The mixture was stirred at room temperature for 24 h. A solution of 105 g (1.23 mol) of piperidine in 125 mL of benzene was added. The mixture was again stirred at room temperature for 24 h and then 180 mL of air-free water was added. The mixture was transferred to a separatory funnel under nitrogen. The layers were separated and the organic layer was treated with an ice-cold solution of 3 N HCl. The resulting fine white precipitate was filtered and recrystallized from hot acetone to yield, in several crops, 14.1 g (89%) of **13** as a white powdery solid: mp 99.0–100.0 °C; NMR ($CDCl_3$) δ 10.26 (s, 1 H), 9.22 (s, 1 H), 7.14 (q, 2 H), 6.48 (s, 1 H), 4.15 (s, 2 H), 3.38 (br t, 2 H), 2.78 (m, 4 H), 1.90 (s, 6 H), 1.25 (s, 26 H), 0.90 (t, 3 H). The mass spectrum showed a small M^+ peak at *m/e* 417.

Anal. Calcd for $C_{27}H_{48}ClNO_2$: C, 71.41; H, 10.65; Cl, 7.81; N, 3.08. Found: C, 71.29; H, 10.72; Cl, 7.82; N, 3.15.

3-Methylguaiacol (15). A mixture of 30.0 g (0.200 mol) of o-vanillin[16] (**14**), 60 mL of ethyl acetate containing six drops of concentrated sulfuric acid, and 1.00 g of 10% palladium on charcoal[14] catalyst was hydrogenated at an initial hydrogen pressure of 60 psi at room temperature for 8 h. The catalyst was filtered off and the filtrate was washed with saturated aqueous bicarbonate until the pH of the aqueous layer remained at 8. It was then dried, and the solvents were evaporated, leaving a clear, brown liquid which solidified in the freezer. Recrystallization from hot hexane yielded as the first crop 16.7 g (60%) of **15** in the form of white needles: mp 41.4–42.8 °C (lit.[17] mp 41–42 °C); NMR δ 6.60 (m, 3 H), 5.66 (s, 1 H), 3.73 (s, 3 H), 2.21 (s, 3 H); IR 3575 cm^{-1} (strong and sharp, –OH), no carbonyl peak.

5-(Piperidinomethyl)-3-methylguaiacol (16). To a solution of 15.0 g (0.109 mol) of **15** in 43 mL of piperidine at 0 °C was added, with stirring, 30.2 g (0.377 mol) of 37% aqueous formaldehyde. The mixture was stirred at room temperature for 1 h and refluxed gently for 2 h. It was diluted with water and ether. The layers were separated. The aqueous layer was extracted with ether. The combined ethereal so-

lution was washed with brine and dried. The solvent was evaporated, leaving a red liquid. Vacuum distillation of the red liquid yielded as the second fraction 15.6 g (61%) of **16** as an extremely viscous yellow liquid: bp 132–135 °C (0.25 mm); NMR δ 6.73 (s, 1 H), 6.62 (s, 1 H), 6.55 (s, 1 H), 3.62 (s, 3 H), 3.25 (s, 2 H), 2.33 (m, 4 H), 2.19 (s, 3 H), 1.50 (m, 6 H).

3-*n*-Pentadecylguaiacol (19). A solution of myristyl Grignard reagent in anhydrous ether was prepared from 51.62 g (0.186 mol) of 1-bromotetradecane[18] and 4.93 g (0.203 mol) of Mg turnings, each in 60 mL of anhydrous ether, and with a crystal of iodine as a catalyst. A 41.0-g (0.169 mol) sample of 2-benzyloxy-3-methoxybenzaldehyde (**17**), prepared according to Merz and Pfäffle,[8] was dissolved in 80 mL of anhydrous ether and added to the Grignard reagent under a nitrogen atmosphere, with stirring and ice-bath cooling to control the reflux. The mixture was then refluxed for 4 h and then cooled to 0 °C. Aqueous 10% HCl (200 mL) was added. After dilution with ether, the layers were separated. The ethereal layer was washed with saturated aqueous bicarbonate. The solvent was evaporated, leaving a yellow oil which was dissolved in 250 mL of hot 95% ethanol and chilled in an ice bath to precipitate hydrocarbon waxes. The waxes were filtered off by gravity and the ethanol was evaporated to give 71 g of the crude carbinol **18** as a viscous yellow-orange oil. The carbinol was hydrogenated in 142 mL of ethyl acetate containing 14 drops of concentrated sulfuric acid and 3.0 g of 10% palladium on charcoal catalyst at an initial hydrogen pressure of 60 psi at room temperature for 24 h. After the usual workup, vacuum distillation of the crude product yielded 37.6 g (67%) of **19** as a white solid: mp 40–44 °C; bp 183–186 °C (0.20 mm). A recrystallization from hexane gave pure 3-*n*-pentadecylguaiacol (**19**): mp 45.5–46.5 °C (lit.[9] mp 46.5–46.8 °C); NMR δ 6.61 (m, 3 H), 5.48 (s, 1 H), 3.80 (s, 3 H), 2.58 (t, 3 H), 1.25 (s, 26 H), 0.90 (s, 3 H).

5-(Piperidinomethyl)-3-*n*-pentadecylguaiacol (20). A mixture of 12.537 g (0.0375 mol) of **19**, 14.7 mL (12.6 g; 0.148 mol) of piperidine, and 9.9 mL (10.5 g; 0.13 mol) of 37% formaldehyde was refluxed overnight. The mixture was diluted with water and ether. The aqueous layer was extracted with ether. The combined ethereal layer was washed with brine and dried. The solvent was evaporated and the residual oil was distilled at 110 °C (0.25 mm) to remove low-boiling materials. The crude product was finally purified by molecular distillation at 125 °C (10^{-3} mm) to yield 12.77 g (79%) of **20** as an extremely viscous oil which crystallized on standing in the freezer (−6 °C) for 24 h into a white waxy solid: mp 42.5–45.5 °C; NMR δ 6.68 (s, 1 H), 6.58 (s, 1 H), 6.20 (s, 1 H), 3.72 (s, 3 H), 3.25 (s, 2 H), 2.60 (t, 2 H), 2.33 (m, 4 H), 1.45 (s, 6 H), 1.25 (s, 26 H), 0.90 (t, 3 H).

5-(Piperidinomethyl)-3-*n*-pentadecylcatechol Hydrochloride (23). Using a solution of 19 g (0.077 mol) of boron tribromide in 50 mL of benzene, a solution of 6.00 g (0.0139 mol) of **20** in 130 mL of benzene, and a solution of 59.3 g (0.695 mol) of piperidine in 70 mL of benzene, the procedure described in the preparation of **13** was followed. After the layers had been separated, the benzene layer was treated with 250 mL of ice-cold 2 N HCl. The resulting emulsion was cautiously[19] reduced until all the benzene was removed. The mixture was then filtered by gravity and then recrystallized from 80 mL of hot acetone to yield 5.52 g (87%) of **23** as white needles: mp 131.5–133.0 °C; NMR ($CDCl_3$) δ 10.20 (s, 1 H), 7.33 (d, 2 H), 6.66 (s, 2 H), 4.02 (s, 2 H), 3.35 (br t, 2 H), 2.59 (m, 6 H), 1.70 (br s, 6 H), 1.25 (s, 26 H), 0.90 (t, 3 H). The mass spectrum showed no observable M^+ peak, which was expected for a heat-sensitive compound of high molecular weight. The fragmentation pattern, however, was very similar to those of **13** and **25**.

Anal. Calcd for $C_{27}H_{48}ClNO_2$: C, 71.41; H, 10.65; Cl, 7.81; N, 3.08. Found: C, 71.37; H, 10.67; Cl, 7.70; N, 3.09.

6-(Piperidinomethyl)-3-*n*-pentadecylcatechol Hydrochloride (25). A solution of 4.20 g (0.0101 mol) of **24** (prepared according to the procedure of Lerner[2]) in 65 mL of ether was shaken with 60 mL (0.060 mol) of ice-cold 1 N HCl. The white precipitate was collected by suction filtration, washed with ether, and recrystallized from 75 mL of hot acetone. A 3.84-g yield (84%) of **25**, mp 83.0–85.0 °C, was collected in several crops as fine, white crystals: NMR ($CDCl_3$) δ 10.10 (s, 1 H), 6.77 (s, 2 H), 6.52 (s, 2 H), 4.21 (s, 2 H), 3.41 (br t, 2 H), 2.60 (m, 6 H), 1.90 (s, 6 H), 1.25 (s, 26 H), 0.90 (t, 3 H). The mass spectrum showed a small M^+ peak at *m/e* 417.

Anal. Calcd for $C_{27}H_{48}ClNO_2$: C, 71.41; H, 10.65; Cl, 7.81; N, 3.08. Found: C, 70.12; H, 10.90; Cl, 7.61; N, 3.02.

***Registry No.*—7**, 91-16-7; **8a**, 66495-60-1; **8b**, 7461-75-8; **9a**, 66495-61-2; **9b**, 66495-62-3; **10**, 66495-63-4; **13**, 66495-64-5; **14**, 148-53-8; **15**, 2896-67-5; **16**, 66495-65-6; **17**, 2011-06-5; **18**, 66495-66-7; **19**, 16825-58-4; **20**, 66495-67-8; **23**, 66495-68-9; **24**, 64022-07-7; **25**, 66495-69-0; 1-bromodecane, 112-29-8; piperidine, 110-89-4; 1-bromotetradecane, 112-71-0.

References and Notes

(1) H. Baer, M. L. Hooton, C. R. Dawson, and D. I. Lerner, *J. Invest. Dermatol.*, **69**, 215 (1977).
(2) D. I. Lerner, Ph.D. Thesis, Columbia University, New York, N.Y., 1974; *Diss. Abstr. Int. B*, **37**, 3419B (1977).
(3) J. S. Byck and C. R. Dawson, *J. Org. Chem.*, **32**, 1084 (1967).
(4) A. P. Kurtz and C. R. Dawson, *J. Med. Chem.*, **14**, 729 (1971).
(5) J. F. W. McOmie, M. L. Watts, and D. E. West, *Tetrahedron*, **24**, 2289 (1968).
(6) (a) C. R. Dawson and G. P. Ng, to be published. (b) G. P. Ng, Ph.D. Thesis, Columbia University, New York, N.Y., 1978.
(7) B. Loev and C. R. Dawson, *J. Am. Chem. Soc.*, **78**, 6095 (1956).
(8) K. W. Merz and H. Pfäffle, *Arch. Pharm. (Weinheim, Ger.)*, **288**, 86 (1955).
(9) P. J. Vithayathil and C. R. Dawson, *J. Org. Chem.*, **23**, 1443 (1958).
(10) J. S. Byck and C. R. Dawson, *J. Org. Chem.*, **33**, 2451 (1968).
(11) H. O. House, "Modern Synthetic Reactions", W. A. Benjamin, New York, N.Y., 1965.
(12) Prepared by the procedure of R. G. Jones and H. Gilman, *Org. React.*, **6**, 352 (1951).
(13) Matheson, Coleman and Bell Manufacturing Chemists, East Rutherford, N.J.
(14) Research Organic/Inorganic Chemical Corp., Belleville, N.J.
(15) C. Schotten, *Chem. Ber.*, **15**, 421 (1882).
(16) Gallard-Schlesinger Manufacturing Co., Carle Place, N.Y.
(17) R. Majima and Y. Okazaki, *Chem. Ber.*, **49**, 1488 (1916).
(18) Eastman Kodak Co., Rochester, N.Y.
(19) The mixture has a great tendency to foam over.

Preparation and Reactions of 5-Alkylpentachloro-1,3-cyclopentadienes. Application to Sesquiterpene Synthesis[1]

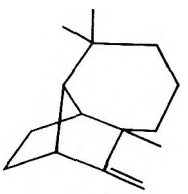
Richard S. Glass,* James D. Herzog, and Ronald L. Sobczak

Department of Chemistry, The University of Arizona, Tuczon, Arizona 85721

Received April 27, 1976

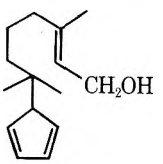
A variety of 5-alkyl-1,2,3,4,5-pentachloro-1,3-cyclopentadienes (**4a–d**) were prepared. The key step in these syntheses involved the reaction of a phosphite with hexachlorocyclopentadiene. Attempts were made to effect intramolecular Diels–Alder cyclization of these compounds without rearrangement in an effort to synthesize longifolene. Thermal cyclization occurred in one case, that of **4b**, in low yield, but rearrangement preceded cyclization. The molecular structure of this cyclization product was unequivocally elucidated as **5a** by X-ray crystallographic analysis. Consideration of this structure, which requires reduction as well as rearrangement, suggested a more efficient synthesis. Reduction of (*E*)-**4b** with lithium aluminum hydride followed by thermal cyclization gave **5a** in good yield. Benzyl ether **5b** was similarly prepared. Both **5a** and **5b** are potential intermediates in a synthesis of isolongifolene.

Longifolene (1) is a tricyclic sesquiterpene whose chemistry and synthesis has evoked considerable interest. Three



1

successful syntheses of longifolene have been reported.[2] An unsuccessful attempted synthesis reported by Brieger[3] drew our attention because of its conciseness and the possibility that the synthetic goal could be realized with some modifications in the approach. Brieger noted that internal Diels–Alder cyclization of **2**, which may be prepared from geraniol

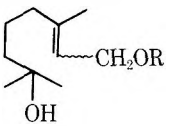


2

and cyclopentadiene, would afford the carbon skeleton of longifolene. However, **2** is a 5-alkyl-1,3-cyclopentadiene and as such is expected to isomerize readily to the 1- and 2-isomers.[4] Furthermore, at equilibrium, at least at room temperature, the 5-isomer is a very minor constituent.[4] Indeed Brieger apparently obtained a mixture consisting predominantly of the 1- and 2-isomers. It was hoped that on heating thermal equilibration would provide the 5-isomer, which would then cyclize. Unfortunately, the only product obtained was apparently that resulting from internal Diels–Alder cyclization of the 1-isomer.[5] It should be noted however, that such an approach proved viable in the intramolecular Diels–Alder cyclization of 1-(3-butenyl)-1,3-cyclopentadiene.[6] In this case, cyclization of the the 5-(3-butenyl)-1,3-cyclopentadiene is favored over the 1-isomer because the transition state of the former cyclization, which leads to brex-4-ene, is less strained than that resulting from cyclization of the 1-isomer. To overcome the difficulties in this attempted synthesis of longifolene securing the 5-isomer and effecting Diels–Alder cyclization *before* isomerization is required. Trapping of 5-alkyl-1,3-cyclopentadienes in Diels–Alder reactions prior to isomerization has been reported in several cases.[7] However, all of these cases involve especially facile Diels–Alder reactions. The difficulty in extending this methodology to less facile Diels–Alder reactions is the ease of isomerization of 5-alkyl-1,3-cyclopentadienes. Since this thermal isomerization involves [1,5]sigmatropic rearrangement[4,8] of a hydrogen atom, replacement of the 5-hydrogen atom with an atom or group which undergoes migration less readily is indicated. The atom selected for the present studies was chlorine and 5-alkyl-1,2,3,4,5-pentachloro-1,3-cyclopentadienes in particular were studied. This choice was determined by the following: (1) 5-alkylpentachloro-1,3-cyclopentadienes undergo isomerization only at elevated temperatures (~150 °C);[9] (2) alkyl group migration is degenerate (although alkyl groups isomerize much less readily than hydrogen atoms[10] anyway except in one special case);[11] (3) hexachloro-1,3-cyclopentadiene, 1,2,3,4,5-pentachloro-1,3-cyclopentadiene, and 5-alkylpentachloro-1,3-cyclopentadienes undergo Diels–Alder reactions with alkenes;[9a,d,12] (4) hexachlorocyclopentadiene undergoes Diels–Alder reactions with inverse electron demand,[12d,13] thus electron-releasing alkyl groups on the dienophile electronically favor reaction (although there is also an adverse steric effect); (5) 5-allylalkoxy-5-morpholino-1,2,3,4-tetrachlorocyclopentadiene reportedly[14] undergoes intramolecular Diels–Alder reaction at room temperature; (6) methods are available for preparing 5-alkylpentachloro-1,3-cyclopentadienes by reaction of alkyl halides with pentachlorocyclopentadienyl anion[9a,15] or by reaction of hexachloro-1,3-cyclopentadiene with alkyl phosphorus esters;[16] (7) all of the chlorine atoms should easily be replaceable by hydrogen atoms in the Diels–Alder adduct.[9a,12c,17] This paper reports attempts to utilize 5-alkylpentachloro-1,3-cyclopentadienes in a synthesis of longifolene.

Results

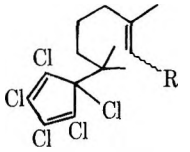
A variety of 5-alkylpentachloro-1,3-cyclopentadienes (**4a–d**), which on intramolecular cyclization without rearrangement would afford products with the carbon skeleton of longifolene, were prepared as follows. A mixture of (*E,Z*)-3,7-dimethyl-2,6-octadien-1-ol was successively acetylated, selectively oxidized with monoperphthalic acid to the 6,7-epoxide, and reduced with lithium aluminum hydride in tetrahydrofuran following the procedure of Mousseron-Canet et al.[18] to yield 1,7-diol **3a**. After purification by column



3a, R = H
b, R = $COCH_3$
c, R = CH_3
d, R = $CH_2C_6H_5$

0022-3263/78/1943-3209$01.00/0

chromatography on silica gel, 1,7-diol **3a** was selectively acetylated. Treatment of hydroxy acetate **3b** so obtained with triethylamine and diethyl phosphorochloridite presumably gave the corresponding mixed phosphite. This intermediate was not isolated and characterized, but treated with hexachlorocyclopentadiene to afford, in analogy with the studies of Mark and co-workers,[16] 5-alkylpentachlorocyclopentadiene **4a** in 39% yield after purification by silica gel chromatography. In a similar manner hydroxy methyl ether **3c** and hydroxy benzyl ether **3d** were transformed into 5-alkylpentachlorocyclopentadienes **4b** and **4c** in 56 and 60% yield, respectively.



4a, R = CH_2OCOCH_3
b, R = CH_2OCH_3
c, R = $CH_2OCH_2C_6H_5$
d, R = CH_2OH

Hydroxy methyl ether **3c**[19] was secured by methylation of (*E,Z*)-3,7-dimethyl-2,6-octadien-1-ol with sodium hydride and methyl iodide, followed by selective oxidation with monoperphthalic acid, and then reduction with lithium aluminum hydride. Hydroxy benzyl ether **3d** was prepared from **3a** by sequential treatment with sodium hydride in tetrahydrofuran and excess benzyl bromide. Acetate **4a**, on exposure to sodium carbonate and methanol, produced alcohol **4d**. This alcohol could be converted easily into a variety of 5-alkylpentachlorocyclopentadienes. On treatment with sodium hydride in tetrahydrofuran and methyl iodide or benzyl bromide, alcohol **4d** gave methyl ether **4b** and benzyl ether **4c**. Both of these ethers were identical with those prepared by the alternative routes already described.

In addition to the *E,Z* isomers of **4** prepared as outlined above, isomerically pure (*E*)-**4b** was prepared from geraniol, (*E*)-3,7-dimethyl-2,6-octadien-1-ol. Successive methylation, selective epoxidation, and reduction of geraniol yielded (*E*)-**3c**. Conversion of (*E*)-**3c** into (*E*)-**4b** was accomplished in the same manner as that for the transformation of (*E,Z*)-**3c** into (*E,Z*)-**4b**.

The structures of 5-alkylpentachlorocyclopentadienes **4a–d** were assigned on the basis of the method of synthesis and spectroscopic data (IR, ^1H NMR, and MS). Data supporting the assignment of these materials as 5-alkylpentachlorocyclopentadienes, as opposed to the 1- or 2-alkyl isomers, was of special interest. In this regard, note should be made that compounds **4a–d** showed no, or at most weak, absorption in or near the 800–815-cm^{-1} region in the IR. Furthermore, the ^{13}C NMR spectrum of (*E*)-**4b** was measured.

Attempts to effect intramolecular Diels–Alder cyclization of 5-alkylpentachlorocyclopentadienes **4a–d** under a variety of conditions appeared to be of no avail with one exception.[20] Heating a dilute solution of **4b** and hydroquinone in decalin at reflux under an argon atmosphere for 1 h gave a mixture which was separated by column chromatography on silica gel. Uncyclized material was recovered but, although the ^1H NMR spectrum of this material was identical with starting **4b**, an absorption band of medium strength at 795 cm^{-1} appeared in the IR spectrum of this material which was not present in that of the starting material. In addition a small amount of a colorless solid was also obtained. ^1H NMR, IR, and UV spectra indicated that this solid was a cyclized product of **4b**, but MS data suggested that a chlorine atom had been replaced by a hydrogen atom. Since only small amounts of this difficulty obtainable material were available its detailed structure was determined by single-crystal X-ray diffraction analysis.

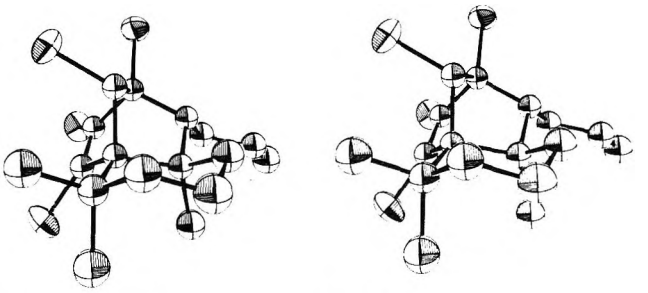
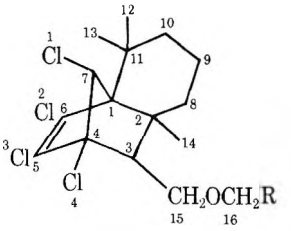


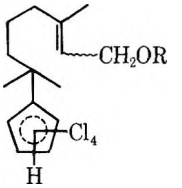
Figure 1. ORTEP[21] stereoscopic view of **5a**.

The molecular structure of this material is shown in **5a**. A stereoscopic view of **5a** is presented in Figure 1.



5a, R = H
b, R = C_6H_5

Once the detailed structure of **5a** had been elucidated a more efficient route to this material was devised. Reduction of (*E*)-**4b** with lithium aluminum hydride in tetrahydrofuran gave (*E*)-tetrachlorocyclopentadiene **6a** in 72–81% yield.



6a, R = CH_3
b, R = $CH_2C_6H_5$

Heating a dilute solution of (*E*)-**6a** and hydroquinone in decalin at reflux under an argon atmosphere for 5 h provided **5a** in 70–80% yield. Similarly, (*E,Z*)-**4c** on reduction with lithium aluminum hydride yielded (*E,Z*)-**6b** in 78% yield. Intramolecular Diels–Alder cyclization of (*E,Z*)-**6b** was effected in a manner similar to that for (*E*)-**6a** to afford **5b** in 41% yield and another isomer in 6% yield. The structure **5b** was assigned on the basis of spectral data, particularly the ^1H NMR spectrum.

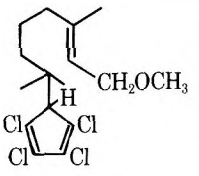
Discussion

An essential aspect to this synthetic approach was the preparation of 5-alkylpentachloro-1,3-cyclopentadienes **4**. To accomplish this, a carbon–carbon bond establishing a quaternary carbon must be formed. This was readily achieved by reaction of alkyl phosphorous esters and hexachloro-1,3-cyclopentadiene.[16] An additional useful aspect of this reaction is that a mixed phosphite could be used owing to the greater ease of transfer of a tertiary over a primary alkyl group.[16a] That 5-alkyl isomers are formed in the reactions of alkyl phosphites with hexachloro-1,3-cyclopentadiene has been previously shown by IR,[9c] Raman,[22] ^1H NMR,[9a] ^{13}C NMR,[9c,23] ESCA,[24] and chemical studies.[9a,12f] Thus the lack of strong absorption in the IR in the 800–815-cm^{-1} region is diagnostic for 5-alkylpentachlorocyclopentadienes. Isomeric 1- and 2-alkylpentachlorocyclopentadienes absorb in this region owing

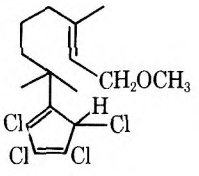
to a CCl_2 vibration.[9c] All of the alkylpentachlorocyclopentadienes prepared in our work by the reaction of phosphites with hexachlorocyclopentadiene are devoid of significant absorption in the 800–815-cm^{-1} region and, therefore, are assigned as the 5-isomers. In addition the ^{13}C NMR spectrum of (*E*)-**4b** supports its assignment as a 5-alkyl isomer. Four peaks occur in the olefinic carbon region. Two of these peaks (those at 122.3 and 138.6 ppm) are due to resonance of the olefinic carbons which are not part of the cyclopentadienyl ring. Thus resonance due to the cyclopentadienyl ring carbons give rise to only two signals (at 129.5 and 134.4 ppm). Therefore, there are only two nonequivalent olefinic carbon atoms in the cyclopentadienyl ring. Only the 5-alkyl isomer is sufficiently symmetric to accommodate this result. Furthermore, the peak at 80.2 ppm,[25] which is assigned to the resonance of the saturated carbon of the cyclopentadienyl ring, is consistent with a 5-alkyl isomer. The chemical shift for C(5) in 5-ethyl-1,2,3,4-5-pentachloro-1,3-cyclopentadiene in deuteriochloroform is 73 ppm. This leads to a calculated[26] chemical shift for the saturated carbon of the cyclopentadienyl ring in (*E*)-**4b** of 79 ppm, which is in good agreement with the observed value.

With the required 5-alkylpentachlorocyclopentadienes in hand a question of key importance for the synthetic approach was would intramolecular Diels–Alder cyclization compete favorably with alternative modes of reaction such as isomerization. The results show that this is not the case. Only a product resulting from cyclization of a 1-substituted isomer was isolated. In addition the recovered uncyclized material showed absorption in the IR at 795 cm^{-1} which was absent in the starting material. This suggests the presence of the 1- and/or 2-alkyl isomers.[27]

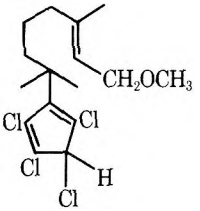
The structure of the cyclization product obtained from (*E,Z*)-**4b** was unambiguously deduced from X-ray studies. The bond lengths, bond angles, and torsion angles determined for **5a** compare favorably with the expected values.[28] The mechanism by which **5a** formed was not investigated in detail, but some pertinent comments can be made. Clearly, isomerization precedes cyclization. Furthermore, a reasonable possibility is that **4b** suffers homolysis of the C(5′)–Cl bond to generate a tetrachlorocyclopentadienyl radical and chlorine atom, which can either recombine to give the isomeric alkylpentachlorocyclopentadienes or the tetrachlorocyclopentadienyl radical abstracts a hydrogen atom. This presumably would lead to a mixture of compounds **7–9**, which can easily



7



8



9

thermally equilibrate by [1,5]sigmatropic rearrangement of hydrogen. Isomer **8** may then undergo Diels–Alder cyclization to produce **5a.** In support of this suggestion it was found that reduction of (*E*)-**4b** with lithium aluminum hydride[29] gave, in good yield, a mixture of tetrachlorocyclopentadienes (NMR analysis suggests 30% of **7** and 70% of **8** and/or **9**) which underwent thermal cyclization, under the conditions used for cyclization of **4b,** to afford **5a** in good yield. The stereochemistry of **5a** results from the expected cis addition[12e] to the (*E*)-alkene.[30] In addition steric factors rather than dipole attractions[12e,31] determine the preference for the *syn*-7-chloro isomer.

Finally it has not escaped our attention that **5a** contains the tricyclic ring system of isolongifolene (**10**).[32] Thus studies

10

aimed at converting **5a** or **5b** into isolongifolene are underway.

Experimental Section

Elemental microanalysis was performed by analysts at the Scandinavian Microanalytical Laboratory, Herlev, Denmark. IR spectra were measured using a Perkin-Elmer Model 137 IR spectrophotometer. ^1H NMR spectra were measured at 60 MHz using a Varian Model T-60 NMR spectrometer on samples containing tetramethylsilane as an internal standard. All coupling constants are reproducible to ±1 Hz. The ^{13}C NMR spectrum was measured at 22.63 MHz using a Bruker Model WH90 NMR spectrometer on a sample with hexadeuterioacetone as solvent and internal standard. Mass spectra were determined employing a Hitachi-Perkin-Elmer Model RMU-6E double focusing mass spectrometer or Hewlett-Packard Model 5930A dodecapole mass spectrometer. The values in parentheses are the ratios of the intensity of the peaks to the base peak in the spectrum. UV spectra were measured using a Cary Model 14 spectrophotometer. Melting points are corrected and were determined in capillary tubes using a Thomas-Hoover melting point apparatus. Tetrahydrofuran (AR) was distilled from lithium aluminum hydride before use. The silica gel (0.063–0.2 mm) used in column chromatography was obtained from ICN Pharmaceuticals, and that used in thin-layer chromatography was obtained from Brinkmann Instruments, Inc. (E. Merck, HF-254).

(*E,Z*)-Hydroxy Acetate 3b. A solution of (*E,Z*)-1,7-diol **3a** (955 mg, 5.5 mmol) in pyridine (2 mL) was cooled in an ice bath. Acetic anhydride (1.0 mL, 10 mmol) was added. The ice bath was removed and the reaction was stirred for 12 days at room temperature. The reaction mixture was poured into ice and extracted three times with petroleum ether (bp 30–60 °C). The combined petroleum ether extracts were washed sequentially with two portions of saturated aqueous cupric sulfate solution, water, saturated aqueous sodium bicarbonate solution, and saturated aqueous sodium chloride solution, dried with anhydrous magnesium sulfate, and concentrated by rotary evaporation to a clear oil. This material was chromatographed on a silica gel column (eluted with petroleum ether–ethyl acetate) and distilled from bulb to bulb under oil pump vacuum to give **3b** (880 mg, 75% yield): IR (neat) 1740 (C=O) cm^{-1}; NMR (neat) δ 0.78–2.38 (m, 18 H, aliphatic), 3.33 (s, 1 H, OH), 4.52 (d, 2 H, J = 7 Hz, allylic CH_2), 5.33 (br t, 1 H, J = 7 Hz, vinyl).

Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35. Found: C, 66.91; H, 9.93.

(*E,Z*)-3,7-Dimethyl-1-methoxy-2-octene 6,7-Oxide. A solution of (*E,Z*)-3,7-dimethyl-1-methoxy-2,6-octadiene (13.4 g, 80 mmol) in anhydrous ethyl ether (20 mL) was cooled in a dry ice–acetone bath and a solution of monoperphthalic acid[31] (160 mL, 0.8 N, 130 mmol) was added over 10 min. The reaction mixture was stored at 0 °C for 14 days. The reaction was cautiously poured into saturated aqueous sodium bicarbonate solution, shaken, and the two layers separated. The aqueous suspension was extracted with ethyl ether (3×). The combined ether extracts were washed sequentially with saturated sodium bicarbonate solution and brine, dried with anhydrous magnesium sulfate, and concentrated by rotary evaporation to a clear oil (14 g, 95% yield). Similar experiments resulted in yields ranging from 80 to 97%: NMR (neat) δ 0.94–2.34 (m, 13 H, aliphatic), 2.57 (t, 1 H, J = 6 Hz, epoxide), 3.18 (s, 3 H, OCH_3), 3.84 (d, 2 H, J = 6 Hz, allylic OCH_2), 5.27 (br t, 1 H, J = 7 Hz, vinyl). This material was used without further purification.

Hydroxy Methyl Ether 3c. A suspension of lithium aluminum hydride (6.0 g, 160 mmol) in anhydrous tetrahydrofuran (150 mL) was cooled in an ice bath and a solution of (*E,Z*)-3,7-dimethyl-1-methoxy-2-octene 6,7-oxide (12.8 g, 70 mmol) in anhydrous tetrahydrofuran (100 mL) was added over 10 min. The reaction mixture was heated at reflux for 18 h. Wet ethyl ether and aqueous sodium potassium tartrate solutions were added sequentially. The aqueous layer was separated and extracted with ethyl ether (3×). The combined ether extracts were washed with brine (2×), dried with anhydrous magnesium sulfate, and concentrated by rotary evaporation to a clear oil which was distilled under vacuum (12.1 g, 93% yield): IR (neat)

3400 (m, OH) cm^{-1}; NMR (neat) δ 0.67–2.40 (m, 15 H, aliphatic), 3.20 (s, 3 H, OCH_3), 3.57 (s, 1 H, OH), 3.87 (d, 2 H, J = 6 Hz, allylic OCH_2), 5.28 (br t, 1 H, J = 7 Hz, vinyl).

Anal. Calcd for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90. Found: C, 70.34; H, 12.19.

Hydroxy Benzyl Ether 3d. Sodium hydride (1.61 g, 57% mineral oil dispersion, 38 mmol), washed twice with ethyl ether, was cooled in an ice bath and a solution of (*E,Z*)-1,7-diol **3a** (5.75 g, 33 mmol) in anhydrous tetrahydrofuran (40 mL) was added. Benzyl bromide (4.8 mL, 40 mmol) was added to the reaction mixture and the ice bath removed. The reaction was stirred for 42 h and then poured into wet ether. The ether extract was washed sequentially with water and saturated aqueous sodium chloride solution, dried with anhydrous magnesium sulfate, and concentrated by rotary evaporation using oil pump vacuum. The residue was chromatographed on silica gel and distilled under oil pump vacuum (6.81 g, 80% yield): IR (neat) 3400 (m, OH) cm^{-1}; NMR (neat) δ 0.80–2.37 (m, 15 H, aliphatic), 3.40 (s, 1 H, OH), 4.03 (d, 2 H, J = 7 Hz, allylic OCH_3), 4.47 (s, 2 H, benzylic OCH_2), 5.48 (br t, 1 H, J = 6 Hz, vinyl), 7.32 (s, 5 H, aromatic).

Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.33; H, 9.84.

Preparation of 4b from Hydroxy Methyl Ether 3c. A solution of (*E,Z*)-hydroxy methyl ether **3c** (5.35 g, 29 mmol) and triethylamine (5.0 mL, 40 mmol) in anhydrous ethyl ether (25 mL) was cooled in an ice bath. Diethyl phosphorochloridite (5.52 g, 35 mmol), prepared by the method of Cook and co-workers,[34] was added. The ice bath was removed and the reaction mixture stirred 18 h at room temperature. The reaction was cooled in a dry ice–acetone bath. Anhydrous ethyl ether (20 mL) and hexachlorocyclopentadiene (5.0 mL, 30 mmol) were added sequentially. The reaction was stirred for 1 h. The dry ice–acetone bath was removed and the reaction stirred for an additional 75 min. The reaction was poured into saturated aqueous sodium bicarbonate solution. The aqueous suspension was extracted with ethyl ether (3×). The combined ether extracts were washed successively with two portions of saturated aqueous cupric sulfate solution, dried with anhydrous magnesium sulfate, and concentrated by rotary evaporation. The resulting oil was chromatographed on a silica gel column by a gradient elution with petroleum ether (bp 30–60 °C) and ethyl acetate. A yellow oil was so obtained (6.5 g, 55% yield): UV (cyclohexane) λ_{max} 314 nm (1800); IR (neat) 1610 (ClC=CCl) cm^{-1}; NMR (CCl_4) δ 0.58–2.35 (m, 15 H, aliphatic), 3.18 (s, 3 H, OCH_3), 3.82 (d, 2 H, J = 7 Hz, allylic OCH_2), 5.20 (br t, 1 H, J = 6 Hz, vinyl); MS *m/e* 410 (0.001), 408 (0.004), 406 (0.006), 169 (0.162), 137 (1.00), 95 (0.128), 81 (0.458); (P − C_5Cl_5) 169.1597 (calcd for $C_{11}H_{21}O$, 169.1592).

(*E*)-**4b** was prepared from geraniol in the same way as (*E,Z*)-**4b** was prepared from (*E,Z*)-3,7-dimethyl-2,6-octadien-1-ol: ^{13}C NMR (CD_3COCD_3) δ 15.8, 22.4, 22.8, 36.5, 39.9, 43.2, 57.0, 68.7, 80.2, 122.3, 129.5, 134.4, and 138.6.

Preparation of 4c from Hydroxy Benzyl Ether 3d. The same procedure as used for the synthesis of **4b** was followed except substituting **3d** for **3c**. The yield was 60% after purification by column chromatography on silica gel: UV (cyclohexane) λ_{max} 313 nm (1800); IR (neat) 1600 (ClC=CCl) cm^{-1}; NMR (CCl_4) δ 0.72–2.25 (m, 15 H, aliphatic), 3.88 (d, 2 H, J = 7 Hz, allylic OCH_2), 4.37 (s, 2 H, benzylic OCH_2), 5.30 (br t, 1 H, J = 7 Hz, vinyl), 7.18 (s, 5 H, aromatic).

Anal. Calcd for $C_{22}H_{25}Cl_5O$: C, 54.74; H, 5.22. Found: C, 55.28; H, 5.39.

Preparation of 4a. The same procedure as used for the synthesis of **4b** was followed except utilizing **3b** in place of **3c**. The yield was 39% after purification by column chromatography on silica gel: IR (neat) 1730 (C=O), 1600 (ClC=CCl) cm^{-1}; NMR (CCl_4) δ 0.47–2.30 (m, 18 H, aliphatic), 4.40 (d, 2 H, J = 7 Hz, allylic OCH_2), 5.28 (t, 1 H, J = 7 Hz, vinyl); MS *m/e* (P − $C_7Cl_5H_3O$) 154.1361 (calcd for $C_{10}H_{18}O$, 154.1358).

Conversion of 4a into 4d. A mixture of (*E,Z*)-**4a** (2.59 g, 6.0 mmol) and sodium carbonate (2 g, 20 mmol) in methanol (25 mL) was stirred for 18 h at room temperature. The mixture was then filtered, poured into water, and extracted with ethyl ether. The ether extract was dried with anhydrous magnesium sulfate, concentrated by rotary evaporation, and chromatographed on silica gel to give a pale yellow oil (1.72 g, 73% yield): IR (neat) 3300 (OH), 1600 (ClC=CCl) cm^{-1}; NMR (CCl_4) δ 0.40–2.35 (m, 15 H, aliphatic), 3.03 (s, 1 H, OH), 3.97 (d, 2 H, J = 7 Hz, allylic OCH_2), 5.32 (br t, 1 H, J = 7 Hz, vinyl); MS *m/e* (P − C_5Cl_5H) 154.1361 (calcd for $C_{10}H_{18}O$, 154.1358).

Preparation of 4c from 4d. Sodium hydride (350 mg, 57% mineral oil dispersion, 14 mmol), washed twice with anhydrous ethyl ether, was cooled in ice and a solution of (*E,Z*)-**4d** (355 mg, 0.90 mmol) in anhydrous tetrahydrofuran (6 mL) was added. Benzyl bromide (0.6 mL, 5 mmol) was added to the reaction mixture and the ice bath was removed. The reaction was stirred for 18 h and then poured into wet ethyl ether. The ether extract was washed with saturated aqueous sodium chloride solution, dried with anhydrous magnesium sulfate, and concentrated by rotary evaporation. Excess benzyl bromide was evaporated under vacuum (oil pump) with heating in a warm water bath overnight, leaving a pale yellow oil (418 mg, 95%). Spectral data was the same as that for material prepared by the alternate procedure.

Table I. Crystal Data for 5a

crystal dimension, mm	0.2 × 0.3 × 0.5
μ	62
min and max transmission	0.37–0.13
space group	$P2_1/n$
mol formula	$C_{16}H_{22}Cl_4O$
mol wt	372
D_{obsd}	1.46
D_{calcd}	1.44
cell dimensions	a = 13.038 (5), b = 9.583 (4), c = 14.274 (5) Å, α = 90, β = 105.878, γ = 90°, V = 1715.3 Å^3, Z = 4.

Preparation of 4b from 4d. When methyl iodide was substituted for benzyl bromide in the preceding procedure, the yield was 73%. The IR and ^1H NMR spectra are the same as that reported in the alternate synthesis of (*E,Z*)-**4b.**

Conversion of 4b into 5a. A solution of (*E,Z*)-**4b** (729 mg, 2.00 mmol) and hydroquinone (77 mg, 0.70 mmol) in decalin (300 mL) under argon was heated at reflux for 1 h. The solution was let cool to room temperature and concentrated by rotary evaporation using oil pump vacuum. The residue was chromatographed on a column of silica gel, eluting with a gradient of petroleum ether (bp 30–60 °C) and benzene. Uncyclized triene (561 mg, 1.40 mmol), recovered from this reaction, had identical ^1H NMR spectrum and R_f on silica gel with that of starting material **4b.** However this recovered triene had a medium absorption band in the IR at 795 cm^{-1}, which was not found in the IR spectrum of **4b.** A solid **5a** (52 mg, 6% conversion) was also isolated, which was recrystallized from a mixture of benzene–petroleum ether (bp 30–60 °C). An X-ray diffraction study was carried out on these crystals: mp 151–153 °C; UV (cyclohexane) end absorption 225 nm (5000); IR (KBr) 1570 (ClC=CCl) cm^{-1}; MS *m/e* 376 (0.01), 374 (0.04), 372 (0.09), 370 (P, 0.08), 245 (1.00), 243 (0.85), 202 (0.68), 85 (0.95), 81 (0.80), 45 (0.82); a ^1H NMR spectrum was taken on the solid before recrystallization. This ^1H NMR spectrum had the same resonance peaks as those recorded for **5a** synthesized from (*E*)-**6a,** but also contained extraneous peaks from impurities.

X-ray Diffraction Structural Determination of 5a. Crystals were obtained from a vapor diffusion crystallization from benzene and petroleum ether (bp 30–60 °C). Weissenberg photographs of a crystal mounted about the c axis revealed a monoclinic system. Systematic absences identified the space group as $P2_1/n$. The crystal was transferred to a Picker FACS-I diffractometer (CuKα, λ = 1.54178 Å, graphite monochromator) and the cell dimensions and orientation matrix were calculated from 12 accurately centered reflections. Table I summarizes the pertinent crystal data.

Intensity data were collected using a scintillation counter with pulse-height analyzer, θ–2θ scan technique (to a maximum 2θ of 120°), 2°/min scan rate, 10-s background counts, attenuators when the count rate exceeded 10^4 counts/s, and 2° scan range with a dispersion factor allowing for α_1–α_2 splitting at large 2θ values. Of 2651 independent reflections measured, 2115 equal to or greater than $3\sigma I$ were used in the structural analysis. No appreciable decrease in intensity of the standard reflections was observed, and no correction was made for absorption.

The structure was solved using MULTAN.[35] All but two nonhydrogen atoms were located on the first E map. The two remaining methyl carbon atoms were located using Fourier difference maps.[36] Anomalous scattering by chlorine was taken into account using scattering factor tables by Cromer and Mann.[37] Full-matrix least-squares refinement with anisotropic thermal parameters for the four chlorine atoms and isotropic thermal parameters for all other nonhydrogen atoms reduced $R = \Sigma(|F_o| - |F_c|)/\Sigma|F_o|$ to 0.094. Refinement was based on F_o, the quantity minimized being $w = 4F_o^2/\sigma^2(F_o^2)$, with unit weights. The maximum shift of parameters with respect to the standard deviation in the final cycle was 1.46 for the nonhydrogen atoms. The standard deviation of an observation of unit weight was 4.654.

Preparation of (*E*)-6a. A suspension of lithium aluminum hydride (442 mg, 11.6 mmol) in anhydrous tetrahydrofuran (30 mL) was cooled in a dry ice–acetone bath and a solution of (*E*)-**4b** (273 mg, 0.67 mmol) in anhydrous tetrahydrofuran (20 mL) was added. The reaction was placed and maintained under argon. The dry ice–acetone bath was removed and the reaction mixture stirred at room temperature overnight. The reaction mixture was poured into iced 1 N aqueous hydrochloric acid solution (50 mL) layered with ether (20 mL). The aqueous layer was separated and extracted three times with ether. The combined ether extracts were dried with anhydrous magnesium sulfate and concentrated by rotary evaporation. The resulting oil was chromatographed on a preparative layer plate of silica gel, using benzene as eluent. The product was washed off the silica gel with ethyl acetate and concentrated by rotary evaporation to a pale yellow oil (180 mg, 72%): UV (cyclohexane) λ_{max} 285 nm (1800); IR (neat) 1600 (ClC=CCl) cm^{-1}; NMR (CCl_4) δ 0.62–2.28 (m, 15 H, aliphatic), 3.18 (s, 3.3 H, OCH_3 and cyclopentadienyl CHR), 3.78 (d, 2 H, J = 6 Hz, allylic OCH_2), 4.63 (s, 0.7 H, cyclopentadienyl CHCl), 5.18 (br t, 1 H, J = 6 Hz vinyl); NMR (C_6H_6) δ 0.37–2.34 (m, 15 H, aliphatic), 2.65 (s, 0.3 H, cyclopentadienyl CHR), 3.15 (s, 3 H, OCH_3), 3.82 (d, 2 H, J = 7 Hz, allylic OCH_2), 4.25 (s, 0.7 H, cyclopentadienyl CHCl), 5.42 (br t, 1 H, J = 6 Hz, vinyl); MS *m/e* 378, 376, 374 (0.02), 372 (0.04), 370 (0.04), 245 (0.57), 209 (0.55), 119 (1.00), 105 (0.77), 91 (0.77), 85 (0.77), 81 (0.72).

Preparation of (*E,Z*)-6b. The same procedure as used for the preparation of (*E*)-**6a** was followed utilizing (*E,Z*)-**4c**. A 78% yield of (*E,Z*)-**6b** was obtained: UV (cyclohexane) λ_{max} 302 nm (1800); IR (neat) 1620 (ClC=CCl) cm^{-1}; NMR (CCl_4) δ 0.45–2.23 (m, 15 H, aliphatic), 3.05 (s, 0.3 H, cyclopentadienyl CHR), 3.9 (d, 2 H, J = 6 Hz, allylic OCH_2), 4.38 (s, 2 H, benzylic OCH_2), 4.62 (s, 0.7 H, cyclopentadienyl CHCl), 5.32 (br t, 1 H, J = 7 Hz, vinyl), 7.2 (s, 5 H, aromatic).

Cyclization of (*E*)-6a to 5a. A solution of (*E*)-**6a** (228 mg, 0.60 mmol) and hydroquinone (24 mg, 0.2 mmol) in decalin (50 mL) under argon was heated at reflux for 1 h. The solution was allowed to cool to room temperature and then concentrated by rotary evaporation under oil pump vacuum. The residue was chromatographed on a preparative layer plate of silica gel, using benzene as eluent. A solid **5a** (114 mg) was isolated. A second fraction (79 mg) was a mixture of uncyclized **6a** and **5a**. This fraction was again chromatographed on a preparative layer plate of silica gel, using benzene as eluent. More solid (15 mg) was isolated, which when combined with the solid first obtained gave 129 mg (57% conversion) of **5a**. The second fraction (64 mg) from this second preparative layer chromatography had identical ^1H NMR spectrum and R_f on silica gel as **6a**. However this second fraction had a weak absorption band in its IR spectrum at 820 cm^{-1} which was not in the IR spectrum of **6a**. Compound **5a** was identical (IR and UV spectra, mixture melting point) with the cyclized product from **4b**: NMR ($CDCl_3$) δ 1.07–2.03 (m, 15 H, aliphatic), 2.20 (d of d, 1 H, J = 11 Hz, J = 3 Hz, C(3)–H), 3.12 (t, 1 H, J = 10 Hz, C(15)–H), 3.30 (s, 3 H, OCH_3), 3.67 (d of d, 1 H, J = 9, 3 Hz, C(15)–H), 4.80 (s, 1 H, C(7–H) (note that the t centered at δ 3.12 and the s centered at 3.30 partially overlap); NMR (C_6H_6) δ 0.40–1.93 (m, 15 H, aliphatic), 2.09 (d of d, 1 H, J = 10, 2 Hz, C(3)–H), 2.95 (s, 3 H, OCH_3), 3.05 (t, 1 H, J = 10 Hz, C(15)–H), 3.67 (d of d, 1 H, J = 7, 3 Hz, C(15)–H), 4.43 (s, 1 H, C(7)–H) (note that the s centered at δ 2.95 and the t centered at 3.05 partially overlap).

Anal. Calcd for $C_{16}H_{22}Cl_4O$: C, 51.64; H, 5.96; Cl, 38.10. Found: C, 51.84; H, 6.15; Cl, 37.73.

An improved procedure for this conversion was developed. A solution of (*E*)-**6a** (51.1 mg, 0.13 mmol) and hydroquinone (5.4 mg, 0.05 mmol) in decalin (25 mL) under argon was heated at reflux for 5 h. The solution was allowed to cool to room temperature and then concentrated by rotary evaporation under oil pump vacuum. The residue was chromatographed on a preparative layer plate of silica gel, using benzene as eluent. A solid (33.9 mg) of mp 123–133 °C was isolated. Its IR was identical with that of previously prepared material. A second fraction of mp 111–122 °C was also collected to give a combined yield of 43 mg (84%).

Cyclization of (*E,Z*)-6b to 5b. The same procedure as used for the preparation of **5a** was followed substituting (*E,Z*)-**6b** for (*E*)-**6a**. This resulted in a 41% conversion to **5b**: UV (cyclohexane) end absorption 225 nm (770); IR (neat) 1610 (ClC=CCl) cm^{-1}; NMR (CCl_4) δ 0.60–2.00 (m, 15 H, aliphatic), 2.20 (d of d, 1 H, J = 10, 3 Hz, OCH_2CH), 3.20 (t, 1 H, J = 10 Hz, OCH), 3.73 (d of d, 1 H, J = 10, 3 Hz, OCH), 4.40 (s, 2 H, benzylic OCH_2), 4.70 (s, 1 H, CHCl), 7.23 (s, 5 H, aromatic); MS (14 eV) *m/e* 452 (0.01), 450 (0.04), 448 (0.07), 446 (0.09), 287 (0.59), 285 (0.90), 251 (0.56), 249 (1.00), 245 (0.51), 243 (0.46), 202 (0.42), 119 (0.45), 117 (0.45), 91 (0.63); (P) 446.0744 (calcd for $C_{22}H_{26}Cl_4O$, 446.0738).

A second cyclized product was also isolated (6% conversion): IR (neat) 1600 (ClC=CCl) cm^{-1}; NMR (CCl_4) δ 0.58–2.27 (m, 20 H), 3.48–3.83 (m, 2 H), 4.47 (s, 2 H), 4.77 (s, 0.5 H), 7.23 (s, 5 H).

Uncyclized (*E,Z*)-**6b** (40% recovery) was also isolated. This recovered material had identical ^1H NMR spectrum and R_f on silica gel with that of starting (*E,Z*)-**6b**. However, the recovered material showed a weak absorption band in the IR at 820 cm^{-1} which is not found in the IR spectrum of starting (*E,Z*)-**6b**.

Acknowledgments. The authors gratefully acknowledge support of this work by the Research Corporation and the Mobil Foundation. The authors thank Drs. R. B. Bates and W. Beavers for measuring the ^{13}C NMR spectra reported in this work and Drs. J. R. Duchek, S. Arora, and P. L. Johnson for assistance in the X-ray structure determination.

Registry No.—(*E*)-**3a**, 57745-82-1; (*Z*)-**3a**, 57745-83-2; (*E*)-**3b**, 66515-42-2; (*Z*)-**3b**, 66515-41-1; (*E*)-**3c**, 66515-40-0; (*Z*)-**3c**, 66515-39-7; (*E*)-**3d**, 66515-38-6; (*Z*)-**3d**, 66515-37-5; (*E*)-**4a**, 66515-51-3; (*Z*)-**4a**, 66515-50-2; (*E*)-**4b**, 66515-49-9; (*Z*)-**4b**, 66515-48-8; (*E*)-**4c**, 66515-47-7; (*Z*)-**4c**, 66515-46-6; (*E*)-**4d**, 66515-52-4; (*Z*)-**4d**, 66515-53-5; **5a**, 66515-45-5; **5b**, 66515-44-4; (*E*)-**6a**, 66551-67-5; (*E*)-**6b**, 66609-60-7; (*Z*)-**6b**, 66538-32-7; (*E*)-3,7-dimethyl-1-methoxy-2-octene 6,7-oxide, 63343-32-8; (*Z*)-3,7-dimethyl-1-methoxy-2-octene 6,7-oxide, 66515-43-3; (*E*)-3,7-dimethyl-1-methoxy-2,6-octadiene, 2565-82-4; (*Z*)-3,7-dimethyl-1-methoxy-2,6-octadiene, 2565-83-5; geraniol, 106-24-1.

Supplementary Material Available: A stereoscopic view of the packing of molecules in the unit cell (Figure 2) and tables of final atomic positional and thermal parameters, bond length, bond angle, torsion angle data, and structure factors for **5a** (Tables I–VI) (4 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Taken in part from the Ph.D. Dissertation of R. S. Sobczak, The University of Arizona, 1976; presented in part at the 172nd National Meeting of the American Chemical Society, San Francisco, Calif., Aug. 31, 1976, Abstract ORGN 75.
(2) E. J. Corey, M. Ohno, P. A. Vatakencherry, and R. B. Mitra, *J. Am. Chem. Soc.*, **83**, 1251 (1961); **86**, 478 (1964); J. McMurry and S. Isser, *ibid.*, **94**, 7132 (1972); R. A. Volkmann, G. C. Andrews, and W. S. Johnson, *ibid.*, **97**, 4777 (1975).
(3) G. Brieger, *J. Am. Chem. Soc.*, **85**, 3783 (1963).
(4) (a) V. A. Mironov, E. V. Sobolev, and A. N. Elizarova, *Tetrahedron*, **19**, 1939 (1963); (b) S. McLean and P. Haynes, *Tetrahedron Lett.*, 2385 (1964); (c) S. McLean and P. Haynes, *Tetrahedron*, **21**, 2329 (1965).
(5) For an application of this reaction see E. J. Corey and R. S. Glass, *J. Am. Chem. Soc.*, **89**, 2600 (1967).
(6) G. Brieger and D. R. Anderson, *J. Org. Chem.*, **36**, 243 (1971). See also J. C. L. Tam and P. Yates, *J. Chem. Soc., Chem. Commun.*, 739 (1975).
(7) G. Kresze, G. Schulz, and H. Walz, *Justus Liebigs Ann. Chem.*, **666**, 45 (1963); S. McLean and P. Haynes, *Tetrahedron*, **21**, 2313 (1965); E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Am. Chem. Soc.*, **91**, 5675 (1969); E. J. Corey, U. Koelliker, and J. Neuffer, *ibid.*, **93**, 1489 (1971); B. M. Trost, R. M. Cory, and (in part) P. H. Scudder and H. B. Neubold, *ibid.*, **95**, 7813 (1973); L. Paquette and M. J. Wyvratt, *ibid.*, **96**, 4671 (1974); D. McNeil, B. R. Vogt, J. J. Sudol, S. Theodoropulos, and E. Hedaya, *ibid.*, **96**, 4673 (1974); C. Moberg and M. Nilsson, *Tetrahedron Lett.*, 4521 (1974).
(8) W. R. Roth, *Tetrahedron Lett.*, 1009 (1964); S. McLean, C. J. Webster, and R. J. D. Rutherford, *Can. J. Chem.*, **47**, 1555 (1969); R. B. Woodward and R. Hoffmann, "The Conservation of Molecular Orbital Symmetry", Verlag Chemie-Academic Press, Weinheim, W. Germany 1970, pp 123–124.
(9) (a) R. A. Hailing, Ph.D. Thesis, Purdue University, 1965; *Diss. Abstr. B*, **27**, 409 (1966); (b) R. P. Levek, Ph.D. Thesis, Purdue University, 1967; Diss. *Abstr. B*, **28**, 2775 (1968); (c) V. Mark and E. D. Weil, *J. Org. Chem.*, **36**, 676 (1971); (d) R. Alexander and D. I. Davies, *J. Chem. Soc., Perkin Trans. 1*, 83 (1973).
(10) Reference 3a, footnote 28; J. de Haan and H. Kloosterziel, *Recl. Trav. Chim. Pays-Bas*, **84**, 1594 (1965); J. W. de Haan and H. Kloosterziel, *ibid.*, **87**, 298 (1968); W. C. Herndon and J. M. Manion, *J. Org. Chem.*, **33**, 4504 (1968); V. A. Mironov, V. S. Pashegorova, T. M. Fadeeva, and A. A. Akhrem, *Tetrahedron Lett.*, 3997 (1968); V. A. Mironov, A. P. Ivanov, Ya. M. Kimelfeld, L. I. Petrovskaya, and A. A. Akhrem, *ibid.*, 3347 (1969); J. M. E. Krekels, J. W. de Haan, and H. Kloosterziel, *ibid.*, 2751 (1970); L. M. Dané, J. W. de Haan, and H. Kloosterziel, *ibid.*, 2755 (1970); S. McLean and D. M. Findlay, *Can. J. Chem.*, **48**, 3107 (1970); M. A. M. Boersma, J. W. de Haan, H. Kloosterziel, and L. J. M. van de Ven, *Chem. Commun.*, 1168 (1970); A. de Meijere, and L.-U. Meyer, *Angew. Chem., Int. Ed., Engl.*, **12**, 858 (1973); M. R. Willcott III and I. M. Rathburn III, *J. Am. Chem. Soc.*, **96**, 938 (1974); R. A. Clark, W. J. Hayles, and D. S. Youngs, *ibid.*, **97**, 1966 (1975).
(11) N. K. Hamer and M. E. Stubbs, *Tetrahedron Lett.*, 3531 (1972); M. Oda and R. Breslow, *ibid.*, 2537 (1973).
(12) (a) E. K. Fields, *J. Am. Chem. Soc.*, **76**, 2709 (1954); (b) H. E. Ungnade and E. T. McBee, *Chem. Rev.*, **58**, 249 (1958); (c) W. L. Dilling, Ph.D. Thesis,

Purdue University, 1962; *Diss. Abstr. B*, **27**, 1083 (1966); (d) J. Sauer and H. Wiest, *Angew. Chem., Int. Ed. Engl.*, **1**, 269 (1962); (e) K. L. Williamson, Y.-F. L. Hsu, R. Lacko, and C. H. Youn, *J. Am. Chem. Soc.*, **91**, 6129 (1969); (f) E. T. McBee, E. P. Wesseler, D. L. Crain, R. Hurnaus, and T. Hodgins, *J. Org. Chem.*, **37**, 683 (1972); (g) V. Mark, *ibid.*, **39**, 3179 (1974); (h) V. Mark, *ibid.*, **39**, 3181 (1974).
(13) J. Sauer, *Angew. Chem., Int. Ed. Engl.*, **6**, 16 (1967).
(14) E. T. McBee, J. O. Stoffer, and H. P. Braendlin, *J. Am. Chem. Soc.*, **84**, 4540 (1962).
(15) J. D. O'Drobinak, M. S. Thesis, Purdue University, 1960; E. T. McBee, U.S. Patent 3 317 497 (1967); *Chem. Abstr.*, **67**, 21492k (1967).
(16) (a) V. Mark, *Tetrahedron Lett.*, 295 (1961); (b) H. V. Brachel, German Patent 1 099 528; *Chem. Abstr.*, **56**, 3372 (1962); German Patent 1 103 327; *Chem. Abstr.*, **56**, 7175 (1962); German Patent 1 103 328 and 1 104 503; *Chem. Abstr.*, **56**, 7176 (1962); (c) V. Mark, Belgian Patent 615 327; *Chem. Abstr.*, **59**, 1503 (1963); (d) V. Mark, R. E. Wann, and H. C. Godt, Jr., *Org. Synth.*, **43**, 90 (1963); (e) V. Mark and J. R. Van Wazer, *J. Org. Chem.*, **29**, 1006 (1964); (f) S. D. Volodkovich, N. N. Mel'nikov, B. A. Khaskin, and S. I. Shestakova, *Zh. Org. Khim.*, **3**, 1229 (1967); *Chem. Abstr.*, **67**, 99681r (1967).
(17) P. Bruck, D. Thompson, and S. Winstein, *Chem. Ind. (London)*, 405 (1960); P. G. Gassman and P. G. Pape, *J. Org. Chem.*, **29**, 160 (1964); C. F. Wilcox, Jr., and J. G. Zajecek, *ibid.*, **29**, 2209 (1964); R. C. Fort, Jr., and P. v. R. Schleyer in "Advances in Alicyclic Chemistry", Vol. 1, H. Hart and G. J. Karabatsos, Ed., Academic Press, New York, N.Y., 1966, p 283; P. G. Gassman and J. L. Marshall, *Org. Synth.*, **48**, 68 (1968); P. G. Gassman, D. H. Aue, and D. S. Patton, *J. Am. Chem. Soc.*, **90**, 7271 (1968); C. W. Jefford and W. Broeckx, *Helv. Chim. Acta*, **54**, 1479 (1971).
(18) M. Mousseron-Canet, M. Mousseron, and C. Levallois, *Bull. Soc. Chim. Fr.*, 297 (1964).
(19) R. F. Bacon, *Chem. Zentralblat.*, II, 945 (1908).
(20) Reinvestigation of the products formed by heating **4c**, subsequent to the preparation of **5b** from **6b**, showed that a trace of material was present which had the same R_f on silica gel as **5b**.
(21) ORTEP, C. K. Johnson, Oak Ridge National Laboratory, Oak Ridge, Tenn.
(22) E. Ziegler, *Fresenius' Z. Anal. Chem.*, **213**, 9 (1965).
(23) G. E. Hawkes, R. A. Smith, and J. D. Roberts, *J. Org. Chem.*, **39**, 1276 (1974).
(24) D. T. Clark, W. J. Feast, M. Foster, and D. Kilcast, *Nature (London), Phys. Sci.*, **236**, 107 (1972).
(25) The range reported for the chemical shift of a doubly allylic dichloromethylene carbon (after conversion to ppm downfield from tetramethylsilane) is 80.8–86.8 ppm and that of a doubly allylic chloromethine carbon is 73.8–79.8 ppm.
(26) D. M. Grant and E. G. Paul, *J. Am. Chem. Soc.*, **86**, 2984 (1964); L. P. Lindeman and J. Q. Adams, *Anal. Chem.*, **43**, 1245 (1971).
(27) Isomerization of 5-alkyl-1,2,3,4,5-pentachloro-1,3-cyclopentadienes at elevated temperatures has been previously reported and [1,5]sigmatropic rearrangement of chlorine was suggested to account for this isomerization.[9b,d] However, in a related isomerization homolysis of the doubly allylic C–Cl bond was suggested followed by recombination of the two radicals.[9c]
(28) "International Tables for X-Ray Crystallography", Vol. III, The Kynoch Press, Birmingham, England, 1962; A. C. Macdonald and J. Trotter, *Acta Crystallogr.*, **19**, 456 (1965); R. Destro, G. Filippini, C. M. Gramaccioli, and M. Simonetta, *Tetrahedron Lett.*, 5955 (1968); G. Filippini, C. M. Gramaccioli, C. Rovere, and M. Simonetta, *Acta Crystallogr., Sect. B.*, **28**, 2869 (1972); C. E. Pfluger, R. L. Harlow, and S. H. Simonsen, *J. Cryst. Mol. Struct.*, **3**, 277 (1973). Those calculated from the atomic coordinates reported for isolongifolene epoxide: J. A. McMillan and I. C. Paul, *Tetrahedron Lett.*, 419 (1974).
(29) E. T. McBee and D. K. Smith, *J. Am. Chem. Soc.*, **77**, 389 (1955).
(30) Recently nonstereospecific Diels–Alder reactions have been reported for hexachlorocyclopentadiene and 5-methyl-1,2,3,4,5-pentachloro-1,3-cyclopentadiene.[12g] Steric hindrance was suggested as the basis for these results.[12g,h]
(31) K. L. Williamson and Y.-F. L. Hsu, *J. Am. Chem. Soc.*, **92**, 7385 (1970).
(32) Isolongifolene is a natural product which was first obtained by acid-catalyzed isomerization of longifolene [U. R. Nayak and S. Dev, *Tetrahedron*, **8**, 42 (1960)] and has been synthesized from camphene-1-carboxylic acid [R. R. Sobti and S. Dev, *Tetrahedron Lett.*, 2893 (1967); R. R. Sobti and S. Dev, *Tetrahedron*, **26**, 649 (1970)].
(33) H. Bohme, "Organic Syntheses", Collect. Vol. III, Wiley, New York, N.Y., 1957, p 619.
(34) H. G. Cook, J. D. Ilett, B. C. Saunders, G. J. Stacey, H. G. Watson, I. G. E. Wilding, and S. J. Woodcock, *J. Chem. Soc.*, 2921 (1949).
(35) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. A*, **27**, 368 (1971).
(36) A. Zalkin, FORDAP, a Fourier program, Lawrence Radiation Laboratory, Livermore, Calif.
(37) D. T. Cromer and J. B. Mann, *Acta Crystallogr., Sect. A*, **24**, 321 (1968).

Synthesis, Photolysis, and Pyrolysis of 10-Substituted *exo*-3,4,5-Triazatricyclo[5.2.1.$0^{2,6}$]dec-3-enes. Preparation of 8-Substituted *exo*- and *endo*-3-Aryl-3-azatricyclo[3.2.1.$0^{2,4}$]octanes

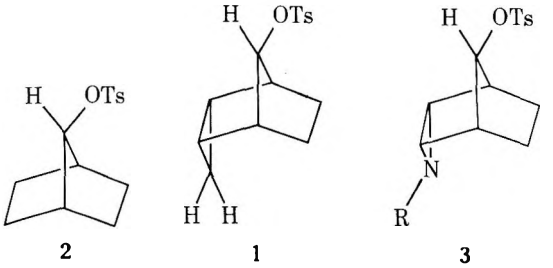
Paul G. Gassman* and John G. Schaffhausen

Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

Received February 2, 1978

A systematic study of the addition of aryl azides to 7-substituted bicyclo[2.2.1]hept-2-enes to yield 10-substituted 5-aryl-*exo*-3,4,5-triazatricyclo[5.2.1.$0^{2,6}$]dec-3-enes has been carried out. The influence of substituents in the 10 position on the pyrolysis and photolysis of these triazatricyclodecenes has been studied. A variety of 8-substituted 3-aryl-3-azatricyclo[3.2.1.$0^{2,4}$]octanes have been prepared.

Perhaps one of the most quoted examples of neighboring group participation in solvolysis reactions is that of the *endo*-cyclopropyl moiety of **1**.[1] The 10^{14} rate difference[2] between **1** and **2**, which results from the vigorous neighboring



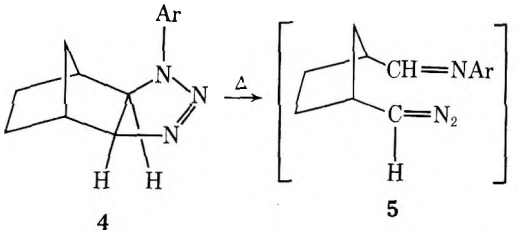
2 **1** **3**

group participation of the strained 2–4 bond of **1**, is among the largest effects recorded for participation by a carbon–carbon bond. In view of this dramatic influence of the cyclopropane portion of **1**, the question of the degree of participation which might be provided by the carbon–carbon bond of similarly situated three-membered heterocyclics became of interest. As part of a general study of participation by the carbon–carbon bond of epoxides, episulfides, and aziridines, we developed a need for a synthetic route to **3**. This paper provides the details of our preliminary investigation of the synthesis of *exo*- and *endo*-3-aryl-3-azatricyclo[3.2.1.$0^{2,4}$]octanes via the photolysis and pyrolysis of 10-substituted 5-aryl-*exo*-3,4,5-triazatricyclo[5.2.1.$0^{2,6}$]dec-3-enes.

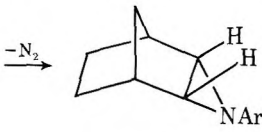
Although numerous methods exist for the synthesis of aziridines,[3] most of those which are available do not lend themselves to the preparation of 8-substituted 3-aryl-*endo*-3-azatricyclo[3.2.1.$0^{2,4}$]octanes. The single approach which appeared to be attractive involved the addition of aryl azides to bicyclo[2.2.1]heptene derivatives[4,5] followed by either photolysis[5–7] or pyrolysis[6a,6b,7b,8] of the resulting 5-aryl-*exo*-3,4,5-triazatricyclo[5.2.1.$0^{2,6}$]dec-3-enes. While the photochemical loss of nitrogen from the exo triazolines gave only exo aziridines, the thermal process resulted in the formation

0022-3263/78/1943-3214$01.00/0

of both exo and endo aziridines. The unusual formation of endo aziridines was rationalized as occurring via thermal opening of **4** to give **5**, followed by subsequent conversion of **5** into **6** with loss of nitrogen.[7b,8h-k,8m] Although extensive



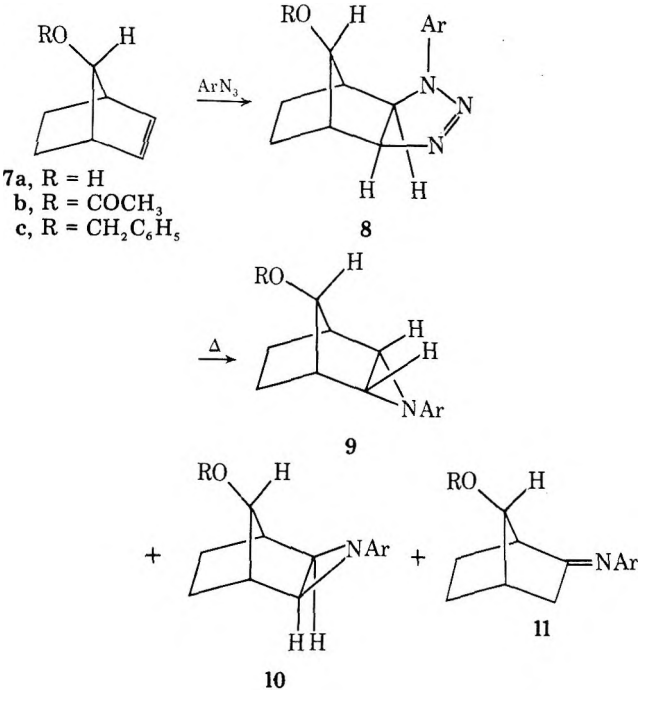
4 **5**



6

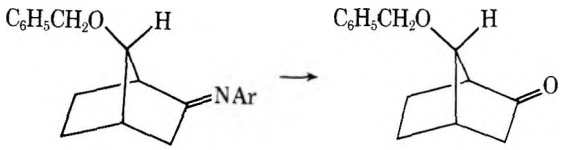
literature exists on the 3-azatricyclo[3.2.1.0^{2,4}]octanes,[5-8] relatively little is known about 8-substituted variants. This is particularly true for derivatives in which the aziridine moiety is endo. Unfortunately, of the three examples which were known,[6b,7a,9] none was suitable for our purposes. Thus, we carried out the following study.

In principle, the most straightforward approach to precursors of **3** would be the conversion of **7** into **8** and subsequent thermolysis of **8** to give mixtures of **9**, **10**, and **11**. Halton and



7a, R = H
b, R = COCH$_3$
c, R = CH$_2$C$_6$H$_5$

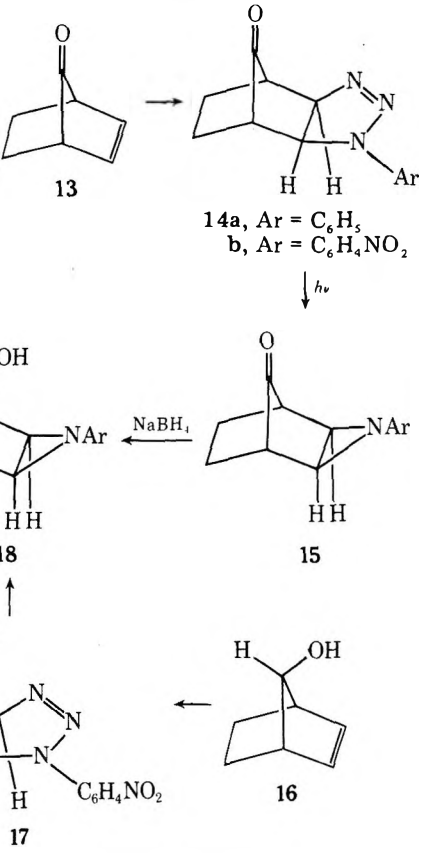
Woolhouse had previously examined the addition of phenyl azide to **7a** to give **8a** (Ar = C_6H_5) and the subsequent pyrolysis and photolysis of this triazoline.[6b] They found that while the 1,3-dipolar addition offered no problems, both pyrolysis and photolysis gave only the exo aziridine, **10a** (Ar = C_6H_5). We were able to confirm the general findings of Halton and Woolhouse on **7a**. In the initial part of our investigation, we utilized *p*-nitrophenyl azide instead of phenyl azide due to the more rapid 1,3-dipolar addition of the *p*-nitro derivative.[10] In view of the failure of **8a** (Ar = C_6H_5) to yield **9**, we decided to investigate two derivatives of **7a**. Both the acetyl derivative,[11] **7b**, and the *O*-benzylated material, **7c**, were treated with *p*-nitrophenyl azide to yield **8b** and **8c** (Ar = *p*-$O_2NC_6H_4$) in 59 and 69% yields, respectively.[12] Pyrolysis of **8b** gave only trace amounts of **10b**.[13] However, similar pyrolysis of **8c** gave 26% of **10c**[13] in addition to 24% of **12**. Presumably, **12** arose from **11c** as a result of hydrolysis under the



11c **12**

workup conditions. No indication of any endo aziridine could be detected in the thermolysis of either **8b** or **8c**. The results obtained with **8b** and **8c**, while demonstrating the existence of a subtle substituent effect, indicated that anti substituents in the 10-position of the exo-3,4,5-triazatricyclo[5.2.1.0^{2,6}]-dec-3-ene skeleton would be ineffective in promoting the formation of an endo-aziridine group.

In a second approach to the synthesis of the 8-substituted *endo*-3-aryl-3-azatricyclo[3.2.1.0^{2,4}]octane structure, we utilized functionality in the 10 position of the precursor which would provide a dramatically different electronic environment. Starting with the readily available bicyclo[2.2.1]hept-2-en-7-one (**13**),[14] we found that phenyl azide and *p*-nitrophenyl azide gave the 1,3-dipolar adducts **14a** and **14b** in 50



13

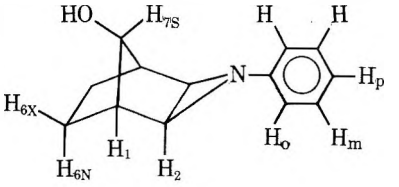
14a, Ar = C_6H_5
b, Ar = $C_6H_4NO_2$

18 **15**

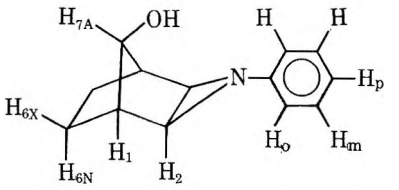
17 **16**

and 41% yield, respectively. Photolysis of **14a** gave 64% of **15a**, while irradiation of **14b** gave only small amounts of **15b** in addition to large amounts of extensively decomposed material.[15] Extensive studies of the pyrolysis of **14a** and **14b**, both neat and in solution, indicated that these thermal fragmentations gave only traces of the corresponding exo aziridines accompanied by extensive decomposition.[16,17] Since the presence of the carbonyl function did not promote the formation of the endo aziridine, and since it made the system more prone to decomposition, the role of a syn-hydroxyl function was explored in the hope that the steric influences of this group would promote the formation of the desired tricyclic skeleton. On the basis of earlier studies,[5] it might have been anticipated that the syn-hydroxyl group of bicyclo[2.2.1]hept-2-en-*syn*-7-ol (**16**)[18] would sterically inhibit

Table I. Least-Squares Slopes of Chemical Shifts vs. Molar Ratio of Eu(fod)$_3$ to Alcohol for 10a and 18a



10a



18a

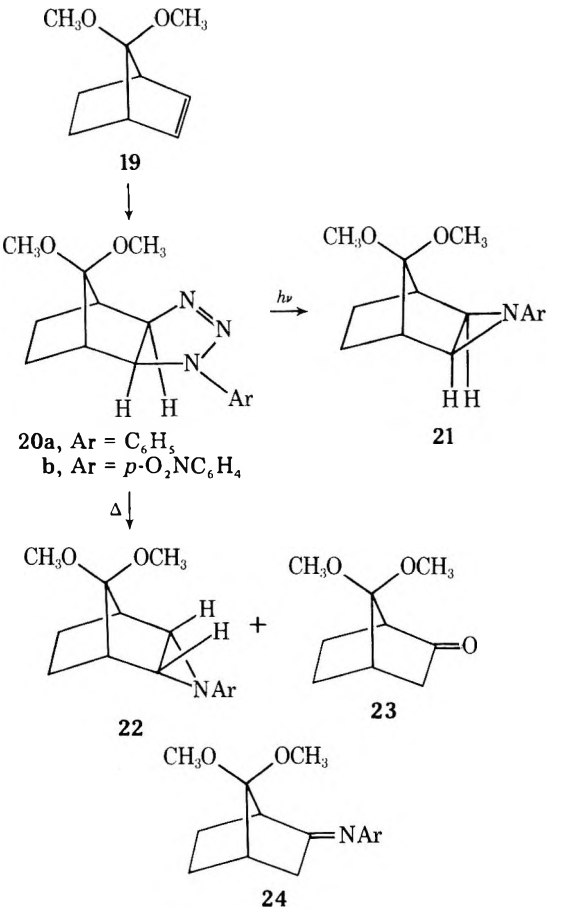
Proton	least-squares slope 10a	18a
H_1	11.35	8.98
H_2	4.21	4.65
H_{6N}	7.10	2.95
H_{6X}	12.88	3.06
H_{7S}	24.5	
H_{7A}		18.12
H_o	0.79[a]	2.97
H_m	0.79[a]	0.90[b]
H_p	0.79[a]	0.90[b]

[a] No distinction occurred between the ortho, meta, and para protons in terms of the induced chemical shift. [b] The meta and para protons were comparably shifted.

addition of the azide. However, **16** reacted readily with *p*-nitrophenyl azide to give a 30% yield of exo triazoline (**17**). Pyrolysis of **17** gave a 30% yield of **18b.** No endo aziridine could be detected.

The aziridines derived from **13** and **16** were readily interrelated. Reduction of **15a** and **15b** with sodium borohydride led to **18a** and **18b** in 71 and 82% yields, respectively. In order to firmly establish the stereochemical relationship between **10a** and **18a** a lanthanide shift study was carried out. Table I gives the least-squares slopes from a plot of chemical shift vs. the molar ratio of shift reagent to the alcohol. The data would indicate that the shift reagent complexed more tightly with **10a** than the **18a.** Presumably, this is due in part to the greater steric congestion in the vicinity of the hydroxyl group of **18a.**

The lack of formation of endo aziridines from bicyclo[2.2.1]heptene derivatives, which possessed immediate hydroxyl group precursors in the 7 position, prompted us to evaluate the use of ketals of **13.** Both phenyl azide and *p*-nitrophenyl azide added to 7,7-dimethoxybicyclo[2.2.1]heptene (**19**)[19] to give **20a** and **20b** in 58 and 65% yields, respectively. In apparent confirmation of our earlier findings on the addition of azides to **16, 19** gave only exo triazolines, as established by NMR spectroscopic studies. Photochemical loss of nitrogen from **20a** gave a 76% yield of **21a.** In contrast to the exclusive formation of exo aziridine in the irradiation of **20a,** pyrolysis of **20b** gave 22% of **22b,**[20] 53% of **23,** and considerable *p*-nitroaniline. No exo aziridine was detected. Thermolysis of **20a** gave only small amounts of **22a.** Again, none of the exo-aziridine **21a** could be found. Thus, the presence of the syn-methoxyl function appeared to be a strong endo-directing influence. The formation of **23** and *p*-nitroaniline from **20b** presumably resulted from the hydrolysis of **24** during the workup of the reaction.



19

20a, Ar = C_6H_5
b, Ar = *p*-$O_2NC_6H_4$

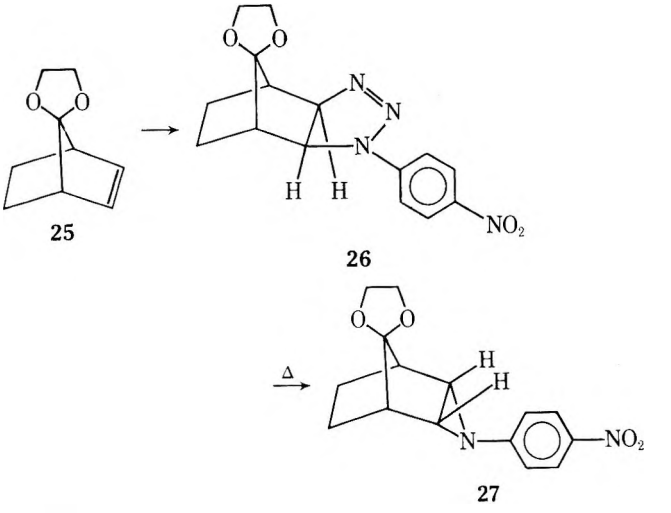
21

22

23

24

In a manner similar to that described above, bicyclo[2.2.1]-hept-2-ene-7-spiro-2′,5′-dioxolane (**25**)[21] gave 79% of **26** on treatment with a slight excess of *p*-nitrophenyl azide. Thermolysis of **26** at 190–200 °C gave a 21% yield of **27.** No exo



25

26

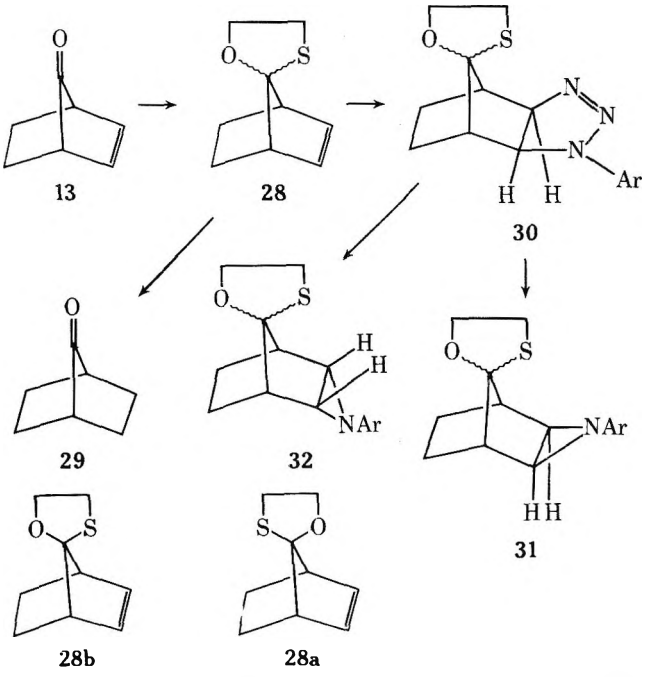
27

aziridine was detected. It is intriguing that the ketal function, even when tied into a dioxolane ring, exerts a strong endo directing influence. Attempts to hydrolyze the ketal functions of **22** and **27** were not successful. Under even very mild conditions, complex mixtures of products were obtained in which the aziridine moiety was no longer intact.

In view of the extreme acid sensitivity of **22** and **27,** it was felt that nonacidic conditions would be necessary for the preparation of our desired system. Thus, the 1,3-oxathiolane group appeared to be an attractive protecting moiety for a carbonyl function, which eventually could be converted to a hydroxyl function. 1,3-Oxathiolanes are readily formed from ketones.[22] Although such oxathiolanes are reasonably stable,

they have been restored to the corresponding ketone either through the use of Raney nickel in acetone (or benzene)[23] or by the recently developed use of chloramine-T.[24]

Treatment of **13** with 2-mercaptoethanol gave **28** as a 3:1 mixture of isomers in 50% yield. Treatment of the 3:1 mixture of **28a** and **28b** with bis(benzonitrile)palladium dichloride

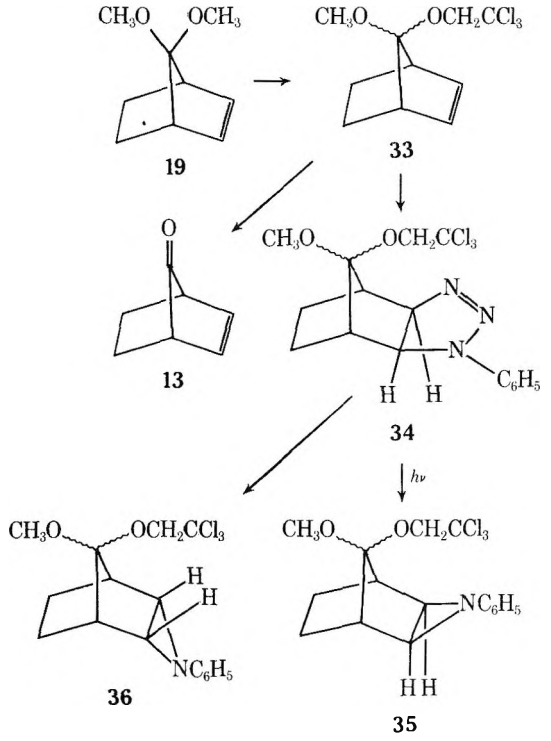


resulted in the immediate precipitation of an orange-red solid. Analysis of the remaining solution by vapor phase chromatography showed only the major isomer. Because of its low-lying d orbitals, sulfur is a much better ligand than is oxygen. Hence, it was assumed that the minor isomer, which formed the complex, had the sulfur syn to the double bond as shown in **28b** which should make **28b** a reasonable bidentate ligand. The major isomer would then possess structure **28a.** Because of the losses which would have occurred in separating the isomers, the mixture of **28a** and **28b** was used for subsequent steps. When **28** was treated with W-2 Raney nickel, a facile conversion of the oxathiolane to the ketone resulted. Unfortunately, this was accompanied by extensive reduction of the double bond to give **29** as the major product. In contrast, chloramine-T readily converted **28** back to **13.** Thus, it appeared that derivatives of **28** should serve as reasonable precursors of the desired system, **3.**

Azide addition to **28** was relatively slow and gave low yields of triazolines; *p*-nitrophenyl azide and phenyl azide added in 21 and 19% yields, respectively, even after days at 50–60 °C. NMR analysis indicated that both adducts had the stereochemistry shown in **30.** Irradiation of **30** (Ar = C_6H_5) gave an 80% yield of **31.** Pyrolysis of **30** (Ar = $C_6H_4NO_2$) gave a 20% yield of **32.** Whereas the NMR of **31** showed the aziridinyl hydrogens as a singlet at δ 2.4, the aziridinyl hydrogens of **32** appeared as a triplet at δ 3.1 (J = 1.8 Hz). These spectral data and analogy to the examples presented above established the stereochemistry as shown. Various attempts at converting **32** to the corresponding ketone were unsuccessful. This was surprising in view of the ease with which **28** had been converted into **13** and **29.**

The data presented thus far strongly support the contention that bulky substituents in the syn position at C-10 of the *exo*-3,4,5-triazatricyclo[5.2.1.0^{2,6}]dec-3-enes promote the formation of endo aziridines on thermolysis. Obviously, the failure of **32** to yield the desired ketone was disconcerting. Therefore one additional approach was used in an attempt to reach our ultimate goal. This utilized the approach of Isador and Carlson,[25] which consists of protecting the carbonyl function as a mono-2,2,2-trichloroethyl ketal, followed by deketalization with activated zinc in tetrahydrofuran.

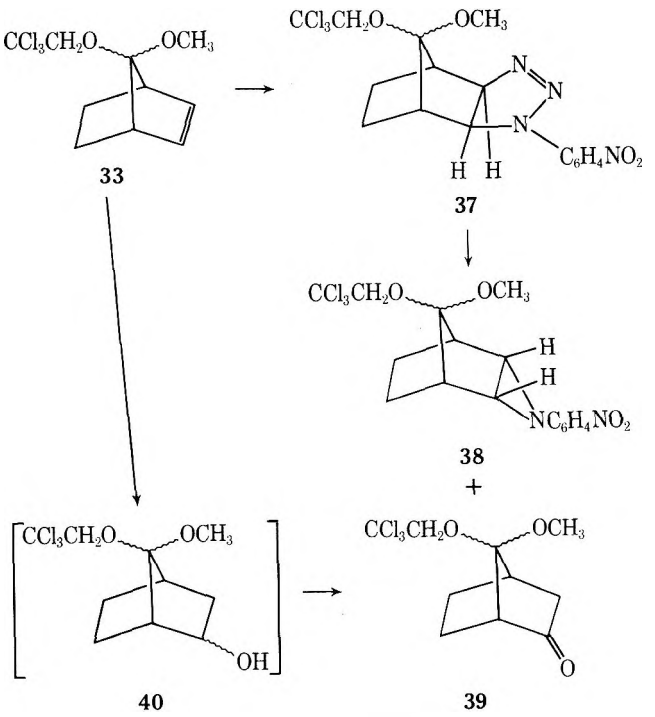
Treatment of **19** with 1.5 equiv of 2,2,2-trichloroethanol and a catalytic amount of *p*-toluenesulfonic acid gave an 82% yield of **33.** NMR spectral analysis indicated that **33** was a 1:1



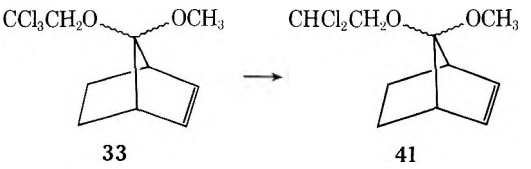
mixture of the two possible stereoisomers. In view of the difficulties encountered in the attempted deketalization of **32,** a thorough investigation of the deketalization of **33** was carried out. It was found that activated zinc dust,[26] precipitated zinc dust,[27] and zinc–copper couple[28] each quantitatively converted **33** back to **13.** These various forms of zinc required 8, 1.5, and 26 h, respectively, in order to afford a quantitative conversion.

Treatment of **33** with phenyl azide for 2 weeks at 50–60 °C gave a 71% yield of **34.** Photolysis of **34** gave **35** in 59% yield. Thermolysis of **34** gave 36% of **36.** Whereas the NMR spectrum of **35** showed the aziridinyl hydrogen as a singlet at δ 2.52, the NMR spectrum of **36** had the aziridinyl proton as a triplet (J = 2 Hz) at δ 2.80.[29] The addition of *p*-nitrophenyl azide to **33** gave 79% of the mixed ketal isomers of **37.** Thermolysis of **37** gave 19% of **38** and 63% of **39.** Presumably, **39** was formed from the corresponding *p*-nitroaniline-derived imine. The structure of **39** was established through comparison with an authentic sample prepared by the hydroboration–oxidation of **33** to give **40,** followed by direct oxidation of crude **40** to **39** with chromium trioxide–pyridine in methylene chloride (Collins reagent).

Numerous attempts at deketalization of **36** and **38** proved unsuccessful, in spite of the ease with which **33** had been converted to **13.** Activated zinc,[26] precipitated zinc,[27] and precipitated magnesium[27] all failed to deketalize **36** and/or **38.** In every case starting material was recovered unchanged. The failure of these deketalization reactions was not able to be easily rationalized. On the possibility that the metal might be complexing with the aziridine nitrogen, large excesses of metal were used. However, this was also ineffective. In an extreme test, refluxing of **38** in tetrahydrofuran with an excess of highly active precipitated zinc[27] failed to promote deketalization. In order to determine whether this resistance to deketalization was due to an abnormally high reduction potential for **36,** the half-wave potentials of **33** and **36** were



measured polarographically in 0.01 N tetra-*n*-butylammonium perchlorate in anhydrous dimethyl formamide at a dropping mercury electrode. The olefin **33** gave a value of −1.73 V, while the aziridine gave a slightly lower value of −1.53 V. Clearly, **36** should have deketalized more readily than **33**. Experimentally, this was obviously not the case! Preparative electrochemical reduction of **33** gave only **41**. This was



presumably due to a one-electron transfer to give a radical intermediate which abstracted hydrogen from the solvent. The dichloro derivative, **41**, was extremely resistant to further reduction. It had a half-wave potential of greater than −2.6 V under the conditions specified above.

In summary, we have developed useful routes to 8-substituted exo- and endo-3-aryl-3-azatricyclo[3.2.1.$0^{2,4}$]octanes. We are continuing to seek ways for the conversion of these interesting compounds into **3**.

Experimental Section[30]

7-*anti*-Hydroxybicyclo[2.2.1]hept-2-ene (7a). This alcohol was prepared stereospecifically in 9% overall yield (three steps) from bicyclo[2.2.1]hepta-2,5-diene by literature[31] methods, mp 110–113 °C [lit.[31] mp 117–118 °C]. Reduction of ketone **13** also afforded **7a** in 89% crude yield; low-temperature recrystallization from hexane afforded pure **7a**.

Phenyl Azide. A literature route[32] was used to prepare phenyl azide in 51% distilled yield, bp 44–47 °C (4 mm) [lit.[32] bp 49–50 °C (5 mm)].

5-Phenyl-10-*anti*-hydroxy-3,4,5-*exo*-triazatricyclo-[5.2.1.$0^{2,6}$]-dec-3-ene (8a). Using the literature method,[6b] **8a** was prepared in 59% yield. Three recrystallizations from benzene–chloroform gave **8a** as white crystals, mp 160.0–160.5 °C [lit.[6b] mp 187–188 °C]; spectra were identical with those published by Halton and Woolhouse[6b] [see preparation of **10a** (Ar = C_6H_5) for further comment on melting point differences].

Photolysis of 8a. Preparation of 3-Phenyl-8-*anti*-hydroxy-3-*exo*-azatricyclo[3.2.1.$0^{2,4}$]octane (10a, Ar = C_6H_5). Photolysis[6b] of crude **8a** gave **10a** (Ar = C_6H_5) in 47% yield after recrystallization. After two further recrystallizations, **10a** was obtained as fine, colorless needles, mp 121–122 °C [lit.[6b] mp 146–147 °C]. The 25–27 °C differences in melting point between the samples of **8a** and **10a** (Ar = C_6H_5) prepared here and those prepared previously must be due to inaccuracies in the melting point determinations of Halton and Woolhouse,[6b] since the compounds were both spectrally identical with the published data.

7-*anti*-Benzyloxybicyclo[2.2.1]hept-2-ene (7c).[33] A mixture of 2.7 g (24.5 mmol) of **7a** and 3.53 g (73.5 mmol) of 50% sodium hydride in mineral oil in 20 mL of anhydrous dimethyl formamide was allowed to stir for 3 h. Benzyl bromide (8.1 g, 49 mmol) was added carefully. After 1 h, 10 mL of additional dimethyl formamide was added to facilitate solution. Ether and methanol were then added and the mixture was extracted with water. The organic layer was dried over $MgSO_4$, filtered, and concentrated. Distillation gave 4.55 g (93%) of **7c** as a colorless oil, bp 85 °C (0.15 mm).

7-*anti*-Acetoxybicyclo[2.2.1]hept-2-ene (7b).[34] Esterification of **7a** with acetic anhydride in pyridine afforded **7b** in 68% yield: bp 83 °C (20 mm); NMR ($CDCl_3$) δ 6.0 (2 H, t, J = 2 Hz), 4.6 (1 H, br s), 2.7 (2 H, m), 2.0 (3 H, s), 1.7 (2 H, m), 1.0 (2 H, m).

***p*-Nitrophenyl Azide.** In analogy to the procedure used for the preparation of *o*-nitrophenyl azide,[36] *p*-nitrophenyl azide was prepared from *p*-nitroaniline and sodium nitrite in 87% yield (after recrystallization), mp 69–70 °C [lit.[36] mp 70 °C].

5-(4-Nitrophenyl)-10-*anti*-benzyloxy-3,4,5-*exo*-triazatricyclo[5.2.1.$0^{2,6}$]dec-3-ene (8c). A solution of 4.47 g (22 mmol) of **7c** and 3.85 g (23.5 mmol) of *p*-nitrophenyl azide in the minimum amount of carbon tetrachloride was allowed to stand in the dark for several days. Filtration then afforded 5.60 g (69%) of **8c** (Ar = $C_6H_4NO_2$) as a yellow solid. Recrystallization from chloroform–hexane gave an analytical sample: mp 180–182 °C dec; NMR (Me_2SO-d_6) δ 8.30 (2 H, d, J = 9 Hz), 7.48 (2 H, d, J = 9 Hz), 7.28 (5 H, s), 4.84 (1 H, d, J = 10 Hz), 4.40 (2 H, s), 4.03 (1 H, d, J = 10 Hz), 2.75 (2 H, m), 1.2–2.2 (4 H, m).

Anal. Calcd for $C_{20}H_{20}N_4O_3$: C, 65.92; H, 5.53; N, 15.37. Found: C, 65.83; H, 5.61; N, 15.41.

5-(4-Nitrophenyl)-10-*anti*-acetoxy-3,4,5-*exo*-triazatricyclo[5.2.1.$0^{2,6}$]dec-3-ene (8b). A solution of 1.0 g (6.6 mmol) of **7b** and 1.13 g (6.9 mmol) of *p*-nitrophenyl azide in the minimum amount of carbon tetrachloride was allowed to stir in the dark. After 2 days, 0.46 g (22%) of **8b** was removed by filtration; after 2 weeks, the total yield was 0.77 g (59%). An analytical sample was obtained after two recrystallizations from cyclohexane–benzene: mp 185–186 °C dec; NMR (Me_2SO-d_6) δ 8.25 (2 H, d, J = 10 Hz), 7.50 (2 H, d, J = 10 Hz), 4.87 (1 H, d, J = 11 Hz), 4.23 (1 H, m), 4.08 (2 H, d, J = 11 Hz), 2.2–2.8 (2 H, m), 1.95 (3 H, s), 1.2–2.4 (4 H, m).

Anal. Calcd for $C_{15}H_{16}N_4O_4$: C, 56.96; H, 5.10; N, 17.71. Found: C, 57.00; H, 5.06; N, 17.73.

Thermolysis of 8c. Preparation of 3-(4-Nitrophenyl)-8-*anti*-benzyloxy-3-*exo*-azatricyclo[3.2.1.$0^{2,4}$]octane (10c) and 7-*anti*-Benzyloxybicyclo[2.2.1]heptan-2-one (12). Triazoline **8c** (4.77 g, 13 mmol) was heated (neat) at 190 °C in a round-bottomed flask until nitrogen evolution was complete. The cooled residue was chromatographed on 200 g of neutral alumina with benzene–chloroform. Eluting first was a mixture of **10c** and **12**. Recrystallization from benzene–hexane gave 1.14 g (26%) of **10c** (Ar = $C_6H_4NO_2$) as yellow crystals. An analytical sample was obtained after two further recrystallizations: mp 148–149 °C; NMR ($CDCl_3$) δ 8.12 (2 H, d, J = 9 Hz), 7.37 (5 H, s), 6.97 (2 H, d, J = 9 Hz), 4.50 (2 H, s), 3.95 (1 H, m), 2.70 (2 H, m), 2.58 (2 H, s), 1.1–2.2 (4 H, m).

Anal. Calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.50; H, 6.08; N, 8.17.

The oily residue from the above recrystallization (0.67 g, 24%) gave **12** as a yellow oil on distillation, bp 135–140 °C (0.75 mm). An analytical sample of **12** was prepared by preparative VPC (6 ft × 0.25 in. 10% SE-30 on 45/60 Chromosorb W column at 175 °C): NMR ($CDCl_3$) δ 7.37 (5 H, s), 4.56 (2 H, s), 3.94 (1 H, m), 2.67 (2 H, m), 1.3–2.4 (6 H, m).

Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.74; H, 7.46. Found: C, 77.61; H, 7.51.

p-Nitroaniline was also isolated.

Thermolysis of 8b. Preparation of 3-(4-Nitrophenyl)-8-*anti*-acetoxy-3-*exo*-azatricyclo[3.2.1.$0^{2,4}$]octane (10b). Triazoline **8b** (3.66 g, 11.6 mmol) was heated (neat) at 190–200 °C in a round-bottomed flask until nitrogen evolution had begun to subside. The flask was then immediately cooled in order to minimize decomposition. Chromatography of the residue on 200 g of neutral alumina with benzene–chloroform gave **10b** (Ar = $C_6H_4NO_2$) as a yellow solid in a very minor first fraction (~100 mg). Later fractions yielded *p*-nitroaniline and an oily mixture. Preparative VPC of this oil gave no identifiable compounds. Aziridine **10b** was recrystallized from hexane (with Norit) to give yellow needles. An analytical sample was obtained after two further recrystallizations: mp 120–122 °C; NMR ($CDCl_3$)

δ 8.10 (2 H, d, J = 9 Hz), 6.95 (2 H, d, J = 9 Hz), 4.9 (1 H, br s), 2.8 (2 H, br s), 2.60 (2 H, s), 2.10 (3 H, s), 0.7–2.0 (4 H, m).

Anal. Calcd[37] *m/e* for $C_{15}H_{16}N_2O_4$: 288.1110. Found: 288.1110.

Bicyclo[2.2.1]hept-2-en-7-one (13). This ketone was prepared according to the literature method[14] from hexachlorocyclopentadiene in 31% overall yield (four steps), bp 95–99 °C (115 mm) [lit.[14] bp 96–100 °C (115 mm)]. Distillation of **13** was simplified if prior workup included washing with 10% sodium bicarbonate solution.

5-(4-Nitrophenyl)-3,4,5-*exo*-triazatricyclo[5.2.1.0^{2,6}]dec-3-en-10-one (14b). A mixture of 8.4 g (78 mmol) of **13** and 13.3 g (82 mmol) of *p*-nitrophenyl azide in 20 mL of methylene chloride was refluxed in the dark for 30 min. Cooling and filtration followed by recrystallization from acetone gave 8.7 g (41%) of **14b** as a yellow solid. Further recrystallizations gave an analytical sample: mp 178–179 °C dec; an NMR spectrum was not obtained due to low solubility of **14b**, but assignment of the *exo*-triazoline ring can be made by analogy with 14a (below).

Anal. Calcd for $C_{13}H_{12}N_4O_3$: C, 57.35; H, 4.44; N, 20.55. Found: C, 57.27; H, 4.45; N, 20.61.

5-Phenyl-3,4,5-*exo*-triazatricyclo[5.2.1.0^{2,6}]dec-3-en-10-one (14a). A solution of 1.0 g (9.3 mmol) of **13** and 1.1 g (9.3 mmol) of phenyl azide was stirred in the dark at 50–60 °C for 2 days. The solution was then cooled and filtered. Recrystallization of the resulting solid from hexane–chloroform gave 1.04 g (50%) of **14a**. A dark brown residue (0.75 g) remained. An analytical sample was obtained through further recrystallization as a colorless solid: mp 159–160 °C dec; NMR ($CDCl_3$) δ 6.8–7.6 (5 H, m), 5.0 (1 H, d, J = 12 Hz), 4.2 (1 H, d, J = 12 Hz), 2.4–2.7 (2 H, m), 1.5–2.4 (4 H, m).

Anal. Calcd for $C_{13}H_{13}N_3O$: C, 68.71; H, 5.77; N, 18.48. Found: C, 68.71; H, 5.91; N, 18.26.

Photolysis of 14b. Preparation of 3-(4-Nitrophenyl)-3-*exo*-azatricyclo[3.2.1.0^{2,4}]octan-8-one (15b). A solution of 1.0 g (3.7 mmol) of triazoline **14b** in 350 mL of reagent grade acetone was irradiated for 2 h with a 450 W Hanovia lamp (Pyrex filter). Removal of the solvent by rotary evaporation gave an oily brown solid. Chromatography of this residue on 200 g of neutral alumina with chloroform gave 300 mg (18%) of **15b**. Recrystallization from hexane–chloroform gave an analytical sample: mp 144–145 °C; NMR ($CDCl_3$) δ 8.0 (2 H, d, J = 10 Hz), 6.9 (2 H, d, J = 10 Hz), 2.9 (2 H, s), 2.6 (2 H, s), 1.8 (4 H, s).

Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.76; H, 4.96; N, 11.49.

Photolysis of 14a. Preparation of 3-Phenyl-3-*exo*-azatricyclo[3.2.1.0^{2,4}]octane-8-one (15a). A solution of 3.5 g (15 mmol) of triazoline **14a** in 300 mL of reagent grade acetone was irradiated for 5 h with a 450 W Hanovia lamp (Pyrex filter). The solvent was removed by rotary evaporation to give a brown solid. Chromatography on 70 g of neutral alumina with benzene–chloroform gave 1.95 g (64%) of **15a** as a colorless solid. Two recrystallizations from hexane gave an analytical sample: mp 114.5–115.5 °C; NMR ($CDCl_3$) δ 6.9–7.4 (5 H, m), 2.82 (2 H, s), 2.57 (2 H, s), 1.80 (4 H, s).

Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.67; H, 6.76; N, 6.75.

7-*syn*-Hydroxybicyclo[2.2.1]hept-2-ene (16). This alcohol was prepared stereospecifically in 28% overall yield (two steps) from bicyclo[2.2.1]hept-2-ene by the literature method.[18] The crude alcohol (83% pure by VPC[18]) was used in further synthetic work.

5-(4-Nitrophenyl)-10-*syn*-hydroxy-3,4,5-*exo*-triazatricyclo[5.2.1.0^{2,6}]dec-3-ene (17). Crude **16** (3 g, 3 mmol) and 5 g (3 mmol) of p-nitrophenyl azide were dissolved in 75 mL of carbon tetrachloride and allowed to stand in the dark at room temperature for several days. Filtration afforded 2.0 g (30%) of **17** as a bright yellow solid. An analytical sample was obtained after recrystallization from ethyl acetate: mp 167–168 °C dec; IR (potassium bromide) 3500, 2940, 1595, 1505, 1490, 1390, 1320, 1180, 1130, 1110, 1085, 990, 930, 905, 850, 750 cm^{-1}; although an NMR spectrum was not obtained due to the extremely low solubility of **17**, structural assignment as exo is based on analogy with other triazolines of this study.

Anal. Calcd for $C_{13}H_{14}N_4O_3$: C, 56.93; H, 5.14; N, 20.43. Found: C, 56.85; H, 5.20; N, 20.33.

Thermolysis of 17. Preparation of 3-(4-Nitrophenyl)-8-*syn*-hydroxy-3-*exo*-azatricyclo[3.2.1.0^{2,4}]octane (18b). Triazoline **17** (150 mg, 0.55 mmol) was heated in a test tube immersed in an oil bath at 200 °C until nitrogen evolution had ceased. The cooled residue was subjected to preparative TLC on alumina with benzene–chloroform to give 40 mg (30%) of **18** as a yellow solid, identified by spectral comparison with material produced by an alternate route (see sodium borohydride reduction of **15b**).

Reduction of 15b. Preparation of 3-(4-Nitrophenyl)-8-*syn*-hydroxy-3-exo-azatricyclo[3.2.1.0^{2,4}]octane (18b, Ar = $C_6H_4NO_2$). To a stirring solution of 102.7 mg (2.70 mmol) of sodium borohydride in 3 mL of absolute ethanol at 0 °C under nitrogen was added a suspension of 159.4 mg (0.65 mmol) of ketone **15b** in 30 mL of absolute ethanol. The ice bath was then removed and the solution was stirred for 5 h at room temperature. Removal of solvent by rotary evaporation gave a brownish-green solid. The solid was dissolved in 30 mL of water and 30 mL of ether. The layers were separated and the aqueous layer was extracted with 15 mL of ether. The combined organic layers were extracted with 15 mL of brine and dried over $MgSO_4$. Filtration and evaporation gave 131.1 mg (82%) of **18b** as bright yellow crystals. Recrystallization from benzene–hexane gave an analytical sample: mp 149–151 °C; NMR ($CDCl_3$) δ 8.1 (2 H, d, J = 10 Hz), 7.1 (2 H, d, J = 10 Hz), 4.8 (1 H, d, J = 12 Hz), 3.7 (1 H, d, J = 12 Hz), 2.9 (2 H, s), 2.6 (2 H, s), 0.6–1.9 (4 H, m). Addition of deuterium oxide to the NMR sample caused the δ 4.8 peak to disappear and the δ 3.7 peak to collapse to a singlet.

Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73. Found: C, 63.46; H, 5.64.

Reduction of 15a. Preparation of 3-Phenyl-8-*syn*-hydroxy-3-*exo*-azatricyclo[3.2.1.0^{2,4}]octane (18a). To a stirring suspension of 1.21 g (31.9 mmol) of sodium borohydride in 10 mL of absolute ethanol at 0 °C under nitrogen was added in one portion a suspension of 1.53 g (7.7 mmol) of ketone **15a** in 140 mL of absolute ethanol. The ice bath was then removed and the solution was stirred for 4 h at room temperature. The solvent was then removed by rotary evaporation to yield a white solid. The solid was dissolved in 100 mL of ether and 100 mL of water. The layers were separated and the aqueous layer was extracted twice with 50-mL portions of ether. The combined ether layers were extracted with brine (50 mL) and dried over $MgSO_4$. Filtration and evaporation gave a slightly yellow solid. Recrystallization from hexane (Norit added) gave 1.10 g (71%) of **18a** as a white solid. Three further recrystallizations gave an analytical sample: mp 85–86 °C; NMR ($CDCl_3$) δ 6.9–7.5 (5 H, m), 5.7 (1 H, br s), 3.7 (1 H, br s), 2.77 (2 H, s), 2.60 (2 H, s), 1.1–1.9 (4 H, m).

Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.70; H, 7.44; N, 6.98.

Procedure Used in Lanthanide Shift Reagent (LSR) Determination of Structure. A 0.6 M solution of purified substrate was made up by dissolving the necessary amount of the substrate in 0.25 mL of deuteriochloroform (containing 1% tetramethylsilane) in an NMR tube. An [LSR]/[substrate] ratio of 0.4 was obtained by adding 62.2 mg (0.06 mmol) of europium tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione) ($Eu(fod)_3$). The spectrum was then recorded. Aliquots of a stock solution 0.6 M in the substrate (same solvent) were then added and the spectrum was rerun. In this way, the [LSR]/[substrate] ratio was varied from 0.4 to 0.13 while [substrate] remained constant at 0.6 M. For each set of protons in the substrate, a plot of the chemical shift vs. the [LRS]/[substrate] ratio was analyzed by the least-squares method[38] to yield the values listed in the text of this paper.

7,7-Dimethoxybicyclo[2.2.1]hept-2-ene (19). Preparation of **19** was carried out in 36% overall yield (three steps) from hexachlorocyclopentadiene according to the literature procedure,[19] bp 72–76 °C (24 mm) [lit.[19] bp 58–68 °C (17 mm)].

5-(4-Nitrophenyl)-10,10-dimethoxy-3,4,5-*exo*-triazatricyclo[5.2.1.0^{2,6}]dec-3-ene (20b). A mixture of 12.0 g (78 mmol) of **19** and 13.4 g (81 mmol) of *p*-nitrophenyl azide in the minimum amount of carbon tetrachloride was allowed to stand in the dark for 10 days. Filtration and recrystallization from acetone gave 15.4 g (65%) of **20b**. Further recrystallizations gave an analytical sample: mp 158–160 °C dec; NMR ($CDCl_3$) δ 8.5 (2 H, d, J = 10 Hz), 7.4 (2 H, d, J = 10 Hz), 4.9 (1 H, d, J = 10 Hz), 3.9 (1 H, d, J = 10 Hz), 3.2 (3 H, s), 3.0 (3 H, s), 2.8 (2 H, m), 1.5–2.2 (2 H. m).

Anal. Calcd for $C_{15}H_{18}N_4O_4$: C, 56.59; H, 5.71; N, 17.60. Found: C, 56.58; H, 5.68; N, 17.63.

5-Phenyl-10,10-dimethoxy-3,4,5-*exo*-triazatricyclo-[5.2.1.0^{2,6}]dec-3-ene (20a). A mixture of 1.0 g (6.49 mmol) of **19** and 0.77 g (6.5 mmol) of phenyl azide in carbon tetrachloride was heated on a steam bath for 2 h. Upon cooling, crystallization occurred. Filtration and recrystallization from hexane–chloroform gave 1.02 g (58%) of **20a**. Further recrystallizations gave an analytical sample: mp 153–155 °C dec; NMR ($CDCl_3$) 7.3 (5 H, m), 4.6 (1 H, d, J = 10 Hz), 3.8 (1 H, d, J = 10 Hz), 3.2 (3 H, s), 3.0 (3 H, s), 2.8 (1 H, m), 2.6 (1 H, m), 1.0–2.2 (4 H, m).

Anal. Calcd for $C_{15}H_{19}N_3O_2$: C, 65.91; H, 7.01; N, 15.37. Found: C, 65.88; H, 7.01; N, 15.42.

Photolysis of 20a. Preparation of 3-Phenyl-8,8-dimethoxy-3-*exo*-azatricyclo[3.2.1.0^{2,4}]octane (21a). A solution of 700 mg (2.6 mmol) of **20a** in 250 mL of reagent grade acetone was irradiated with a 450 W Hanovia lamp (Pyrex filter) for 2.5 h. Removal of solvent by

rotary evaporation gave a reddish-brown solid. After recrystallization from hexane (with Norit), 0.48 g (76%) of **21a** was obtained as colorless needles. Further recrystallizations gave an analytical sample: mp 91–92 °C; NMR ($CDCl_3$) δ 6.7–7.3 (5 H, m), 3.5 (6 H, 2s), 2.5 (m), and 2.4 (s) (4 H together), 1.1–2.0 (4 H, m).

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.50; H, 7.76; N, 5.65.

Thermolysis of 20b. Preparation of 3-(4-Nitrophenyl)-10,10-dimethoxy-3-*endo*-azatricyclo[3.2.1.0^{2,4}]octane (22b) and 7,7-Dimethoxybicyclo[2.2.1]heptan-2-one (23). A small, round-bottomed flask containing 5.1 g (16 mmol) of **20b** was placed in an oil bath at 180–190 °C. As the solid melted, nitrogen was rapidly given off. Immediately following cessation of gas evolution, the flask was cooled and the residue was chromatographed on 200 g of neutral alumina with benzene–chloroform, followed by ethyl acetate. Three fractions were obtained: (1) 1.0 g (22%) of **22b** as a yellow solid; (2) 1.44 g (53%) of **23** (identified by spectral comparisons with authentic material[39]), and (3) 1.37 g of a relatively insoluble solid, consisting primarily of *p*-nitroaniline. Recrystallization of **22b** from hexane gave an analytical sample: mp 148–150 °C; NMR ($CDCl_3$) δ 8.1 (2 H, d, J = 10 Hz), 6.9 (2 H, d, J = 10 Hz), 3.30 and 3.25 (6 H, 2s), 2.9 (2 H, t, J = 2 Hz), 2.4 (2 H, m), 1.6 (4 H, m).

Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.06; H, 6.25; N, 9.65. Found: C, 61.95; H, 6.34; N, 9.66.

Thermolysis of **20b** was also carried out by heating a solution of **20b** in decalin at 180 °C. After removal of decalin by vacuum distillation [60 °C (7 mm)], preparative TLC gave a product distribution similar to that described above.

Bicyclo[2.2.1]hept-2-ene-7-spiro-2′,5′-dioxolane (25). Spiroketal **25** was prepared in 68% yield from **13** according to the method of Gassman and Macmillan,[21] bp 110 °C (25 mm) [lit.[21] bp 122–125 °C (76 mm)].

5-(4-Nitrophenyl)-3,4,5-*exo*-triazatricyclo[5.2.1.0^{2,6}]dec-3-ene-10-spiro-2′,5′-dioxolane (26). A mixture of 2.2 g (13 mmol) of **25** and 2.16 g (13.2 mmol) of *p*-nitrophenyl azide in 10 mL of carbon tetrachloride was stirred at 50–60 °C in the dark for 1 day. Upon cooling, filtration afforded 3.23 g (79%) of **26** as a yellow solid. Recrystallization from benzene gave an analytical sample: mp 164–166 °C dec; NMR ($CDCl_3$) δ 8.2 (2 H, d, J = 10 Hz), 7.2 (2 H, d, J = 10 Hz), 4.8 (1 H, d, J = 10 Hz), 3.6–4.0 (5 H, overlapping d and 2s), 1.2–2.6 (6 H, m).

Anal. Calcd for $C_{15}H_{16}N_4O_4$: C, 56.96; H, 5.10; N, 17.71. Found: C, 57.16; H, 5.16; N, 17.69.

Thermolysis of 26. Preparation of 3-(4-Nitrophenyl)-3-*endo*-azatricyclo[3.2.1.0^{2,4}]octane-8-spiro-2′,5′-dioxolane (27). A 1.7-g (5.4 mmol) portion of **26** in a small, round-bottomed flask was heated at 190–200 °C until nitrogen evolution had ceased. The flask was then cooled and the residue was chromatographed on 40 g of neutral alumina with benzene–chloroform to yield 330 mg (21%) of **27** as a yellow solid. Recrystallizations from hexane–chloroform gave an analytical sample: mp 163.5–165.5 °C; NMR ($CDCl_3$) δ 8.0 (2 H, d, J = 9 Hz), 6.8 (2 H, d, J = 9 Hz), 3.9 (4 H, s), 2.9 (2 H, t, J = 2 Hz), 2.1 (2 H, m), 1.5 (4 H, m).

Anal. Calcd for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.87; H, 5.80; N, 9.43.

Bicyclo[2.2.1]hept-2-ene-7-spiro- 2′,5′- oxathiolane (28). Following the literature procedure,[22] 7.8 g (74 mmol) of the ketone **13**, 8.6 g (111 mmol) of 2-mercaptoethanol, 15 g of freshly fused zinc chloride, and 15.8 g of anhydrous sodium sulfate yielded 6.0 g (50%) of **28**, bp 60–62 °C (0.3 mm). The 3:1 mixture of epimers was separated by preparative VPC (6 ft × 0.25 in. 10% DC 200 on 60/80 Chromosorb W column at 100 °C). For the major isomer, the following spectral data were recorded: NMR ($CDCl_3$) δ 6.2 (2 H, t, J = 2 Hz), 4.13 (2 H, t, J = 5 Hz), 2.92 (2 H, t, J = 5 Hz), 2.8 (2 H, m), 2.0 (2 H, m), 1.1 (2 H, m). For the minor isomer, the δ 4.13 and 2.92 peaks were shifted to δ 4.00 and 3.00.

Anal. Calcd for $C_9H_{12}OS$: C, 64.25; H, 7.19. Found: C, 64.04; H, 7.32.

Addition of 300 mg of **28** to 680 mg of bis(benzonitrile)palladium dichloride in 200 mL of benzene gave an immediate precipitation of a red-orange solid. Filtration and concentration of the remaining solution gave a residue which showed only the major isomer on GLC analysis (column described above). The major isomer was thus identified as **28a**. An attempt was made to recover **28b** by refluxing the precipitate in 70 mL of anhydrous ether with 200 mg of potassium cyanide for several days. Cooling of the solution followed by filtration and concentration failed to yield **28b**.

5-(4-Nitrophenyl)-3,4,5-*exo*-triazatricyclo[5.2.1.0^{2,6}]dec-3-ene-10-spiro-2′,5′-oxathiolane (30, Ar = $C_6H_4NO_2$). A mixture of 2.0 g (11.9 mmol) of **28** and 1.95 g (11.9 mmol) of *p*-nitrophenyl azide in carbon tetrachloride was heated at 50–60 °C in the dark for 15 days. Cooling and filtration gave 0.83 g (21%) of **30**.[40] Recrystallizations from hexane–chloroform gave an analytical sample: mp 166–168 °C dec; NMR ($CDCl_3$) δ 8.12 (2 H, d, J = 10 Hz), 7.2 (2 H, d, J = 10 Hz), 4.8 (1 H, d, J = 10 Hz), 3.9 (3 H, m), 2.8 (3 H, m), 2.5 (1 H, m), 1.1–2.3 (4 H, m).

Anal. Calcd for $C_{15}H_{16}N_4O_3S$: C, 54.21; H, 4.85; N, 16.86. Found: C, 54.42; H, 5.06; N, 16.67.

5-Phenyl-3,4,5-*exo*-triazatricyclo[5.2.1.0^{2,6}]dec-3-ene-10-spiro-2′,5′-oxathiolane (30, Ar = C_6H_5). A mixture of 2.0 g (11.9 mmol) of **28** and 1.42 g (11.9 mmol) of phenyl azide was stirred at 50–60 °C in the dark for 3 days. Trituration of the cooled solution with hexane gave 410 mg (19%) of **30**.[40] Recrystallizations from hexane–chloroform gave an analytical sample: mp 119–121 °C; NMR ($CDCl_3$) δ 7.3 (5 H, m), 4.7 (1 H, d, J = 11 Hz), 3.9 (3 H, d and t), 2.8–3.0 (4 H, m), 1.3–2.4 (4 H, m).

Anal. Calcd for $C_{15}H_{17}N_3OS$: C, 62.69; H, 5.96; N, 14.62. Found: C, 62.85; H, 6.00; N, 14.55.

Photolysis of 30 (Ar = C_6H_5). Preparation of 3-Phenyl-3-*exo*-azatricyclo[3.2.1.0^{2,4}]octene-8-spiro-2′,5′-oxathiolane (31, Ar = C_6H_5). A solution of 750 mg (2.6 mmol) of **30** in 300 mL of reagent grade acetone was irradiated with a 450 W Hanovia lamp (Pyrex filter) for 0.75 h. After removal of solvent by rotary evaporation, the residue was chromatographed on 40 g of neutral alumina with benzene–chloroform to give 540 mg (80%) of **31**.[40] Recrystallizations from hexane gave an analytical sample: mp 138–139 °C; NMR ($CDCl_3$) δ 6.7–7.4 (5 H, m), 3.9 (2 H, t, J = 6 Hz), 2.7 (2 H, t, J = 6 Hz), 2.4 (4 H, s in m), 1.2–2.1 (4 H, m).

Anal. Calcd for $C_{15}H_{17}NOS$: C, 69.46; H, 6.61; N, 5.40. Found: C, 69.29; H, 6.61; N, 5.40.

Thermolysis of 30 (Ar = $C_6H_4NO_2$). Preparation of 3-(4-Nitrophenyl)-3-*endo*-azatricyclo[3.2.1.0^{2,4}]octane-8-spiro-2′,5′-oxathiolane (32, Ar = $C_6H_4NO_2$). Careful heating of 4.1 g (12.3 mmol) of **30** (in small portions) at 190 °C followed by immediate cooling gave a dark residue. Chromatography on 215 g of neutral alumina with benzene–chloroform gave as the first fraction 1.31 g of a mixture of **32** and the isomeric imine.[41] Trituration of this mixture with hexane gave 750 mg (20%) of **32** (Ar = $C_6H_4NO_2$) as pale yellow crystals. Recrystallizations from hexane gave an analytical sample: mp 205–206 °C; NMR ($CDCl_3$) δ 8.0 (2 H, d, J = 10 Hz), 6.9 (2 H, d, J = 10 Hz), 4.1 (2 H, t, J = 6 Hz), 3.1 (4 H, m), 2.4 (2 H, m), 1.6 (4 H, s). The multiplet at δ 3.1 was resolved into two triplets (J = 6 and 1.8 Hz) by the addition of $Eu(fod)_3$ and by analysis on a 270 MHz NMR.

Anal. Calcd for $C_{15}H_{16}N_2O_3S$: C, 59.19; H, 5.30; N, 9.20. Found: C, 59.04; H, 5.27; N, 9.11.

Reaction of 28 with Raney Nickel. Treatment of 500 mg of **28** with 2.25 teaspoonfuls of Raney nickel in acetone was carried out by standard procedures. After the solvents were removed by distillation (to avoid volatile loss of the expected product, **13**), GLC analysis (on a 6 ft × 0.25 in. 10% DC 200 on 60/80 Chromosorb W column at 110 °C) showed only traces of **13**; the major product was **29**.[42]

Treatment of 400 mg of **28** with 6 g of W-2 Raney nickel in 100 mL of benzene at reflux for 19 h followed by cooling, filtration, and careful rotary evaporation at room temperature gave 320 mg of a yellow oil, identified by GLC analysis as **29**.

Reaction of 28 with Chloramine-T. Reaction of 200 mg (1.2 mmol) of **28** with 330 mg (1.2 mmol) of chloramine-T gave only **13** (the expected product) by GLC analysis on a 15% OV-101 on Chromosorb G column at 45 °C (comparison with authentic **13**).

Attempted Deketalization of 32 (Ar = $C_6H_4NO_2$). Reaction of **32** with W-2 Raney nickel in acetone followed by chromatography on alumina with benzene–chloroform gave a brown solid identified as the product of nitro group reduction to the amine: the $-OCH_2CH_2S-$ group was still evident in the NMR spectrum, while the aryl region had collapsed to a narrowly separated AB quartet. Further reaction of this brown solid with W-2 Raney nickel in refluxing benzene for 18 h led to complete material loss.

A 130-mg portion of **32** (Ar = $C_6H_4NO_2$) in 6 mL of dimethyl formamide (to enhance solubility) was reacted with 363 mg of chloramine-T in 5 mL of 85% methanol–water. The reaction mixture was first stirred at room temperature and then briefly warmed to 70 °C. After cooling, the reaction mixture was worked up as described above for the deketalization of **28**. Preparative TLC on alumina with benzene gave less than 20 mg of a solid. Due to the low yield, characterization was not completed.

7-(2,2,2-Trichloroethoxy)-7-methoxybicyclo[2.2.1]hept-2-ene (33). Ketal **19** (35.0 g, 0.23 mol), 50.9 g (0.34 mol) of 2,2,2-trichloroethanol (distilled), and 1.0 g of *p*-toluenesulfonic acid were heated in benzene in a flask equipped with a Dean–Stark trap. After ~250

mL of benzene had been removed (2 h), the hydroxyl absorption of the azeotroped benzene reached a minimum (by IR analysis). The solution was then cooled and solid sodium carbonate was added. The solution was stirred for 0.5 h at room temperature and then filtered, concentrated via rotary evaporation, and fractionally distilled to yield 50.5 g (82%) of **33** as a pale yellow oil, bp 88–92 °C (0.1 mm). Ketal **33** appeared as a single peak on several GLC columns. An analytical sample was prepared by preparative VPC on a 6 ft × 0.25 in. 5% FFAP on potassium hydroxide washed Chromosorb P column at 145 °C: NMR ($CDCl_3$) δ 6.2 (2 H, m), 4.1 and 4.0 (2 H, 2s), 3.3 and 3.4 (3 H, 2s), 2.9 (2 H, m), 1.6–2.3 (2 H, m), 0.8–1.6 (2 H, m). NMR integration of the pairs of singlets at δ 4.1–4.0 as well as δ 3.3 and 3.4 indicated a syn/anti ratio of nearly 1:1.

Anal. Calcd for $C_{10}H_{13}Cl_3O_2$: C, 44.23; H, 4.79. Found: C, 44.56; H, 4.93.

Metal-Promoted Deketalizations of 33. (a) A 1.0-g portion of **33** was refluxed in 20 mL of tetrahydrofuran with 2.0 g of acid-activated[26] zinc dust. Monitoring of the reaction by TLC showed that complete disappearance of **33** required 8 h. At this point, the reaction mixture was cooled and 20 mL of ether was added. The resulting solution was then filtered, washed with two 20-mL portions of 1% hydrochloric acid, two 20-mL portions of 5% sodium bicarbonate, and 10 mL of brine, and then dried over anhydrous magnesium sulfate. Filtration and removal of solvent by distillation at atmospheric pressure gave a residue containing the expected bicyclo[2.2.1]hept-2-en-7-one (**13**) (identified by GLC and NMR comparisons with authentic material).

(b) Into a 25-mL, side-armed flask equipped with a rubber septum and reflux condenser was placed 480 mg (2.1 mmol) of zinc bromide [dried for 18 h at 150 °C (0.25 mm)]. The flask was then flushed with nitrogen and 2 mL of tetrahydrofuran (distilled from lithium aluminum hydride) was added. Potassium (160 mg) was then added to the stirred solution. The solution eventually became black as the temperature was raised to reflux and maintained for 4 h.[27] A solution of 500 mg (1.84 mmol) of **33** in 2 mL of tetrahydrofuran was injected into the flask at this point via syringe. The progress of the reaction was followed by GLC; formation of **13** was essentially complete after 1.5 h.

(c) Reaction of 1.0 g (3.7 mmol) of **33** with 2.0 g of zinc–copper couple[28] in refluxing tetrahydrofuran was followed by GLC analysis. The rate of the reaction was less than with zinc but appeared to be complete after 26 h. Workup analogous to that described for the acid-activated zinc gave **13** (identified by GLC and NMR comparisons with authentic material).

(d) Into a 50-mL, side-armed flask equipped with a rubber septum and reflux condenser was placed 1 g of sodium in small pieces and 10 mL of tetrahydrofuran (distilled from lithium aluminum hydride). The flask was flushed with nitrogen and cooled to ca. −25 °C. A solution of 1.0 g of **33** was added slowly. The solution was maintained at −25 °C for 1 h and then allowed to warm to room temperature. After several hours, the solution was filtered and worked up as described above. NMR analysis showed only **33**. This procedure was repeated with a brief period of reflux: extensive solvent breakdown occurred and no product could be isolated.

(e) The procedure used for the reaction of acid-activated zinc with **33** was followed using highly active magnesium powder.[27] Thus, 500 mg of **33** and 1 g of magnesium powder after reflux for 18 h in tetrahydrofuran gave 610 mg of a dark oil. NMR analysis indicated the presence of **33** (and the absence of **13**).

(f) Treatment of 400 mg of **33** with 800 mg of copper powder in refluxing tetrahydrofuran resulted in no formation of **13** as indicated by GLC analysis.

5-Phenyl-10-(2,2,2-trichloroethoxy)-10-methoxy-3,4,5-*exo*-triazatricyclo[5.2.1.$0^{2,6}$]dec-3-ene (34). A mixture of 15 g (55 mmol) of **33** and 7.9 g (66 mmol) of phenyl azide in carbon tetrachloride was heated at 50–60 °C in the dark for 2 weeks. The solution was then diluted with hexane and stored in the freezer for several days. Filtration afforded 15.3 g (71%) of crude **34**.[40] Recrystallizations from hexane gave relatively pure **34**: mp 140–141 °C dec; NMR ($CDCl_3$) δ 7.25 (5 H, br s), 4.65 (1 H, d, J = 11 Hz), 3.8 (3 H, s and d), 3.1 (3 H, s), 2.9 (1 H, m), 2.6 (1 H, m), 1.4–2.1 (4 H, m). Despite two attempts, acceptable elemental analyses were not obtained. However, the *p*-nitrophenyl azide adduct did analyze satisfactorily (vide post).

Photolysis of 34. Preparation of 3-Phenyl-8-(2,2,2-trichloroethoxy)-8-methoxy-3-*exo*-azatricyclo[3.2.1.$0^{2,4}$]octane (35). A solution of 1.7 g (4.3 mmol) of **34** in 350 mL of reagent grade acetone was irradiated with a 450 W Hanovia lamp (Pyrex filter) for several hours. Removal of solvent via rotary evaporation followed by purification of the crude **35** by passage through a 6 in. column of alumina with hexane and recrystallization from hexane gave 0.94 g (59%) of **35** as colorless crystals. Further recrystallizations from hexane gave an analytical sample: mp 93–95 °C; NMR ($CDCl_3$) δ 6.8–7.4 (5 H, m), 4.16 (2 H, s), 3.37 (3 H, s), 2.6 (2 H, m), 2.52 (2 H, s), 2.0 (2 H, m), 1.3 (2 H, m).

Anal. Calcd for $C_{16}H_{18}Cl_3NO_2$: C, 52.99; H, 5.00; N, 3.86. Found: C, 53.07; H, 5.07; N, 4.09.

Thermolysis of 34. Preparation of 3-Phenyl-8-(2,2,2-trichloroethoxy)-8-methoxy-3-*endo*-azatricyclo[3.2.1.$0^{2,4}$]octane (36). A 1.6-g (4.1 mmol) portion of **34** was added to a stirred flask of decalin at 190 °C. Nitrogen evolution lasted ca. 0.5 h. After 45 min, the solution was cooled and the decalin was removed by vacuum distillation [45 °C (1 mm)]. Chromatography of the residue on 75 g of neutral alumina with benzene–hexane gave 0.53 g (36%) of **36** as a colorless solid after recrystallization from hexane. Further recrystallizations from hexane gave an analytical sample: mp 100.0–100.5 °C; NMR ($CDCl_3$) δ 6.7–7.4 (5 H, m), 4.02 (2 H, s), 3.38 (3 H, s), 2.80 (2 H, t, J = 2 Hz), 2.5 (2 H, m), 1.68 (4 H, br s).

Anal. Calcd for $C_{16}H_{18}Cl_3NO_2$: C, 52.99; H, 5.00; N, 3.86. Found: C, 53.12; H, 5.04; N, 3.92.

5-(4-Nitrophenyl)-10-(2,2,2-trichloroethoxy)-10-methoxy-3,4,5-*exo*-triazatricyclo[5.2.1.$0^{2,6}$]dec-3-ene (37). A mixture of 25 g (92 mmol) of **33** and 15.1 g (92 mmol) of *p*-nitrophenyl azide in the minimum amount of carbon tetrachloride was allowed to stand in the dark for 11 days. Filtration gave 15.85 g (40%) of **37**. The filtrate was then allowed to stand for 3 months in the dark to afford 15.76 g of additional **37** (total yield 31.6 g, 79%).[40] Recrystallization from chloroform–hexane gave an analytical sample: mp 195–196 °C dec; NMR (Me_2SO-d_6) δ 8.3 (2 H, d, J = 9 Hz), 7.5 (2 H, d, J = 9 Hz), 4.9 (1 H, d, J = 11 Hz), 4.1 (1 H, d, J = 11 Hz), 3.9 (2 H, s), 3.4 (3 H, s), 2.9 (1 H, m), 2.7 (1 H, m), 1.2–2.0 (4 H, m).

Anal. Calcd for $C_{16}H_{17}Cl_3N_4O_4$: C, 44.11; H, 3.93; N, 12.86. Found: C, 43.88; H, 3.97; N, 12.90.

Thermolysis of 37. Preparation of 3-(4-Nitrophenyl)-8-(2,2,2-trichloroethoxy)-8-methoxy-3-*endo*-azatricyclo-[3.2.1.$0^{2,4}$]octane (38) and 7-(2,2,2-Trichloroethoxy)-7-methoxybicyclo[2.2.1]heptan-2-one (39). Thermolysis of 5.76 g (13 mmol) of **37** (neat) in several portions at 195–200 °C followed by cooling and chromatography of the combined residues on 400 g of neutral alumina with benzene–chloroform gave four major fractions: (1) 1.02 g (19%) of the endo aziridine, **38**, as a yellow solid; (2) 0.65 g of a mixture of **38** and **39** (predominately the latter); (3) 1.9 g (63%) of **39**; and (4) 1.63 g of insoluble material containing *p*-nitroaniline.

An analytical sample of **38** was obtained after recrystallization from hexane: mp 174–175 °C; NMR ($CDCl_3$) δ 8.1 (2 H, d, J = 10 Hz), 6.9 (2 H, d, J = 10 Hz), 4.1 (2 H, s), 3.4 (3 H, s), 3.0 (2 H, t, J = 2 Hz), 2.5 (2 H, m), 1.6 (4 H, m).

Anal. Calcd for $C_{16}H_{17}Cl_3N_2O_4$: C, 47.14; H, 4.20; N, 6.87. Found: C, 47.31; H, 4.28; N, 6.84.

Vacuum transfer of the crude **39** gave a thick oil which solidified upon cooling. An analytical sample was prepared by recrystallization from hexane: mp 69.5–70.5 °C; NMR ($CDCl_3$) δ 4.1 (2 H, AB quartet), 3.4 (3 H, s), 2.7 (2 H, m), 1.4–2.7 (6 H, m).

Anal. Calcd for $C_{10}H_{13}Cl_3O_3$: C, 41.77; H, 4.56. Found: C, 41.96; H, 4.62.

Preparation of 7-(2,2,2-Trichloroethoxy)-7-methoxybicyclo[2.2.1]heptan-2-one (39) from 7-(2,2,2-Trichloroethoxy)-7-methoxybicyclo[2.2.1]hept-2-ene (33). A solution of 3.0 g (11 mmol) of **33** in 75 mL of tetrahydrofuran (distilled from lithium aluminum hydride) was brought to 0 °C under an argon atmosphere in a flask equipped with a rubber septum. An excess of 1.0 M diborane in tetrahydrofuran was added via syringe. After stirring several hours at 0 °C, 5 mL of water was added cautiously, followed by the dropwise additions of 5 mL of 3 N sodium hydroxide and 5 mL of 30% hydrogen peroxide. The resulting solution was stirred for 0.5 h at room temperature. The layers were then separated and the aqueous layer was extracted with 25 mL of ether. The combined organic phases were diluted with ether, washed with two 40-mL portions of water and 40 mL of brine, and dried over anhydrous magnesium sulfate. Filtration and evaporation gave 2.96 g (92%) of **40** as a pale yellow oil (δ 6.2 peak absent in NMR spectrum; IR shows a 3600 cm^{-1} absorption). This oil was used without further purification. A solution of this oil in 25 mL of dry methylene chloride was added all at once to a solution (that had previously been stirred for 15 min) of chromium trioxide (6.0 g, 60 mmol) and 9.5 g (120 mmol) of dry pyridine (distilled from barium oxide) in 75 mL of methylene chloride. After 15 min of additional stirring, the solution was decanted from the dark residue. The residue was rinsed with 100 mL of ether and the combined organic solutions were allowed to evaporate and then concentrated under vacuum to remove pyridine. The residue was taken up in ether, filtered, washed

with dilute sodium hydroxide and brine solutions, and dried over $MgSO_4$. Filtration and evaporation gave 1.33 g (46%) of **39**, identical spectrally with the material described above.

Attempted Deketalization of 36 and 38. (a) A 550-mg (1.4 mmol) portion of **38** was treated with 1.1 g of acid-activated zinc dust[26] in 10 mL of refluxing tetrahydrofuran. The reaction was periodically monitored by removal of a small amount via syringe, filtration through glass wool and Celite, followed by IR examination for the presence of the carbonyl absorption. After 24 h, no carbonyl was observed. An additional 1.0 g of zinc and 10 mL of solvent were then added and reflux was continued for 3 days with no carbonyl absorption detected. The solution was then cooled, filtered, and evaporated to give 510 mg of a solid identical spectrally with **38**.

(b) This procedure was repeated using dimethyl formamide at 100 °C as the solvent. After several days, TLC analysis showed that **38** was absent. The suspension was cooled, filtered, and diluted with water and ether. The layers were separated and the ether layer was extracted several times with water and once with brine and dried over anhydrous magnesium sulfate. Filtration and evaporation gave an oil whose NMR spectrum showed none of the peaks expected for the desired ketone. This material was not characterized further.

(c) Treatment of 120 mg of crude **38** with 1 g of magnesium powder in 10 mL of dimethyl formamide at 100 °C for 3 days, followed by workup as in the acid-activated zinc attempt, gave only unchanged **38**.

(d) Using the procedure described for activated zinc deketalization of **33**, 500 mg (1.23 mmol) of **38** and precipitated zinc [from 320 mg (1.41 mmol) of zinc bromide and 110 mg of potassium][28] were stirred in refluxing tetrahydrofuran for 18 days. The mixture was then cooled and chromatographed on 25 g of neutral alumina with benzene–chloroform to give a yellow oil, identified as **38** by spectral comparison with authentic material.

(e) To a side-armed flask equipped with reflux condenser and rubber septum was added 134 mg (1.41 mmol) of $MgSO_4$, 106 mg (0.64 mmol) of potassium iodide, and 4 mL of tetrahydrofuran (distilled from lithium aluminum hydride). The flask was maintained under argon during the reaction. Approximately 100 mg of potassium was added in small pieces.[28] The temperature was raised to reflux and maintained for 2.5 h. A solution of 250 mg (0.64 mmol) of **36** in 5 mL of tetrahydrofuran was added next via syringe. After 18 h of reflux, the solution was cooled. Water and ether were added and workup was completed as in the activated zinc procedure to give an oil (230 mg) containing only unchanged **36**. This procedure was repeated with **38**, which also gave unchanged starting material.

Polarographic Procedure. Half-wave potentials were obtained by polarography with a PAR Model 174 polarographic analyzer. A dual compartment cell with separation of the cells via a coarse glass frit was used. A dropping mercury electrode served as the cathode in the main compartment. Also placed in this compartment was a platinum wire auxiliary electrode. A saturated calomel reference electrode was connected to the second compartment via a salt bridge. Dimethylformamide of sufficient purity (transparent to ca. −2.8 V) was obtained by treatment of reagent grade dimethylformamide with several batches of 3 Å molecular sieves followed by distillation. The electrolytes were stored in a desiccator. All compounds used in these determinations were of analytical purity. To obtain the $E_{1/2}$ value, each cell was filled with the solvent–electrolyte solution and then degassed with nitrogen for at least 15 min. A polarogram was then run on the blank solvent to establish the background current. After addition of several milligrams of the desired compound, the polarogram was rerun. The surfactant Triton X-100 was used in some cases to remove maxima. The $E_{1/2}$ values were taken either from the inflection point of the polarographic wave(s) or from the maximum of the differential pulse peak(s).

Procedure for Controlled Potential Reductions. Reductions were carried out at controlled potential (±0.03 V) with a Tacussel Type ASA 50-2 potentiostat connected to a cell in series with a coulometer for monitoring current flow. A cell similar to that used for polarographic work was employed in which the main compartment required ca. 60 mL of solution. The electrodes were a mercury pool as cathode and a platinum gauze anode. A saturated calomel reference electrode was connected to the cell via a salt bridge. The main compartment also contained a magnetic stirring bar and was cooled to 0–25 °C with an ice bath. Reagent grade dimethylformamide, distilled tetramethylurea, or distilled dimethyl sulfoxide were used as solvents. Lithium perchlorate or tetra-*n*-butylammonium perchlorate were used as electrolytes (0.1 N). For each run, a solution of the appropriate compound in ca. 60 mL of the electrolyte solution was cooled, degassed at least 15 min, and then maintained under nitrogen during reduction. When passage of the desired amount of current was observed, the solution in the main compartment was poured into 100 mL of water and 100 mL of ether. The layers were separated and the aqueous layer was extracted with three 100-mL portions of ether. The combined ether layers were treated with three 100-mL portions of water and 100 mL of brine and finally dried over anhydrous magnesium sulfate. Filtration and concentration via rotary evaporation yielded a residue which was analyzed by NMR and GLC.

Electrochemical Reduction of 33. Preparation of 7-(2,2-Dichloroethoxy)-7-methoxybicyclo[2.2.1]hept-2-ene (41). (a) Reduction of 1.0 g (3.7 mmol) of **33** at −1.85 V (600 C; 710 C = 2 equiv) in dimethylformamide-tetra-*n*-butylammonium perchlorate afforded an oil which contained no **13** by NMR and GLC analysis. Vacuum transfer gave 580 mg (67%) of **41**. An analytical sample was obtained by preparative VPC on a 6 ft × 0.25 in. 5% FFAP on potassium hydroxide washed Chromosorb P column at 130 °C: NMR ($CDCl_3$) δ 6.10 (2 H, m), 5.78 and 5.70 (1 H, 2t, J = 6 Hz), 3.82 and 3.72 (2 H, d, J = 6 Hz), 3.27 and 3.21 (3 H, 2s), 2.79 (2 H, m), 1.7–2.1 (2 H, m), 1.0 (2 H, m). The pairs of peaks (δ 5.7, 3.7–3.8, and 3.2) indicated the presence of unseparated syn and anti isomers.

Anal. Calcd for $C_{10}H_{14}Cl_2O_2$: C, 50.65; H, 5.95. Found: C, 50.63; H, 5.93.

(b) Reduction of 650 mg (2.4 mmol) of **33** at −1.85 V (411 C; 460 C = 2 equiv) in dimethylformamide with lithium perchlorate as the electrolyte gave a residue containing only **41** (as determined by NMR analysis).

(c) Reduction of 500 mg (1.8 mmol) of **33** at −1.65 V (250 C; 360 C = 2 equiv) gave a residue containing only **41** (as determined by NMR analysis).

Acknowledgment. We are indebted to the National Cancer Institute of the Public Health Service and to the National Science Foundation for grants which supported this investigation.

Supplementary Material Available: Detailed infrared data of selected compounds (3 pages). Ordering information is given on any current masthead page.

Registry No.—**7a**, 694-70-2; **7b**, 13426-55-6; **7c**, 66323-71-5; **8a** (Ar-Ph), 66428-44-2; **8b** (Ar = $C_6H_4NO_2$), 66323-72-6; **8c** (Ar = $C_6H_4NO_2$), 66323-73-7; **10a** (Ar = Ph), 42103-77-5; **10b** (Ar = $C_6H_4NO_2$), 66323-74-8; **10c** (Ar = $C_6H_4NO_2$), 66323-75-9; **12**, 66323-76-0; **13**, 694-71-3; **14a**, 66323-77-1; **14b**, 66323-78-2; **15a**, 66323-79-3; **15b**, 66323-80-6; **16**, 13118-70-2; **17**, 66323-81-7; **18a**, 66428-45-3; **18b**, 66323-82-8; **19**, 875-04-7; **20a**, 66323-83-9; **20b**, 66323-84-0; **21a**, 66323-85-1; **22b**, 66323-86-2; **23**, 10265-39-1; **25**, 1491-12-9; **26**, 66323-54-4; **27**, 66323-55-5; **28a**, 66323-56-6; **28b**, 66428-37-3; **29**, 10218-02-7; *syn*-**30** (Ar = $C_6H_4NO_2$), 66323-57-7; *anti*-**30** (Ar = $C_6H_4NO_2$), 66428-38-4; *syn*-**30** (Ar = Ph), 66323-58-8; *anti*-**30** (Ar = Ph), 66428-39-5; *syn*-**31** (Ar = Ph), 66323-59-9; *anti*-**31** (Ar = Ph), 66428-40-8; *syn*-**32** (Ar = $C_6H_4NO_2$), 66323-60-2; *anti*-**32** (Ar = $C_6H_4NO_2$), 66428-41-9; *syn*-**33**, 66323-61-3; *anti*-**33**, 66323-62-4; *syn*-**34**, 66323-63-5; *anti*-**34**, 66428-42-0; **35**, 66323-64-6; *syn*-**37**, 66323-65-7; *anti*-**37**, 66428-43-1; **38**, 66323-66-8; **39**, 66323-67-9; **40**, 66323-68-0; *syn*-**41**, 66323-69-1; *anti*-**41**, 66323-70-4; phenyl azide, 622-37-7; *p*-nitrophenyl azide, 1516-60-5; 2,2,2-trichloroethanol, 115-20-8.

References and Notes

(1) J. Haywood-Farmer, *Chem. Rev.*, **74**, 315 (1974).
(2) H. Tanida, T. Tsuji, and T. Irie, *J. Am. Chem. Soc.*, **89**, 1953 (1967); M. A. Battiste, C. L. Deyrup, R. E. Pincock, and J. Haywood-Farmer, *ibid.*, **89**, 1954 (1967); J. S. Haywood-Farmer and R. E. Pincock, *ibid.*, **91**, 3020 (1969).
(3) For an excellent review see O. C. Dermer and G. E. Ham, "Ethylenimine and Other Aziridines", Academic Press, New York, N.Y., 1969.
(4) K. Alder and G. Stein, *Justus Liebigs Ann. Chem.*, **485**, 211, 223 (1931); G. Komppa and S. Beckmann, *ibid.*, **512**, 172 (1934); for general reviews of 1,3-dipolar additions see G. L'abbe, *Chem. Rev.*, **69**, 345 (1969); R. Huisgen, R. Grashey, and J. Sauer, "Chemistry of Alkenes", S. Patai, Ed., Interscience, New York, N.Y., 1964, p 739; R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 565 (1963).
(5) Additions of aryl azides to bicyclo[2.2.1]hept-2-enes have been shown to give exclusively exo triazolines. In those cases where substitution in the 7 position severely hindered the exo side, no 1,3-cycloaddition was observed: K. Alder and G. Stein, *Justus Liebigs Ann. Chem.*, **501**, 1 (1933). An exception to this generality is the addition of phenyl azide to bicyclo[2.2.1]hepta-2,5-diene which yielded 5.5% of the *endo*-triazoline: S. McLean and D. M. Findlay, *Tetrahedron Lett.*, 2219 (1969).
(6) For selected examples of the photochemical conversion of 5-aryl-*exo*-3,4,5-triazatricyclo[5.2.1.$0^{2,6}$]dec-3-enes into 3-aryl-*exo*-3-azatricyclo[3.2.1.$0^{2,4}$]octanes see: (a) P. Scheiner, *Tetrahedron*, **24**, 2757 (1968); R. Huisgen, L. Moebius, G. Mueller, H. Stangl, G. Szeimies, and J. M. Vernon, *Chem. Ber.*, **98**, 3992 (1965); P. Scheiner, "Selective Organic

Transformations", B. S. Thyagarajan, Ed., Wiley, New York, N.Y., 1970, p 327; (b) B. Halton and A. D. Woolhouse, *Aust. J. Chem.*, **26**, 619, 1373 (1973); (c) P. Scheiner, *J. Org. Chem.*, **30**, 7 (1965).
(7) *endo*-3,4,5-Triazatricyclo[5.2.1.$0^{2,6}$]dec-3-enes have been shown to photochemically convert to *endo*-3-azatricyclo[3.2.1.$0^{2,4}$]octanes. For examples see: (a) G. W. Klumpp, A. H. Veefkind, W. L. de Graaf, and F. Bickelhaupt, *Justus Liebigs Ann. Chem.*, **706**, 47 (1967); (b) L. H. Zalkow and R. H. Hill, *Tetrahedron Lett.*, 2819 (1972).
(8) (a) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 565 (1963); (b) J. E. Franz and C. Osuch, *Tetrahedron Lett.*, 837 (1963); (c) J. E. Franz, C. Osuch, and M. W. Dietrich, *J. Org. Chem.*, **29**, 2922 (1964); (d) L. H. Zalkow, A. C. Oehlschlager, G. A. Cabat, and R. L. Hale, *Chem. Ind. (London)*, 1556 (1964); (e) A. C. Oehlschlager and L. H. Zalkow, *J. Org. Chem.*, **30**, 4205 (1965); (f) L. H. Zalkow and C. D. Kennedy, *ibid.*, **28**, 3309 (1963); (g) A. C. Oehlschlager and L. H. Zalkow, *Chem. Commun.*, 70 (1965); (h) A. C. Oehlschlager and L. H. Zalkow, *Can. J. Chem.*, **47**, 461 (1969); (i) R. S. McDaniel and A. C. Oehlschlager, *Tetrahedron*, **25**, 1381 (1969); (j) R. L. Hale and L. H. Zalkow, *ibid.*, **25**, 1393 (1969); (k) A. C. Oehlschlager, R. S. McDaniel, A. Thakore, P. Tillman, and L. H. Zalkow, *Can. J. Chem.*, **47**, 4367 (1969); (l) F. D. Marsh, *J. Org. Chem.*, **37**, 2969 (1972); (m) L. H. Zalkow and R. H. Hill, *Tetrahedron*, **31**, 831 (1975)
(9) Y. Girault, M. Decouzon, and M. Azzaro, *Tetrahedron Lett.*, 1175 (1976); K. Alder and R. Ruehman, *Justus Liebigs Ann. Chem.*, **566**, 1, 27, 58 (1960).
(10) P. Scheiner, J. H. Schomaker, S. Deming, W. J. Libbey, and G. P. Nowack, *J. Am. Chem. Soc.*, **87**, 306 (1965).
(11) E. I. Snyder and B. Franzus, *J. Am. Chem. Soc.*, **86**, 1166 (1964).
(12) The exo nature of these triazolines was established by NMR spectral analysis. The endo-H2 and endo-H6 proton signals appear at approximately δ 4.8 and 4.1, respectively, with J = ca. 10 Hz.
(13) The exo stereochemistry of the aziridine ring was substantiated on the basis of NMR spectral studies. The endo-2H and endo-4H proton signals appear as a sharp singlet at approximately δ 2.6.
(14) P. G. Gassman and J. L. Marshall, *Org. Synth.*, **48**, 25 (1968).
(15) In general, photolysis of *p*-nitrophenyl-substituted triazolines gave extremely complex mixtures of products. Spectroscopic analysis indicated that only trace amounts of aziridine containing products were present. Thus, isolation and purification of these trace amounts was not generally attempted.
(16) In view of the studies of Clarke and Johnson,[17] it might be anticipated that the endo isomer of **15** would be extremely labile due to the thermally promoted loss of carbon monoxide. This would be expected to be accompanied by concerted opening of the aziridine moiety.
(17) S. C. Clarke and B. L. Johnson, *Tetrahedron*, **27**, 3555 (1971).
(18) W. C. Baird, Jr., *J. Org. Chem.*, **31**, 2411 (1966).
(19) P. G. Gassman and J. L. Marshall, *Org. Synth.*, **48**, 68 (1968).
(20) Confirmation of the endo stereochemistry was available from the NMR spectrum of **22b**, which showed the exo-2H and exo-4H at δ 2.9 as a triplet with J = 2 Hz. The corresponding endo protons in the exo aziridine appear as a singlet at δ 2.4.
(21) P. G. Gassman and J. G. Macmillan, *J. Am. Chem. Soc.*, **91**, 5527 (1969).
(22) C. Djerassi, J. Romo, and G. Rosenkranz, *J. Am. Chem. Soc.*, **73**, 4961 (1951); G. E. Wilson, Jr., M. G. Huang, and W. W. Schloman, Jr., *J. Org. Chem.*, **33**, 2133 (1968).
(23) C. Djerassi, M. Shamma, and T. Y. Kan, *J. Am. Chem. Soc.*, **80**, 4723 (1958); C. Djerassi, E. Batres, J. Romo, and G. Rosenkranz, *ibid.*, **74**, 3634 (1952).
(24) D. W. Emerson and H. Wynberg, *Tetrahedron Lett.*, 3445 (1971); H. Wynberg, D. W. Emerson, and W. F. J. Huurdeman, U.S. Patent 3 794 669 (1974).
(25) J. L. Isador and R. M. Carlson, *J. Org. Chem.*, **38**, 554 (1973).
(26) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. I, Wiley, New York, N.Y., pp 1276–1286 (1967); Vol. II, pp 458–462 (1969); Vol. III, pp 334–336 (1972); Vol. V, pp 753–758 (1975).
(27) R. D. Rieke, S. J. Uhm, and P. M. Hudnall, *Chem. Commun.*, 269 (1973); R. D. Rieke and S. E. Bales, *J. Am. Chem. Soc.*, **96**, 1775 (1974).
(28) R. S. Shank and H. Shechter, *J. Org. Chem.*, **24**, 1825 (1959).
(29) It is interesting to note that **34**, **35**, and **36** are single compounds after purification.
(30) Melting points and boiling points are uncorrected. Proton magnetic spectra were recorded on Varian T-60, A60A, HA-100, and XL-100 nuclear magnetic resonance spectrometers. Infrared spectra were recorded on Perkin-Elmer Model 137 Infracord and Beckman Model 4240 infrared spectrophotometers. High-resolution mass spectra were recorded on AEI-MS9 and AEI-MS30 double beam mass spectrometers. Analytical VPC work was done on a Varian Aerograph Series 1200 chromatograph while preparative VPC was done on a Varian Aerograph Model 700 chromatograph. Elemental analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark.
(31) P. R. Story and S. R. Fahrenholtz, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 151; P. R. Story, *J. Org. Chem.*, **26**, 287 (1961).
(32) R. O. Lindsay and C. F. H. Allen, "Organic Syntheses", Collect. Vol. III, Wiley, New York, N.Y., 1955, p 710.
(33) G. W. Klumpp and R. F. Schmitz, *Tetrahedron Lett.*, 2911 (1974).
(34) This compound has been previously reported, but without spectral characterization.[35]
(35) E. I. Snyder and B. Franzus, *J. Am. Chem. Soc.*, **86**, 1166 (1964).
(36) P. A. S. Smith and J. H. Boyer, *Org. Synth.*, **31**, 14 (1951); H. O. Spauschus and J. M. Scott, *J. Am. Chem. Soc.*, **73**, 208 (1951).
(37) Due to the small amounts of this material which were available C, H, and N elemental analyses were not obtained.
(38) T. L. Isenhour and P. C. Jurs, "Introduction to Computer Programming for Chemists", Allyn and Bacon, New York, N.Y., 1972, p 178.
(39) P. G. Gassman and J. L. Marshall, *J. Am. Chem. Soc.*, **88**, 2822 (1966).
(40) NMR analysis on the crude product prior to recrystallization indicated the presence of two isomers (syn and anti) by the slight splitting observed in the aryl and H-2 regions.
(41) Imines were observed in the spectra of the crude reaction mixture; hydrolysis to the corresponding ketones occurred on chromatography. However, these ketones were generally not isolated.
(42) P. G. Gassman and P. G. Pape, *J. Org. Chem.*, **29**, 160 (1964).

Electrosynthesis of Hetero–Hetero Atom Bonds. 2. An Efficient Preparation of (2-Benzothiazolyl)- and Thiocarbamoylsulfenamides by Electrolytic Cross-Coupling Reaction of 2-Mercaptobenzothiazole, Bis(2-benzothiazolyl) Disulfide, and/or Bis(dialkylthiocarbamoyl) Disulfides with Various Amines

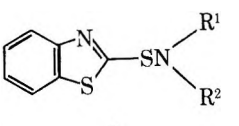
Sigeru Torii,* Hideo Tanaka, and Masasi Ukida

Department of Industrial Chemistry, School of Engineering, Okayama University, Okayama, Japan 700

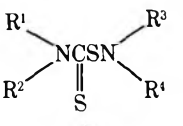
Received March 13, 1978

Two series of sulfenamides bearing 2-benzothiazolyl and thiocarbamoyl moieties were synthesized smoothly by electrolytic cross-coupling of either 2-mercaptobenzothiazole (3), bis(2-benzothiazolyl) disulfide (4) or bis(dialkylthiocarbamoyl) disulfides (5) with various amines in *N*,*N*-dimethylformamide. Electrolysis was carried out under constant voltages of 2–3 V (0.95–1.20 V vs. SCE) in an undivided cell, fitted with two platinum and/or two stainless steel Sus 27 electrodes. Direct electrosynthesis of thiocarbamoylsulfenamides (2) from dialkylamines and carbon disulfide was also accomplished in 81–96% yields.

During the last couple of decades, a number of synthetic methods for preparing (2-benzothiazolyl)- and thiocarbamoylsulfenamides (1 and 2) as important industrial chemicals[1] have been developed. The S–N bond-making reactions comprise the reaction of sulfenyl chlorides with amines,[2] coupling



1



2

0022-3263/78/1943-3223$01.00/0

Table I. Electrolytic Cross-Coupling of 3 and/or 4 with Cyclohexylamine[a]

entry	substrate (mmol)	cyclohexylamine,[2] mmol	electrodes (6 cm²)	current, mA/cm²	time,[b] h	sulfenamide 1 yield, %[c]
1	3[g] (0.90)	0.96	Pt	2.7–0	24	96[g]
2	3 (1.00)	1.00	Pt	1.7[e]	2.7	97[f]
3	4[g] (1.00)	2.00	Pt	3.0–0	16	95
4	4 (0.45)[d]	2.70	Pt	3.3–0	24	97
5	4 (0.45)	2.70	Sus	3.0–0	20	90
6	4 (0.45)	2.70	C	3.2–0	19	42

[a] Carried out in DMF (20 mL)–Et_4NClO_4 (100 mg) under a constant applied voltage of 2.0 V at 25–28 °C. [b] Being passed 2.0–2.5 faradays/mol of electricity based on substrates 3 or 4 except for entry 2 (1.0 faraday/mol). [c] Isolated yields. [d] Used wet DMF containing 0.5 mL of water. [e] Electrolyzed with a constant current (applied voltage 1.8–2.1). [f] Produced the disulfide 4. [g] Registry no.: 3, 149-30-4; 4, 120-78-5; 1, 95-33-0; cyclohexylamine, 108-91-8.

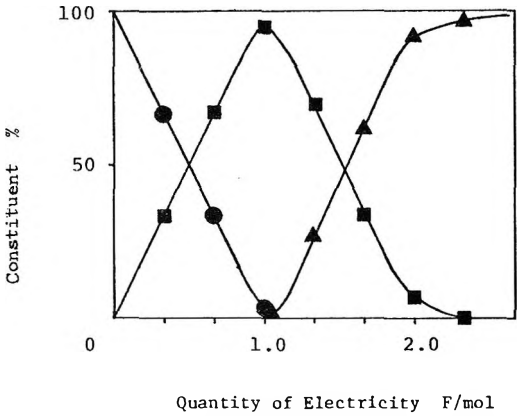


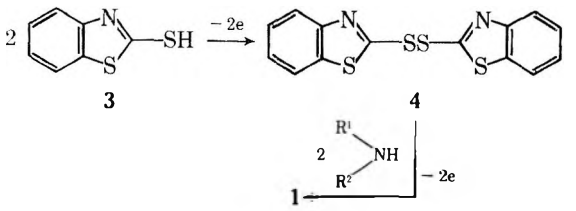
Figure 1. Experimental points (Table I, entry 1) are given every 0.33 faraday/mol for 1 (▲), 3 (●), and 4 (■).

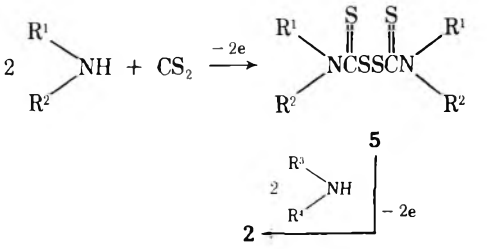
of metal mercaptides with *N*-chloroamines,[3] the amine-exchange reaction of sulfenamides,[4] the metal-assisted reaction of disulfides with amines,[5] and hydrogenation of thiooximes.[6] For large-scale preparations of 1 and 2, the oxidative cross-coupling reaction of 2-mercaptobenzothiazole (3),[7] dithiocarbamates,[8] and the related disulfides 4[9] and 5[10] with amines has been most frequently employed. However, use of stoichiometric amounts of oxidizing agents, e.g., sodium hypochlorite solution,[4a,7,8,9,10] hydrogen peroxide solution,[10b] chlorine,[7e] bromine,[7b] iodine,[7d] etc., brings about serious environmental problems.

As a simple and nonpolluting procedure for obtaining 1 and 2, we examined the electrochemical oxidation of 3, 4, and 5 under a controlled applied voltage in the presence of suitable amines and found a novel synthetic method for obtaining the sulfenamides 1 and 2.

Results and Discussion

(2-Benzothiazolyl)sulfenamides (1). According to the following general procedure, the sulfenamides 1 were electrosynthesized in an undivided cell equipped with two platinum electrodes. Electrolysis of the thiol 3 and cyclohexylamine in *N*,*N*-dimethylformamide (DMF) in the presence of tetraethylammonium perchlorate was conducted under a constant voltage of 2 V (0.95–1.2 V vs. SCE) at 26–28 °C. During the electrolysis the current varied from 2.7 mA/cm²





to almost zero. After ~2 faradays/mol of electricity had been passed for 24 h, workup of the reaction mixture gave *N*-cyclohexyl(2-benzothiazolyl)sulfenamide (1, R^1 = cyclohexyl; R^2 = H) in 96% yield (Table I, entry 1).

To follow the change of constituents in the electrolysis solution under the above electrolysis conditions, samples were taken by a microinjector at intervals of 0.33 faraday/mol. Figure 1 shows the relationship between constituents and current for entry 1. It reveals that most of the thiol 3 was converted into bis(2-benzothiazolyl) disulfide (4) when 1 faraday/mol of electricity was passed (Table I, entry 2). The most interesting fact is that further transformation of the disulfide 4 into the sulfenamide 1 is the major process in the continuing electrolysis. Thus, conversion of 3 into 1 was performed in quantitative yield after 2.1 faradays/mol of electricity were passed. It will be noted that no change of the constituent was observed when the mixture of 4 and cyclohexylamine in the same medium was stirred at room temperature for 24 h without passing electric current. The presence of excess cyclohexylamine in the electrolysis of 4 (entries 3 and 4) did not affect the yield of 1. In the latter case, stainless steel electrodes Sus 27 can be used instead of platinum electrodes without decreasing the yield of 1 (entry 5), whereas use of carbon electrodes decreases the yield to 42% due to absorption of some of the products on the electrode surface (entry 6). In a practical sense, the electrolysis reaction affording 1 from 4 is considered to be valuable as a general method for preparing 1. The results from the electrolysis of the disulfide 4 with various amines are shown in Table II.

Thiocarbamoylsulfenamides (2). The electrochemical S–N bond-making reaction can be extended with success to the synthesis of *N*-alkylthiocarbamoylsulfenamides (2), since electrolysis of a solution of bis(dialkylthiocarbamoyl) disulfides (5) and *N*-alkylamines in DMF was conducted under a constant applied voltage of 3 V (0.95–1.3 V vs. SCE) using either two platinum or stainless electrodes. After 2.1–2.5 faradays/mol, there were obtained the corresponding sulfenamides 2 in 74–98% yield (Table III).

A direct synthesis of 2 (R^1 = R^2 = R^3 = R^4) from carbon disulfide and dialkylamines was explored. Recently, the disulfides 5 have been electrosynthesized by the anodic oxidative coupling of dialkylammonium dithiocarbamates prepared in situ from carbon disulfide and dialkylamines in DMF.[11] The

Table II. (2-Benzothiazolyl)sulfenamides 1 from 4 by Electrolysis with Amines[a]

entry	amine	registry no.	electrodes (6 cm²)	applied voltage, V	current, mA/cm²	time,[b] h	sulfenamide 1 yield,[c] %	sulfenamide 1 mp (bp), °C (°C/Torr)	sulfenamide 1 registry no.
7	*n*-propylamine	107-10-8	Sus	3.0	1.8–0	6	98	(96–99/2)[d]	66552-53-2
8	isopropylamine	75-31-0	Sus	3.0	3.3–0	5	93	93.5–94.5[d]	10220-34-5
9	*tert*-butylamine	75-64-9	Sus	3.0	2.5–0	8	90	107.5–109[e]	95-31-8
10	morpholine	110-91-8	Pt	2.0	2.0–0	16	97	84.5–85.5[d]	102-77-2
11	piperidine	110-89-4	Sus	3.0	2.5–0	16	96	77–79[d]	26773-65-9
12	pyrrolidine	123-75-1	Sus	3.0	2.0–0	20	92	53–54[f]	17689-13-3
13	diethylamine	109-89-7	Sus	3.0	2.5–0	15	80	(89–92/2)[d]	2720-65-2
14	di-*n*-butylamine	111-92-2	Sus	3.0	2.5–0	19	89	(107–109/2)[d]	63451-39-8
15	diisopropylamine	108-18-9	Pt	2.0	1.0–0	15	25	58.5–59.5[g]	95-29-4
16	dicyclohexylamine	101-83-7	Pt	2.0	1.3–0	24	26	101–102[h]	4979-32-2

[a] Carried out in DMF (20 mL)–Et_4NClO_4 (100 mg) at 15–22 °C. [b] Being passed 2.1–2.5 faradays/mol of electricity based on **4**. [c] Isolated yields based on added **4**. [d] Reference 7e. [e] Reference 9. [f] Reference 4a. [g] Reference 3b. [h] Reference 14.

Table III. Sulfenamides 2 from 5 by Electrolysis with Amines[a]

entry	disulfides 5 R¹	disulfides 5 R²	disulfides 5 registry no.	amine	electrodes (6 cm²)	current, mA/cm²	time,[b] h	sulfenamide 2 yield,[c] %	sulfenamide 2 mp (bp), °C (°C/Torr)	sulfenamide 2 registry no.
17	Me	Me	137-26-8	cyclohexylamine	Pt	3.7–0.3	23	98	(100–102/2)[d]	52243-24-0
18	Me	Me		cyclohexylamine	Sus	4.7–0.7	20	98		
19	Me	Me		dimethylamine[g]	Sus	8.7–2.3	24	70	49.5–50[e]	2801-22-1
20	Et	Et	97-77-8	cyclohexylamine	Pt	3.3–0.4	29	95	63.5–64.5[d]	52185-80-5
21	Et	Et		piperidine	Sus	2.5–0.4	53	85	(84–87/2)[d]	66552-54-3
22	Et	Et		pyrrolidine	Sus	2.3–0.4	48	74	(83–86/2)	66552-55-4
23	*n*-Pr	*n*-Pr	2556-42-5	cyclohexylamine	Pt	3.0–0.5	43	92	(92–94/2)[f]	55947-00-7
24	*n*-Bu	*n*-Bu	1634-02-2	cyclohexylamime	Pt	3.3–0.3	41	84	(92–95/2)[d]	55947-01-8
25	$-(CH_2)_5-$		94-37-1	cyclohexylamine	Pt	6.3–0.5	24	89	74.5–75.5[d]	66552-56-5
26	$-(CH_2)_4-$		496-08-2	cyclohexylamine	Pt	7.2–0.8	42	82	(120–123/2)	66552-57-6

[a] Carried out under a constant applied voltage of 3 V in DMF (20 mL)–Et_4NClO_4 (100 mg) at 10–20 °C. [b] Being passed 2.1–2.5 faradays/mol of electricity based on **5**. [c] Isolated yields based on added **5**. [d] Reference 8d. [e] Reference 8c. [f] Reference 8b. [g] Registry no.: 124-40-3.

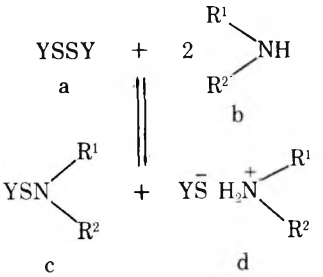
Table IV. Direct Electrosyntheses of Sulfenamides 2 from Amines and Carbon Disulfide[a]

entry	amine (mmol)	CS_2, mmol	solvent (20 mL)	current, mA/cm²	time,[b] h	sulfenamide 2 yield, %[c]	sulfenamide 2 mp, °C	sulfenamide 2 registry no.
27	piperidine (30)	6	DMF	8.0–0.4	24	92	100.5–101.5[d]	6250-27-7
28	piperidine (10)	2	MeCN	14.2–1.0	20	96	100.5–101.5[d]	
29	pyrrolidine (30)	6	DMF	8.0–0.2	25	93	86–87[e]	52345-73-0
30	morpholine (30)	6	DMF	6.2–0.2	37	81	136–137[e]	13752-51-7

[a] Carried out under a constant applied voltage of 3 V of 24–27 °C using two Pt electrodes (6 cm²) in the presence of Et_4NClO_4 (100 mg). [b] Being passed 2.5–3 faradays/mol of electricity based on CS_2. [c] Isolated yields based on added CS_2. [d] Reference 8d. [e] Reference 3a.

electrolysis solution thus obtained was submitted to the further electrochemical oxidation in the presence of excess dialkylamines (sixfold) to give the desired sulfenamides **2** smoothly (Table IV). The total conversion of carbon disulfide and dialkylamine into **2** required 2.1–2.5 faradays/mol of electricity referring to added carbon disulfide.

Mechanistic Consideration of S–N Bond Formation. To our knowledge, the electrosynthesis of the sulfenamides **1** and **2**, as mentioned above, is the first example of the electrochemical S–N bond-making reaction, involving oxidative cross-coupling of the disulfides **4** or **5** with amines. In the preparation of the sulfenamides **1** and **2** by chemical oxidation,[7c,8c] Carr et al. suggest that the reaction of disulfides (a) and amines (b) proceeds to give sulfenamides (c) and mercaptide ion (d). The latter anion (d) can be chemically oxidizing in situ to regenerate a. Recently, the metal-assisted synthesis of **1** without using oxidizing agents has been reported, where the generating mercaptide ion is removed by



filtration as insoluble metal complexes.[5] Independently, we confirmed the presence of sulfenamides (c) on a TLC plate in a stirring mixture of a and excess cyclohexylamine in DMF, although concentration of the mixed solution under diminished pressure afforded only the disulfide (a). In addition, removal of most of volatile materials from a mixture of equimolar amounts of c and d in DMF provided also a as a sole product. These experiments clearly demonstrate that the

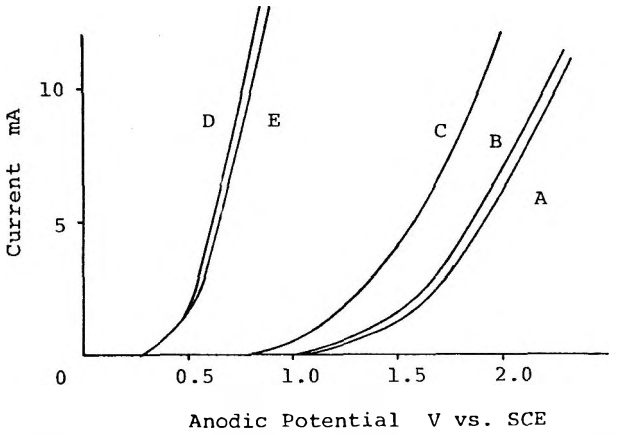
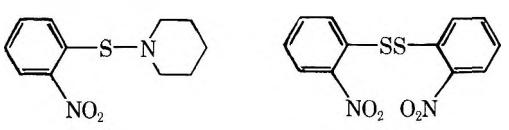


Figure 2. Current–potential curves: system A, Et_4NClO_4 (100 mg)–DMF (20 mL); system B, 4 (0.45 mmol)–Et_4NClO_4–DMF; system C, cyclohexylamine (1.03 mmol)–Et_4NClO_4–DMF; system D, 4–cyclohexylamine–Et_4NClO_4–DMF; system E, 3 (0.45 mmol)–cyclohexylamine–Et_4NClO_4–DMF.

sulfenamide formation reaction is reversible in the medium.

The present electrolysis reaction can also be rationalized by assuming that the reaction pathway involves anodic oxidation of the mercaptide ion, giving disulfide through the coupling of thio radical intermediates.[12] This assumption is consistent with the following results. The current–potential curves of various systems of the disulfide **4**, cyclohexylamine, and Et_4NClO_4 in DMF are shown in Figure 2, indicating that discharge potentials of A, B, and C systems occur over 0.8 V vs. SCE. However, in the D system the current begins to pass strikingly at lower potential, ~0.3–0.5 V vs. SCE, as similar to the corresponding thiol–cyclohexylamine system (curve E). This result in similarity on oxidation potentials implies that in the D system, stirring a mixture of **4** with cyclohexylamine in DMF would provide more or less the corresponding sulfenamide (c) as well as mercaptide ion (d) as the result of reversible reaction and the latter ion would be immediately oxidized on the anode, given a.

The above results are in sharp contrast to the unfruitful ones obtained under the same electrolysis conditions with di-*tert*-butyl disulfide, diphenyl disulfide, and dibenzyl disulfide, which have no electron-withdrawing group attached to the sulfur atom of the disulfide function. However, electrolysis of bis(o-nitrophenyl) disulfide (**6**) with piperidine in the same conditions afforded the corresponding sulfenamide



7 **6**

7 in 40% yield. It will be noted as supporting evidence for the formation of mercaptide ion (d) that increase of electrophilic character of the sulfur atom ascribable to the nitro group of **6** would be allowed to undergo attack by amines.

Experimental Section

All melting points and boiling points are uncorrected. IR spectra were determined with a JASCO IRA-I infrared spectrophotometer fitted with a grating. NMR spectra were taken at 60 MHz with a Hitachi R-24 spectrometer.

Materials. Commercially available 2-mercaptobenzothiazole (**3**) and bis(2-benzothiazolyl) disulfide (**4**) were used. Bis(dialkylthiocarbamoyl) disulfides (**5**) were prepared by electrolysis of the corresponding dialkylamines and carbon disulfide according to the procedure described in the preceding paper.[11]

General Procedure of the Electrolysis. The electrolysis was carried out in a water-jacketed beaker (3.5-cm in diameter and 10-cm high) fitted with a thermometer, a stirring bar, a gas lead pipe, and two platinum foil electrodes (6 cm^2) or two stainless steel electrodes (Sus 27, 6 cm^2), being placed parallel 5 mm apart. The regulated dc power was supplied by a Metronix Model-543B instrument. The reaction conditions and the results are summarized in Tables I, II, III, and IV. The typical experimental procedures are shown below.

***N*-Cyclohexyl(2-benzothiazolyl)sulfenamide (1, R^1 = H; R^2 = cyclohexyl) from 2-Mercaptobenzothioazole (3) and Cyclohexylamine (entry 1).** A mixture of 3 (150 mg, 0.90 mmol) and cyclohexylamine (85 mg, 0.96 mmol) in DMF (20 mL) containing Et_4NClO_4 (100 mg) was electrolyzed at 2 V (0.95–1.20 V vs. SCE) at 26–28 °C using two Pt electrodes (6 cm^2). During the course of the reaction the current density varied from 2.7 mA/cm^2 to almost zero. After 2.0 faradays/mol of electricity were passed (24 h), the reaction mixture was concentrated in vacuo and the residue was chromatographed (SiO_2, benzene) to give **1** (227 mg, 96%) as white crystals: mp 98–100 °C from hexane (lit.[4c] mp 99–101 °C); IR (Nujol) 3220 (NH), 3055 (HC=C), 1430 cm^{-1}; NMR ($CDCl_3$) δ 0.80–2.50 (m, 10 H), 2.88 (br, 1 H), 3.28 (m, 1 H), 6.90–8.10 (m, 4 H).

***N*-Cyclohexyl(2-benzothiazolyl)sulfenamide (1, R^1 = H; R^2 = cyclohexyl) from Bis(2-benzothiazolyl) Disulfide (4) and Cyclohexylamine (entry 3).** A mixture of 4 (333 mg, 1.00 mmol) and cyclohexylamine (198 mg, 2.00 mmol) in DMF (20 mL) containing Et_4NClO_4 (100 mg) was electrolyzed using two Pt electrodes (6 cm^2) at 2 V (1.0–1.3 V vs. SCE) at 26 °C. The initial current of 3.0 mA/cm^2 dropped to almost zero after ~2.2×10^{-3} faradays of electricity were passed (16 h). The reaction mixture was concentrated in vacuo and the residue was chromatographed (SiO_2, benzene) to give **1** (504 mg, 95%): mp 98–100 °C from ether–hexane (lit.[4c] mp 99–101 °C).

***N*-Cyclohexyl(*N'*,*N'*-diethylthiocarbamoyl)sulfenamide (2, R^1 = R^2 = Et; R^3 = H, R^4 = cyclohexyl) from Bis(diethylthiocarbamoyl) Disulfide (5, R^1 = R^2 = Et) and Cyclohexylamine (entry 20).** A mixture of **5** (0.88 g, 3.0 mmol) and cyclohexylamine (1.81 g, 18.3 mmol) in DMF (20 mL) containing Et_4NClO_4 (100 mg) was electrolyzed at 3 V (0.95–1.30 V vs. SCE) at 11–13 °C using two Pt electrodes (6 cm^2). The initial current of 3.3 mA/cm^2 dropped to 0.4 mA/cm^2 after 7×10^{-3} faradays of electricity was passed (29 h). After evaporation of the solvent the residue was taken up with ether, washed with brine, and dried (Na_2SO_4). Removal of the solvent followed by recrystallization from hexane gave **2** (1.40 g, 95%): mp 63.5–64.5 °C (lit.[8d] mp 64–65 °C); IR (Nujol) 3230 (NH), 1498, 1423, 1270 cm^{-1}; NMR ($CDCl_3$) δ 1.00–2.30 (m, 10 H), 1.27 (t, J = 7 Hz, 6 H), 2.77 (br, 1 H), 3.30–4.30 (m, 5 H).

Similarly, electrolysis of a mixture of **5** (R^1 = R^2 = Et, 0.89 g, 3.0 mmol) and pyrrolidine (1.28 g, 18.0 mmol) in DMF (entry 22) gave **2** (R^1 = R^2 = Et; R^3, R^4 = $-(CH_2)_4-$, 0.97 mg, 74%): bp 83–86 °C (2 mm); IR (neat) 1490, 1418, 1268 cm^{-1}; NMR ($CDCl_3$) δ 1.26 (t, J = 7 Hz, 6 H), 1.65–2.30 (m, 4 H), 2.70–4.20 (m, 8 H).

Anal. Calcd for $C_9H_{18}N_2S_2$: C, 49.50; H, 8.31. Found: C, 49,64; H, 8.42.

In a similar fashion, **5** (R^1, R^2 = $-(CH_2)_4-$, 0.89 g, 3.0 mmol) and cyclohexylamine (1.81 g, 18.3 mmol) afforded **2** (R^1, R^2 = $-(CH_2)_3-$, 1.22 g, 82%) (entry 26): bp 120–123 °C (2 mm); IR (neat) 3250 (NH), 1458, 1436, 1181, 1157, 1003, 955 cm^{-1}; NMR ($CDCl_3$) δ 0.60–2.40 (m, 14 H), 2.50–3.10 (m, 1 H), 3.20–4.10 (m, 5 H).

Anal. Calcd for $C_{11}H_{20}N_2S_2$: C, 54.06; H, 8.25. Found: C, 53.89; H, 8.08.

***N*,*N*-Pentamethylene(*N'*,*N'*-pentamethylenethiocarbamoyl)sulfenamide [2, R^1, R^2 = $-(CH_2)_5-$; R^3, R^4 = $-(CH_2)_5-$] from Piperidine and Carbon Disulfide (entry 27).** A mixture of piperidine (2.55 g, 30.0 mmol) and CS_2 (0.36 mL, 6.0 mmol) in DMF (20 ml) containing Et_4NClO_4 (100 mg) was electrolyzed at 3 V (0.85–1.20 V vs. SCE, 8.0–0.4 mA/cm^2) at 27 °C for 24 h. Workup in a similar way as that above gave **2** (1.49 g, 92%): mp 100.5–101.5 °C from hexane (lit.[8d] mp 100–102 °C); IR (Nujol) 1482, 1431, 1241 cm^{-1}; NMR ($CDCl_3$) δ 1.40–1.90 (m, 12 H), 3.20–4.20 (m, 8 H).

***N*,*N*-Pentamethylene-o-nitrophenylsulfenamide (7) from Bis(o-nitrophenyl) Disulfide (6) and Piperidine.** A mixture of **6** (308 mg, 1.00 mmol) and piperidine (517 mg, 6.07 mmol) in DMF (20 mL) containing Et_4NClO_4 (100 mg) was electrolyzed at 3.0 V (2–0.9 mA/cm^2) at 25 °C using two Pt electrodes (6 cm^2). After being passed 4.8×10^{-3} faradays of electricity (26 h), the mixture was concentrated in vacuo and the residue was chromatographed (SiO_2, benzene) to give **7** (192 mg, 40%): bp 77–80 °C (2 mm); IR (neat) 3080, 3055 (CH=C), 1592, 1564, 1506, 1333 cm^{-1}; NMR ($CDCl_3$) δ 1.00–2.30 (m, 6 H), 2.60–3.60 (m, 4 H), 7.00–8.50 (m, 4 H).

Anal. Calcd for $C_{11}H_{14}N_2O_2S$: C, 55.44; H, 5.92. Found: C, 55.51; H, 6.03.

Similar electrolysis of di-*tert*-butyl, diphenyl, and dibenzyl disul-

fides in DMF in the presence of piperidine (sixfold) gave no detectable amounts of sulfenamides, resulting in recovery of the starting materials.

Registry No.—6, 1155-00-6; 7, 66552-58-7; carbon disulfide, 75-15-0.

References and Notes

(1) (a) K. T. Potts, E. G. Brugel, J. J. D'Amico, and E. Morita, *Rubber Chem. Technol.*, **45**, 160 (1972); (b) C. Matolcsy and G. Josepovits, *Acta Chim. Acad. Sci. Hung.*, **51**, 319 (1967).
(2) E. A. Parfenov and V. A. Fomin, *Zh. Obshch. Khim.*, **45**, 1129 (1975).
(3) (a) R. D. Taylor, German Offen. 2 324 933 (1973); *Chem. Abstr.*, **80**, 146841 (1974); (b) H. Cherlow and R. H. Ebel, U.S. Patent 2 776 297 (1957); *Chem. Abstr.*, **51**, 7427 (1957).
(4) (a) R. H. Campbell and J. J. D'Amico, German Offen. 1 941 884 (1970); *Chem. Abstr.*, **72**, 90445 (1970); (b) J. J. D'Amico, *J. Org. Chem.*, **26**, 3436 (1961); (c) L. H. Howland, U. S. Patent 2 382 793 (1945); *Chem. Abstr.*, **40**, 368 (1946).
(5) (a) F. A. Davis, A. J. Friedman, E. W. Kluger, E. B. Skibo, E. R. Fretz, A. P. Milicia, W. C. LeMasters, M. D. Bentley, J. A. Lacadie, and I. B. Douglass, *J. Org. Chem.*, **42**, 967 (1977); (b) M. D. Bentley, I. B. Douglass, J. A. Lacadie, D. C. Weaver, F. A. Davis, and S. J. Eitelman, *Chem. Commun.*, 1625 (1971).
(6) F. A. Davis, W. A. R. Slegeir, S. Evans, A. Schwartz, D. L. Goff, and R. Palmer, *J. Org. Chem.*, **38**, 2809 (1973). See also ref 4b.
(7) (a) J. Korman, *J. Org. Chem.*, **23**, 1768 (1958); (b) G. Alliger, U. S. Patent 2 822 367 (1958); *Chem. Abstr.*, **52**, 10205 (1958); (c) J. A. Barltrop and K. J. Morgan, *J. Chem. Soc.*, 3072 (1957); (d) J. J. D'Amico, M. W. Harman, and R. H. Cooper, *J. Am. Chem. Soc.*, **79**, 5270 (1957); (e) E. L. Carr, G. E. P. Smith, Jr., and G. Alliger, *J. Org. Chem.*, **14**, 921 (1949).
(8) (a) M. V. Goretik, T. P. Kononova, M. S. Fel'dshtein, and I. S. Urakova, *Zh. Obshch. Khim.*, **34**, 1577 (1964); (b) J. J. D'Amico, French Patent 1 549 002 (1968); *Chem. Abstr.*, **71**, 70592 (1969); (c) P. Lipsitz, U.S. Patent 2 692 862 (1954); *Chem. Abstr.*, **49**, 2102 (1955); (d) G. E. P. Smith, Jr., G. Alliger, E. L. Carr, and K. C. Young, *J. Org. Chem.*, **14**, 935 (1949).
(9) Monsanto Co., British Patent 1 106 577 (1968); *Chem. Abstr.*, **68**, 96660 (1968).
(10) (a) J. J. D'Amico and E. Morita, *Rubber Chem. Technol.*, **44**, 889 (1971); (b) P. T. Paul and B. A. Hunter, U.S. Patent 2 419 283 (1947); *Chem. Abstr.*, **41**, 4517 (1947).
(11) S. Torii, H. Tanaka, and K. Misima, *Bull. Chem. Soc. Jpn.*, **51**, 1575 (1978).
(12) (a) H. Berge, H. Millat, and B. Strübing, *Z. Chem.*, **15**, 37 (1975); (b) E. C. Gregg and W. P. Tyler, *J. Am. Chem. Soc.*, **72**, 4561 (1950).
(13) R. S. Hanslick, U.S. Patent 2 386 457 (1945); *Chem. Abstr.*, **40**, 764 (1946).
(14) A. F. Hardman, U.S. Patent 3 022 300 (1962); *Chem. Abstr.*, **57**, 4673 (1962).

Identification of 2,5-Dihydropyridine Intermediates in the Reactions of 2-Alkyl(phenyl)-1-lithio-1,2-dihydropyridines with Alkyl Halides

Robert F. Francis,* Clayton D. Crews, and Britt S. Scott

Department of Chemistry, The University of Texas at Arlington, Arlington, Texas 76010

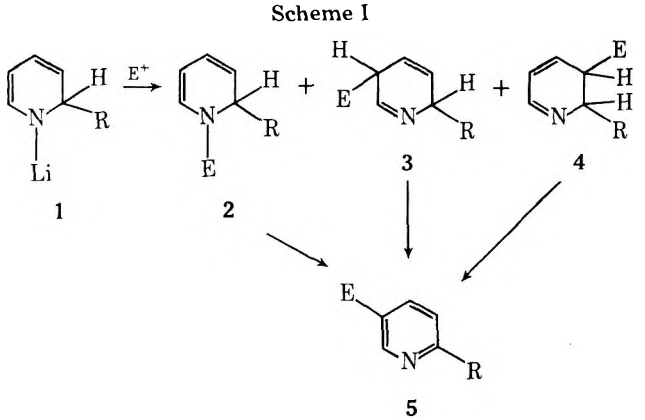
Received January 27, 1978

A series of 2,5-disubstituted 2,5-dihydropyridines (**10**) have been prepared from 2-alkyl(phenyl)-1-lithio-1,2-dihydropyridines (**1**) and alkyl halides and have been characterized by their IR and NMR spectra. Each 2,5-dialkyl-2,5-dihydropyridine (**10a–d**) decomposes on exposure to air or when heated to a mixture containing the corresponding 2,5-dialkylpyridine (**11a–d**) and the 2,5-dialkyl-1,2,5,6-tetrahydropyridine (**12a–d**). However, decomposition of a 5-alkyl-2-phenyl-2,5-dihydropyridine (**10d,f**) gives only the 5-alkyl-2-phenylpyridine (**11e,f**). The 2,5-dihydropyridines (**10**) are converted to the corresponding tetrahydropyridines (**12**) by lithium aluminum hydride reduction.

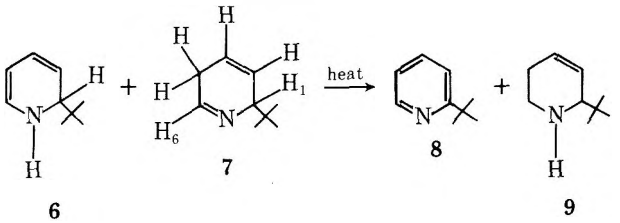
There has been little direct evidence for the existence of unstable 2,5-dihydropyridines.[1] However, they have been proposed as intermediates in reactions which include the sodium borohydride reduction of pyridinium salts,[2,3] the synthesis of 8-azasteroids,[4] the dehydrogenation of a 1,4-dihydropyridine,[5] and the reactions of lithium tetrakis(*N*-dihydropyridyl)aluminate with alkyl halides and bromine.[6]

The reactions of 1-alkyl(aryl)-1,2-dihydropyridines (**1**) with electrophiles can, in theory, lead to 1,2-, 2,5-, and 2,3-dihydropyridines as shown in Scheme I. The stable acylation products[7,8] of complex **1** (R = phenyl) are 1,2-dihydropyridines (**2**) which result from *N*-acylation and 2,5-disubstituted pyridines (**5**) which involve *C*-acylation. The latter are assumed to form from decomposition of 2,5-dihydropyridine intermediates (**3**). Alkylation[8,9,10] of complex **1** (R = phenyl) by the use of alkyl halides leads to 5-alkyl-2-phenylpyridines (**5**) which also presumably are formed on the decomposition of 2,5-dihydropyridines (**3**). Products obtained from the reaction of **1** with bromine,[9] cyanogen bromide,[11] benzophenone,[12] and phenyl disulfide[13] also are assumed to involve 2,5-dihydropyridine precursors.

Scheme I



Scheme II



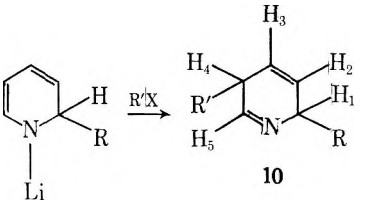
The first direct evidence for a 2,5-dihydropyridine, formed in the reaction of 2-*tert*-butyl-1-lithio-1,2-dihydropyridine (**1a**) with methanol, was reported[14] from this laboratory. This reaction gave dihydropyridines **6** and **7** which were decomposed by heat to 2-*tert*-butylpyridine (**8**) and 2-*tert*-butyl-1,2,5,6-tetrahydropyridine (**9**).

Results and Discussion

We have now identified the 2,5-dihydropyridines (**10**) obtained from the reactions of pyridine–alkyllithium complexes (**1**) with methyl and ethyl halides (Table I). Structural as-

0022-3263/78/1943-3227$01.00/0

Table I. Pyridine–Alkyllithium Complexes (1), 2,5-Dihydropyridines (10), and Vinyl Proton Absorptions of 2,5-Dihydropyridines



1 10

no.	registry no.	R	no.	R	R′	registry no.	chemical shifts for vinyl protons of **10**, δ H_5	H_2,H_3
1a	42540-75-0	*t*-Bu	**10a**	*t*-Bu	CH_3	66562-50-3	8.45	6.00
1b	20180-25-0	*n*-Bu	**10b**	*t*-Bu	C_2H_5		8.09	5.80
ac	24724-75-2	phenyl	**10c**	*n*-Bu	CH_3		8.05	5.73
			10d	phenyl	CH_3	66562-51-4	8.30	5.92
			10e	phenyl	C_2H_5	66562-52-5	8.15	5.87

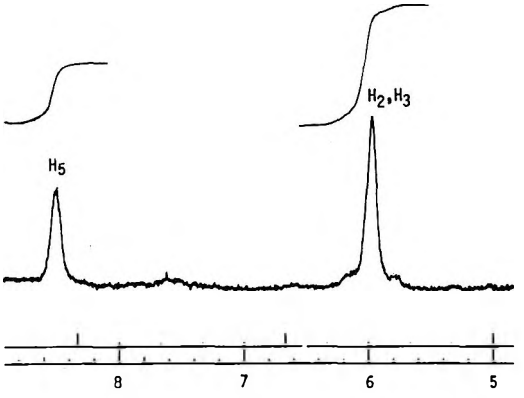


Figure 1. NMR spectrum of the vinyl proton absorptions of 2-*tert*-butyl-5-methyl-2,5-dihydropyridine (**10a**).

signments for these 2,5-dihydropyridines are based on their NMR and IR spectra, their decomposition products, and their facile reduction (lithium aluminum hydride) to the corresponding tetrahydropyridines (**12**). A series of pyridine–alkyllithium complexes (**1**) were prepared as yellow crystalline solids from pyridine and the appropriate alkyllithium compound. The reaction of each complex (**1**) with methyl iodide or ethyl bromide gave a 2,5-dialkyl(aryl)-2,5-dihydropyridine (**10**).

The NMR spectrum of 2-*tert*-butyl-5-methyl-2,5-dihydropyridine (**10a**) is representative of those obtained for other 2,5-dialkyl-2,5-dihydropyridines. It showed a broad absorption at δ 8.45 (1 H) assigned to H_5, a broad absorption at δ 6.00 (2 H) assigned to H_2 and H_3, and a multriplet at δ 4.40 (1 H) assigned to H_4. Other absorptions of **10a** were obscured by those of the solvent. The vinyl proton absorptions for **10a** are shown in Figure 1. A summary of vinyl proton absorptions for all 2,5-dialkyl-2,5-dihydropyridines (**10**) is given in Table I.

The reactions of complexes **1a–c** with alkyl halides could also give 1,2-dialkyl-1,2-dihydropyridines as a result of *N*-alkylation. However, the general absorption patterns reported[1] for the NMR spectra of alkyl-substituted 1,2-dihydropyridines differ substantially in the vinyl proton region from patterns observed in the NMR spectra obtained in these studies. Thus these reactions gave no detectable amounts of the 1,2-dihydropyridines.

The NMR spectra of some solutions containing 2,5-dihydropyridines showed additional absorptions of much lower intensity near those reported for vinyl protons H_2, H_3, and H_5. These absorptions suggest the presence of stereoisomeric 2,5-dihydropyridines in some of these mixtures. This aspect of the structures of the 2,5-dihydropyridines formed in the reactions of complex **1** with alkyl halides is currently under investigation.

Acylation of complex **1a** with acetyl chloride gave, as expected,[8,9] 1,2-dihydropyridine **13** which was sufficiently stable to be collected by preparative GLC at 150 °C.

The reactions of lithium tetrakis(*N*-dihydropyridyl)aluminate[6] and complex **1c**[9] with bromine have been reported to give 3-bromopyridine and 5-bromo-2-phenylpyridine, respectively. However, treatment of complex **1a** with either bromine or pyridinium perbromide gave no detectable amount of 5-bromo-2-*tert*-butylpyridine but did afford 6,6′-di-*tert*-butyl-3,3′-dipyridyl (**16**). The formation of dipyridyl **16** may involve 2,5-dihydropyridine intermediates **14** and **15** (Scheme III). Experiments aimed at identification of these intermediates are currently underway. Dipyridyls also have been reported[10,11] in the reactions of complexes **1b** and **1c** with other halogenating agents.

Workup and analysis of a sample of each 2,5-dialkyl-2,5-dihydropyridine (**10a–c**) revealed that each had decomposed to a mixture containing the corresponding 2,5-dialkylpyridine (**11a–c**) and the 2,5-dialkyl-1,2,5,6-tetrahydropyridine (**12a–c**). The relative percentage of dialkyltetrahydropyridine (**12**) in each reaction was less than that of the dialkylpyridine (**11**). The tetrahydropyridine may have been formed by transfer of a hydride ion from one 2,5-dihydropyridine mol-

Scheme III

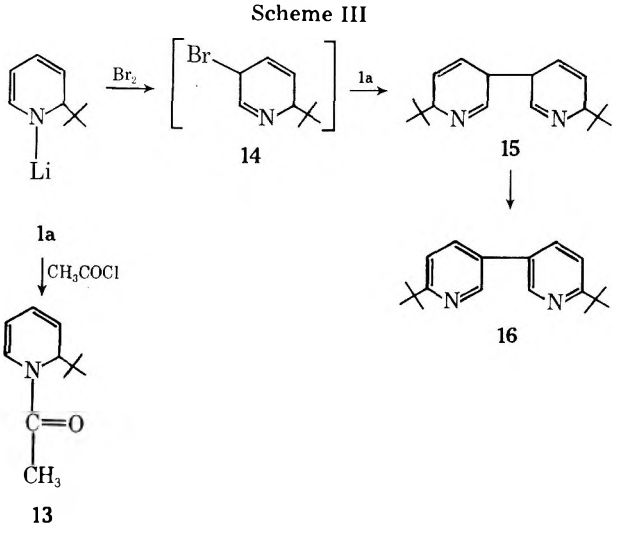
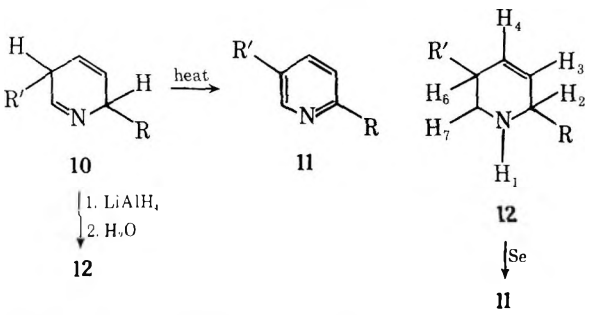


Table II. Vinyl Proton Absorptions and Elemental Analyses of Tetrahydropyridines 12a–e

compd	registry no.	vinyl protons, δ	elemental analysis: calcd C	calcd H	calcd N	found C	found H	found N
12a	66562-53-6	5.62	78.37	12.49	9.14	78.25	12.61	9.29
12b		5.65[a]	78.97	12.96	8.37	78.89	12.84	8.13
12c		5.60[b]	78.43	12.42	9.15	78.40	12.37	9.17
12d	66562-54-7	5.70	83.24	8.67	8.09	83.40	8.60	8.01
12e	66562-55-8	5.70	83.42	9.09	7.49	83.52	9.03	7.49

[a]Two broad absorptions, approximate ratio 5:1. [b]Two broad absorptions, approximate ratio 2:1.

Scheme IV



ecule to the C=N moiety of another. Compounds **11** and **12** generally could not be separated cleanly by distillation or preparative GLC. In each case a pure sample of the 2,5-dialkylpyridine (**11**) for spectral and elemental analyses was obtained from these mixtures by selenium oxidation of **12** to **11**. A pure sample of the 2,5-dialkyl-1,2,5,6-tetrahydropyridine (**12**) was prepared by the hydride reduction of the 2,5-dialkyl-2,5-dihydropyridine (**10**). These reactions are shown in Scheme IV. Decomposition of each 5-alkyl-2-phenyl-2,5-dihydropyridine (**10d** and **10e**) gave only the 5-alkyl-2-phenypyridine (**11d** and **11e**). A summary of the data obtained from these reactions is given in Table II.

The 2,5-dialkyl(phenyl)-2,5-dihydropyridines (**10**) obtained from the reactions of complex **1** with alkyl halides were expected to undergo hydride reduction at the C=N bond; accordingly, each was treated with lithium aluminum hydride. On reduction, 2,5-dihydropyridines **10a, 10d,** and **10e** each gave a single tetrahydropyridine according to GLC and NMR analyses. However, the NMR spectrum of each of the reduction products of 2,5-dihydropyridines **10b** and **10c** suggested the presence of two stereoisomeric tetrahydropyridines.

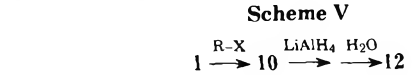
The hydride reductions described above generally gave high yields of tetrahydropyridines, and the reaction sequence shown in Scheme V may serve as a convenient synthesis of a variety of 2,5-dialkyl-1,2,5,6-tetrahydropyridines (**12**).

Experimental Section

General. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Nuclear magnetic resonance spectra were obtained on Varian T-60 and HA-100 instruments. Analyses of reaction product mixtures and relative percentage yields of products were obtained on a Varian Aerograph 90-P3 gas chromograph equipped with a 20 ft × 3/8 in. column composed of 30% SE-30 on Chromosorb W (60/80 mesh). Infrared spectra were recorded on a Perkin-Elmer 621 instrument. *tert*-Butyllithium in pentane was obtained from Lithium Corporation of America. Other alkyllithium compounds were prepared by standard procedures.

2-*tert*-Butyl-1-lithio-1,2-dihydropyridine (1a).[14] In a nitrogen-flushed drybox, 0.06 mol of *tert*-butyllithium was added to a 25 × 200 mm test tube. The test tube was sealed with a serum cap, removed from the drybox and cooled to about −70° in a dry ice–isopropyl alcohol bath. A solution of 0.04 mol of pyridine in about 10 mL of dry pentane was added slowly over a period of about 10 min by use of a syringe. The mixture was shaken vigorously after each addition. Complex **1a** began crystallizing as a yellow solid in about 1 h. The mixture was generally allowed to stand at −70 °C overnight to assure maximum crystallization.

Scheme V



2-*n*-Butyl-1-lithio-1,2-dihydropyridine (1b)[15] was prepared according to the procedure described for **1a**. Complex **1b** was obtained from pyridine and butyllithium in hexane as a yellow solid. NMR (ethyl ether): δ 6.70 (1 H, d, H_5), 5.95 (1 H, m, H_3), 4.87 (1 H, t, H_1), 4.43 (2 H, m, H_2 and H_4).

1-Lithio-2-phenyl-1,2-dihydropyridine (1c)[17] was prepared according to the procedure described previously for complex **1a** except that 0.04 mol of pyridine was added to 0.08 mol of phenyllithium[18] in ethyl ether which had been cooled to 0 °C in an ice–water bath. The mixture was allowed to stand at room temperature until the yellow complex **1c** crystallized. The mixture was generally refrigerated overnight to insure maximum crystallization. An NMR spectrum obtained for complex **1c** in tetramethylethylenediamine with Me_4Si as the internal standard agreed with that previously reported.[17]

2-*tert*-Butyl-5-methyl-2,5-dihydropyridine (10a). A syringe was used to remove the supernatent liquid from complex **1a**. The complex was washed by injecting 10 mL of dry ethyl ether or pentane into the test tube, shaking the mixture, allowing the solid to settle, and withdrawing the liquid. This procedure was repeated. A mixture of complex **1a** and about 20 mL of dry ethyl ether was slowly added by use of a syringe. As the components reacted, the solid complex dissolved. The mixture was allowed to stand at 0 °C for 2–3 h. The resultant clear, yellow solution was transferred with a syringe to a small round-bottomed flask which had been flushed with nitrogen, fitted with a serum cap, and cooled in an ice–water bath. The flask was placed on a rotary evaporator, and the mixture was concentrated at 0 °C. A sample of the concentrate was transferred with a syringe to an NMR tube, Me_4Si was added, and an NMR spectrum of complex **1a** in ethyl ether was obtained: δ 8.45 (1 H, br s, H_5), 6.00 (2 H, br s, H_2, H_3), 4.40 (1 H, m, H_4). IR: 1715, 1675, 1640 cm^{-1}.

The signals from H_1 and the methyl and *tert*-butyl groups in the NMR spectrum were obscured by absorptions from the solvent. Attempted removal of the last traces of solvent resulted in considerable decomposition of the 2,5-dihydropyridine **10a** to aromatic compound **11a** and tetrahydropyridine **12a**.

2-*tert*-Butyl-5-ethyl-2,5-dihydropyridine (10b) was prepared according to the procedure described for 2,5-dihydropyridine **10a**. Because complex **10b** proved to be more stable than complex **10a**, most reaction solvent could be removed from the sample by rotary evaporation. An NMR spectrum was obtained on a sample of **10b** in deuteriochloroform with Me_4Si: δ 8.09 (1 H, br s, H_5), 5.80 (2 H, br s, H_2, H_3), 4.02 (1 H, m, H_4), 3.64 (1 H, br, H_1), 2.41 (2 H, q, CH_3CH_2), 1.60 (3 H, t, CH_3CH_2). IR: 1710 (C=N), 1675 and 1655 cm^{-1} (C=C).

2-n-Butyl-5-methyl-2,5-dihydropyridine (10c) was prepared from complex **1b** and methyl iodide according to the procedure described for 2,5-dihydropyridine **10a**: NMR δ 8.05 (1 H, br s, H_5), 5.73 (2 H, br s, H_2, H_3), 4.48 (1 H, m, H_1). Absorptions from the methyl and butyl groups were obscured by absorptions from the solvent (pentane).

5-Methyl-2-phenyl-2,5-dihydropyridine (10d) was prepared from complex **1c** and methyl iodide by the procedure described for 2,5-dihydropyridine **10a**. The methyl iodide–ethyl ether mixture was added to complex **1c** in ethyl ether at 0 °C: NMR δ 8.30 (1 H, br s, H_5), 7.57 (5 H, s, phenyl), 5.92 (2 H, br s, H_2, H_3). Other absorptions were obscured by those of the solvent.

5-Ethyl-2-phenyl-2,5-dihydropyridine (10e) was prepared from complex **1c** and ethyl bromide by the procedure described for 2,5-dihydropyridine **10a**. The ethyl bromide–ethyl ether mixture was added to complex **1c** in ethyl ether at 0 °C. NMR δ 8.15 (1 H, br s, H_5),

5.87 (2 H, br s, H_2, H_3). Other absorptions were obscured by those from the solvent.

1-Acetyl-2-*tert*-butyl-1,2-dihydropyridine (13) was prepared from complex 1a and 0.04 mol of acetyl chloride at −70 °C. The mixture was allowed to warm to 0 °C and stand at this temperature for an additional hour. Workup as described above gave a yellow oil which GLC analysis showed to contain a single major product which was collected by preparative GLC as a colorless oil: NMR δ 6.45 (1 H, d, H_5), 6.02 (1 H, m, H_4), 5.60 (1 H, m, H_3), 5.00 (1 H, d, H_1), 2.20 (3 H, s, CH_3), 1.00 (9 H, s, *t*-Bu); IR 1680 (C=O), 1595 and 1575 cm^{-1} C=C). Anal. Calcd for $C_{11}H_{17}NO$: C, 73.76; H, 9.49; N, 7.81. Found: C, 73.59; H, 9.33; N, 7.79.

6,6′-Di-*tert*-butyl-3,3′-dipyridyl (16) was prepared from complex 1a and bromine dissolved in pentane or pyridine perbromide[19] dissolved in tetrahydrofuran by the general procedure described for 2,5-dihydropyridine **10a**. The addition of the brominating reagent to complex **1a** (−70 °C) resulted in immediate formation of a yellow solid. The mixture was shaken frequently. The resultant mixture, a clear yellow solution, was refluxed for 2 h, cooled, and shaken with 25 mL of water. The organic layer was separated and dried (K_2CO_3), and the solvent was removed by rotary evaporation. The residue, microdistilled at 10 mm, gave a mixture which by GLC analysis contained 2-*tert*-butylpyridine, 2-*tert*-butyl-1,2,5,6-tetrahydropyridine, and 6,6′-di-*tert*-butyl-3,3′-bipyridyl (**16**). Bipyridyl **16** was collected by preparative GLC as a yellow solid: mp 121–122 °C; NMR δ 8.40 (2 H, s, C_6–H, C_6′–H), 7.40 (4 H, m C_3–H, C_4–H, C_3′–H, C_4′–H), 1.25 (18 H, s, *t*-Bu, *t*-Bu′). Anal. Calcd for $C_{18}H_{24}N_2$: C, 80.61; H, 8.94; N, 10.44. Found: C, 80.69; H, 8.88; N, 10.40.

Decomposition of 2,5-Dihydropyridines. Samples (0.04 mol) of 2,5-dialkyl(aryl)-2,5-dihydropyridines were prepared as described in the previous sections. About 2 mL of water was cautiously added to each sample and the mixture was shaken. The organic layer was separated, the aqueous layer was extracted with three 10-mL portions of ethyl ether, and the combined organic portions were dried (K_2CO_3). The solvent was removed by rotary evaporation, and the residue was distilled at 10 mm of pressure. Each distillate was analyzed by GLC. Decomposition of each 2,5-dialkyl-2,5-dihydropyridine (**10a–d**) gave a mixture containing the 2,5-dialkylpyridine (**11a–d**) and the 2,5-dialkyl-1,2,5,6-tetrahydropyridine (**12a–d**). The relative percentages of **11** and **12** formed by decomposition of **10** were: **10a**, 57:43; **10b**, 74:26; **10c**, 77:23; **10d**, 100:0; **10e**, 100:0. The dialkylpyridines and dialkyltetrahydropyridines obtained in these reactions generally could not be separated completely by distillation or GLC, and the relative percentages reported are approximate. Pure samples of these products were obtained by the procedures described in subsequent sections where the spectral and elemental analyses are also reported.

Decomposition of each 5-alkyl-2-phenyl-2,5-dihydropyridine (**10d** and **10e**) gave only the 5-alkyl-2-phenylpyridine (**11e** and **11f**).

5-Methyl-2-phenylpyridine (11d) was obtained as a yellow solid from decomposition of 2,5-dihydropyridine **10d**: NMR δ 8.45 (1 H, m, H_5), 7.90 (2 H, m, H_2, H_3), 7.40 (5 H, m, phenyl), 2.33 (3 H, s, CH_3); IR 1660, 1600, 1563 cm^{-1}. Anal. Calcd for $C_{12}H_{11}N$: C, 85.21; H, 6.51; N, 8.28. Found: C, 85.04; H, 6.70; N, 8.26.

5-Ethyl-2-phenylpyridine (11e) was obtained as a yellow solid from decomposition of 2,5-dihydropyridine **10e**: NMR δ 8.15 (1 H, m, H_5), 8.33 (2 H, m, H_2, H_3), 7.73 (5 H, m, phenyl), 3.03 (2 H, q, CH_2CH_3), 1.63 (3 H, t, CH_2CH_3); IR 1647, 1595, and 1560 cm^{-1}. Anal. Calcd for $C_{13}H_{13}N$: C, 85.25; H, 7.10; N, 7.65. Found: C, 85.18; H, 7.08; N, 7.56.

General Procedure for Preparing Pure 2,5-Dialkylpyridines (11). The crude product containing a 2,5-dialkylpyridine (**11**) and a 2,5-dialkyl-1,2,5,6-tetrahydropyridine (**12**) obtained from decomposition of approximately 0.04 mol of 2,5-dialkyl-2,5-dihydropyridine (**10**) was refluxed with a small excess of selenium (5.0g) in 100 mL of phenyl ether for 36–48 h. The mixture was filtered to remove excess selenium and the filtrate was extracted with five 15-mL portions of 6 N hydrochloric acid. The aqueous layer was separated and made basic with dilute aqueous sodium hydroxide. The aqueous layer was extracted with ethyl ether, the extracts were dried (K_2CO_3), and the ether was removed by rotary evaporation. The residue was analyzed by GLC and samples of 2,5-dialkylpyridines were obtained by preparative GLC as colorless oils.

(a) 2-*tert*-Butyl-5-methylpyridine (11a): NMR δ 8.45 (1 H, s, H_5), 7.40 (2 H, m, H_2, H_3), 2.23 (3 H, s, CH_3), 1.00 (9 H, s, *t*-Bu). Anal. Calcd for $C_{10}H_{15}N$: C, 80.55; H, 10.06; N, 9.38. Found: C, 80.39; H, 9.88; N, 9.19.

(b) 2-*tert*-Butyl-5-ethylpyridine (11b): NMR δ 8.40 (1 H, s, H_5), 7.25 (2 H, m, H_2, H_3), 2.60 (2 H, q, CH_2CH_3), 1.20 (3 H, t, CH_2CH_3), 1.00 (9 H, s, *t*-Bu). Anal. Calcd for $C_{11}H_{17}N$: C, 80.99; H, 10.42; N, 8.58. Found: C, 80.77; H, 10.56; N, 8.70.

(c) 2-*n*-Butyl-5-methylpyridine (11c): NMR δ 8.38 (1 H, br s, H_5), 7.20 (2 H, m, H_2, H_3), 2.78 (2 H, t, $CH_2CH_2CH_3$), 2.30 (3 H, s, $-CH_3$), 1.55 (4 H, m, $CH_2CH_2CH_2CH_3$), 0.97 (3 H, t, $CH_2CH_2CH_2CH_3$). Anal. Calcd. for $C_{10}H_{15}N$: C, 80.54; H, 10.07; N, 9.40. Found: C, 80.46; H, 10.20; N, 9.39.

General Procedure for Preparing 2,5-Dialkyl-1,2,5,6-tetrahydropyridines (12). Pure samples of 2,5-dialkyl-1,2,5,6-tetrahydropyridines, which were formed along with the corresponding aromatic compounds when 2,5-dihydropyridines were decomposed, were prepared according to the following procedure. A 0.04-mol sample of a 2,5-dialkyl-2,5-dihydropyridine (**10**) prepared as previously described was slowly added by use of a syringe to a stirred mixture of 0.02 mol of lithium aluminum hydride in 100 mL of dry ethyl ether at 0 °C. The mixture was allowed to warm to room temperature and was stirred overnight. The reaction was quenched by the slow addition of cold water, and the layers were separated. The aqueous layer was extracted with three 100-mL portions of ethyl ether, and the combined extracts and organic layer were dried (anhydrous K_2CO_3). The crude product obtained on removal of ethyl ether by rotary evaporation was analyzed by GLC.

The NMR spectrum of each of the tetrahydropyridines **12a, 12d,** and **12e** showed a single broad absorption near δ 5.6 which suggested that a single isomer was present. However, the NMR spectrum of each of the tetrahydropyridines **12b** and **12c** was apparently that of a mixture of two stereoisomeric tetrahydropyridines as suggested by the presence of two broad absorptions near δ 5.6 as well as the presence of two sets of absorptions for other protons in the region δ 3.4–0.9. Detailed analyses of these spectra were not attempted; however, the vinyl proton absorptions and the elemental analyses of the tetrahydropyridines are summarized in Table II.

Acknowledgment. The authors wish to express appreciation for support of this research from the Robert A. Welch Foundation and the Organized Research Fund of The University of Texas at Arlington.

Registry No.—*cis*-**10b**, 66562-56-9; *trans*-**10b**, 66562-57-0; *cis*-**10c**, 66562-58-1; *trans*-**10c**, 66562-59-2; **11a**, 56029-43-7; **11b**, 66562-60-5; **11c**, 27012-26-6; **11d**, 27012-22-2; **11e**, 66562-61-6; *cis*-**12b**, 66562-62-7; *trans*-**12b**, 66562-63-8; *cis*-**12c**, 66562-64-9; *trans*-**12c**, 66562-65-0; **13**, 66562-66-1; **16**, 66562-67-2; pyridine, 110-86-1; *tert*-butyllithium, 594-19-4; butyllithium, 109-72-8; phenyllithium, 591-51-5.

References and Notes

(1) U. Eisner and J. Kuthan, *Chem. Rev.*, **72**, 1 (1972).
(2) R. E. Lyle, D. A. Nelson, and P. S. Anderson, *Tetrahedron Lett.*, 553 (1962).
(3) P. S. Anderson and R. E. Lyle, *Tetrahedron Lett.*, 153 (1964).
(4) A. I. Meyers, B. J. Betrus, N. K. Ralhan, and K. B. Rao, *J. Heterocycl. Chem.*, **1**, 13 (1964).
(5) O. Mumm and J. Diederiechsen, *Justus Liebigs Ann. Chem.*, **538**, 195 (1939).
(6) C. S. Giam and S. D. Abbott, *J. Am. Chem. Soc.*, 93, 1924 (1971).
(7) C. S. Giam and E. E. Knaus, *Tetrahedron Lett.*, 4961 (1971).
(8) C. S. Giam, E. E. Knaus, and F. M. Pasutto, *J. Org. Chem.*, **39**, 3565 (1974).
(9) C. S. Giam and J. L. Stout, *Chem. Commun.*, 478 (1970).
(10) C. S. Giam, E. E. Knaus, R. A. Lockhart, and I. G. Keener, *Can. J. Chem.*, **53**, 2305 (1975).
(11) E. E. Knaus, T. A. Ondrus, and C. S. Giam, *J. Heterocycl. Chem.*, **13**, 789 (1976).
(12) R. Levine and W. M. Kadunce, *Chem. Commun.*, 921 (1970).
(13) N. Finch and G. W. Gemenden, *J. Org. Chem.*, **40**, 569 (1975).
(14) R. F. Francis, W. Davis, and J. T. Wisener, *J. Org. Chem.*, **39**, 59 (1974).
(15) G. Fraenkel and J. C. Cooper, *Tetrahedron Lett.*, 1825 (1968).
(16) A. I. Vogel, "Practical Organic Chemistry", 3rd ed, Longman Group Limited, London, England, 1970, p 948.
(17) C. S. Giam and J. L. Stout, *Chem. Commun.*, 142 (1969).
(18) "Organic Synthesis", Collect. Vol. 2, 1st ed, Wiley, New York, N.Y., 1943, p 517.
(19) D. M. Williams, *J. Chem. Soc.*, 2783 (1931).

Chemistry of Diaminomaleonitrile. 3. Reaction with Isocyanate: A Novel Pyrimidine Synthesis[1]

Yozo Ohtsuka

Sagami Chemical Research Center, Nishi-Ohnuma, Sagamihara, Kanagawa 229, Japan

Received February 28, 1978

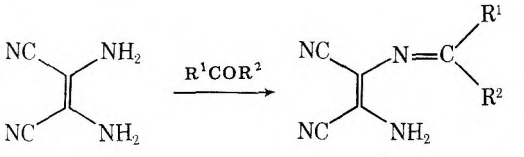
New urea derivatives of diaminomaleonitrile (DAMN, **1**) are prepared and their cyclization reactions investigated. 3-Substituted 5-alkylideneamino-6-cyanocytosines (**7**) are obtained from DAMN Schiff bases (**2**) and isocyanates by a novel trans cyclization. Similar cyclization of DAMN urea derivatives (**3**) with ketones and aldehydes was accompanied with hydration of the nitrile group to give 3-substituted 5-alkylideneaminocytosine-6-carboxamides (**9**) and 3,6-disubstituted 4-aminopyrimido[5,4-*d*]pyrimidine-2,8-diols (**10**), respectively.

Several nitrogen heterocycles, including imidazoles,[1-3] pyrazines,[4] and diazepines,[1,3] have been prepared from diaminomaleonitrile (DAMN, **1**), the tetramer of hydrogen cyanide. These syntheses have generally been based on a single reaction pattern in which **1** is used as a *cis*-1,2-diaminoethylene component. To extend synthetic versatility, a variety of the reaction pattern of **1** is desirable. One approach is exemplified by the photochemical conversion of **1** to 4-amino-5-cyanoimidazole,[5] which appears to result from the trans isomer, diaminofumaronitrile.[6] No chemical reactions of the trans isomer, however, are known mainly because it reverts to the cis isomer (**1**) under the influence of acid, base, charcoal, or light or on heating.[7] Some derivatives of **1**, such as tetramethyl[3] and bisanil compounds,[8] are known to have the trans geometry about the central carbon–carbon double bond of the skeleton of **1**. Again the chemical properties of these compounds have not yet been examined.

Here, we want to present a new reaction pattern of DAMN, in which **1** is used as a *trans*-1,2-diaminoethylene component. This is demonstrated by the successive reaction of **1** with carbonyl compounds and isocyanates to give pyrimidine derivatives.

Results and Discussion

Open-Chain Compounds. Condensation of **1** with aldehydes or ketones is known to afford Schiff bases.[1,3] These compounds are generally believed to have maleonitrile structure **2** (cis configuration) from their IR spectra, the presence of two nitrile bands near 2230 and 2200 cm^{-1}, and their chemical properties, especially the facile formation of



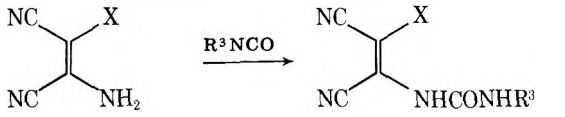
1 **2**

a, R^1 = Ph; R^2 = H
b, R^1 = 4-ClC_6H_4; R^2 = H
c, R^1 = 4-$CH_3OC_6H_4$; R^2 = H
d, R^1 = 4-$NO_2C_6H_4$; R^2 = H
e, R^1 = 2-furyl; R^2 = H
f, R^1 = R^2 = Ph

1,4-diaza heterocycles. DAMN Schiff bases **2a–f**[1,3,9] were prepared for the present study.

Synthesis of the phenylurea derivative **3e** (see Table I) from **1** and phenyl isocyanate[3] has been extended here to the preparation of alkyl derivatives. The reaction proceeded at room temperature without catalyst in acetonitrile solvent to give the corresponding monourea derivatives **3a–d** in moderate yields as shown in Table I. *N*-Benzyl DAMN's **4a–c**, prepared from **2a–c** by sodium borohydride reduction,[3] reacted similarly with isocyanates, and *N*-benzyl-*N'*-urea derivatives **5a–c** were obtained (Table I). Table I also includes an *N*-benzylidene-*N'*-urea derivative (**6a**) which was isolated by a base-catalyzed reaction of **2b** and methyl isocyanate in acetone, but the latter reaction generally afforded cyclized products (vide post).

Spectroscopic data of these open-chain ureas are presented in the supplement of Table I (see supplementary material). Two nitrile absorptions in the IR spectra of **3, 5,** and **6a** are observed in regions at 2250–2228 and 2210–2195 cm^{-1}. The spectral similarity with Schiff bases **2** and the facile formation of **3** and **5** without any acid or base catalyst suggest that the compounds in Table I also have cis configurations. The



1, X = NH_2
4, X = $NHCH_2Ar$
2b, X = N=CHC_6H_4Cl
3, X = NH_2
5, X = $NHCH_2Ar$
6a, X = N=CHC_6H_4Cl

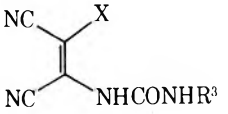
characteristic mass pattern is a molecular ion of low intensity and the fragmentation by loss of alkyl- or arylamine.

Cytosine Derivatives (Table II). By reaction of isocyanates and DAMN Schiff bases (**2a–c** and **2f**), 3-substituted 5-alkylideneamino-6-cyanocytosines (**7a–d**) were obtained. Proof of the structure rests primarily on microanalytical and spectral evidence. The IR spectra of **7** exhibit one nitrile band at 2200 cm^{-1} and two characteristic absorptions in the 1733–1740 and 1630–1660 cm^{-1} regions. The mass spectra contain a molecular ion of moderate intensity, loss of the substituent at position 3 and loss of alkyl or aryl cyanide at position 5, indicating the presence of a stable ring. The lack of alkyl- or arylamine splitting in the major fragmentation process almost excludes the possibility that the products are open-chain compounds (Table I) or 4-alkylamino- or 4-arylaminocytosines by the Dimroth rearrangement. The NMR spectra of **7** exhibit two NH protons (exchangeable), for **7d** at δ 8.93 and 8.62, and a diffused signal at δ 11–12.[10] In the spectra of **7a–c**, the azomethine proton on the side chain at position 5 is observed as two signals: for **7b** at δ 8.47 and 8.43. When **7a,b** were subjected to sodium borohydride reduction, the spectra of the products (**8a,b**) showed the signal of benzyl protons at δ 4.4 and no azomethine proton signal. The structure having an azomethine side chain was confirmed by the above result, but attempts to hydrolyze either the 5-azomethine or 6-cyano groups were unsuccessful. In most cases, **7** was recovered unchanged. Prolonged treatment of **7a** with CH_3CO_2H–H_2O_2 gave 4-amino-3,6-diphenylpyrimido[5,4-*d*]pyrimidine-2,8-diol (**10g**).

Cytosine **7b** was prepared by the reaction of **2b** and CH_3NCO with Et_3N in acetonitrile. As mentioned above, the open-chain compound **6a** was isolated when the same reaction was performed in acetone, in which **6a** is sparingly soluble. Therefore, it seems that **6a** is an intermediate of the reaction

0022-3263/78/1943-3231$01.00/0

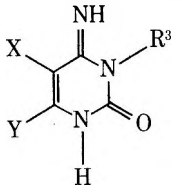
Table I. Open-Chain Urea Derivatives of Diaminomaleonitrile



Compd[a,b]	R^3	X	Yield, %	Recrystn solvent	Decompn point, °C
3a	Me	NH_2	85	CH_3CN	~167
3b	*i*-Pr	NH_2	67	CH_3CN	~184
3c	*n*-Bu	NH_2	62	$CH_3COOC_2H_5$	~162
3d	Cyclohexyl	NH_2	40	$CH_3COOC_2H_5$	~173
3e	Ph	NH_2	92	CH_3CN	~230[c]
5a	Me	$PhCH_2NH$	47	$CH_3COOC_2H_5$	151–152
5b	Me	4-$ClC_6H_4CH_2NH$	20	$CH_3COOC_2H_5$	174–175
5c	*i*-Pr	4-$CH_3OC_6H_4CH_2NH$	42	$CH_3COOC_2H_5$ + *n*-hexane	138–141
6a	Me	4-$ClC_6H_4CH{=}N$	75	CH_3CN	208–210

[a] Satisfactory analytical data (±0.4% for C, H, N, and Cl) were reported for all new compounds listed in the table (see the supplementary material). [b] For spectral data, see the supplementary material. [c] Reference 3.

Table II. Substituted Cytosines



Compd[a,b]	Y	X	R^3	Reaction time, h (temp, °C)	Yield, %	Recrystn solvent	Mp, °C
7a	CN	$PhCH{=}N$	Ph	0.1 (70)	97	CH_3CN	233–235 dec
7b	CN	4-$ClC_6H_4CH{=}N$	Me	0.2 (70)	64	CH_3NO_2	235–238 dec
7c	CN	4-$CH_3OC_6H_4CH{=}N$	*i*-Pr	18 (RT)[c]	90	CH_3CN	213–215 dec
7d	CN	$Ph_2C{=}N$	*n*-Bu	2 (RT)	18	C_2H_5OH (aq)	196–197 dec
8a	CN	$PhCH_2NH$	Ph	0.25 (5)	85	CH_3CN	159–160 dec
8b	CN	4-$ClC_6H_4CH_2NH$	Me	0.25 (5)	82	CH_3CN	172–173 dec
9a	$CONH_2$	$Me_2C{=}N$	Ph	1 (RT)	59	CH_3CN	>300
9b	$CONH_2$	4-$NO_2C_6H_4C(Me){=}N$	Me	3 (RT)	58	CH_3CN	>300

[a] Satisfactory analytical data (±0.4% for C, H, N, and Cl) were reported for all new compounds listed in the table (see supplementary material). [b] For spectral data, see the supplementary material. [c] RT = room temperature.

to give **7b**, and it was separated as a precipitate at an early stage of the reaction by the latter experiment. In fact, treatment of **6a** with aqueous sodium hydroxide followed by neutralization gave **7b**. Compound **7b** was also obtained by oxidation of **5b** with manganese dioxide in dimethylformamide. The oxidation conditions have been developed by Begland[8] for the preparation of benzylidene derivatives of **1** from the corresponding benzyl derivatives. Hence, the oxidation of **5b** gave presumably **6a**, which would afford **7b** in situ by the same mechanism.

The reaction to give **7** seems to demand the presence of a base catalyst since **6a** is recovered unchanged from the hot acetonitrile solution. Previous preparations of DAMN derivatives have generally been carried out under neutral or acidic conditions, and the trans-type (fumaronitrile-type) reaction of **1** has not been observed (except in a case[8] that will be discussed below). We postulated that the cytosine **7** synthesis proceeded through a base-catalyzed isomerization of **6** to **6′**, as illustrated in Scheme I.

Oxidation of **1** is known to result in a trans compound, diiminosuccinonitrile.[11] The patent on a bisanil dye,[8] Ar-CH=NC(CN)=C(CN)N=CHAr′, states that the trans compound is prepared from **1** and an aldehyde with concentrated sulfuric acid, whereas the cis isomer is obtained under milder conditions, and that the cis isomer can be converted into the trans isomer by heating it in benzene containing a small amount of iodine. Hydrogen abstraction from **1** is presumably the initiation step of the photochemical cis–trans isomerization of **1**.[6] These previous examples seem to indicate the importance of oxidation [probably at the amino or imino group adjacent to the C=C bond] for the isomerization. Accordingly, it is probable to consider that the isomerization of **6** into **6′** in Scheme I is initiated by such a hydrogen abstraction with triethylamine, but further evidence was not obtained in the present investigation. We are seeking clearer evidence

Scheme I

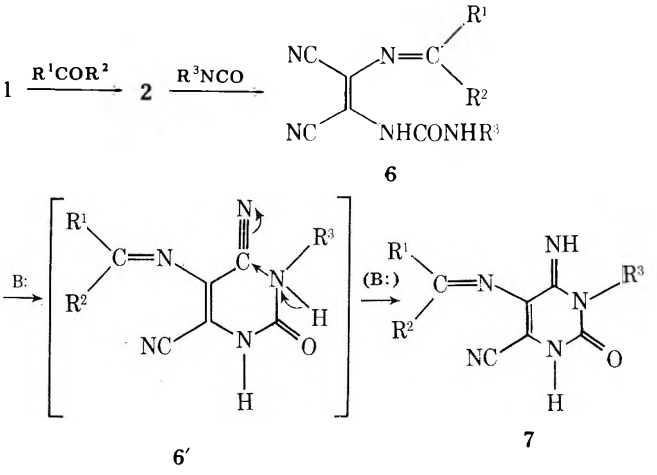
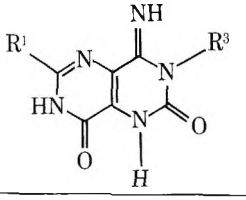


Table III. Pyrimido[5,4-*d*]pyrimidines



Compd[a,b]	R^1	R^3	Method[c]	Reaction time, h	Yield, %	Recrystn solvent	Mp, °C
10a	Me	Me	A	24	37	EtOH	294–295
			B	18	44		
10b	Me	*n*-Bu	A	24	12	CH_3CN	260–261
10c	Ph	*n*-Bu	A	6	56	CH_3CN	296–298
10d	2-Furyl	Cyclohexyl	A	2	53	CH_3CN	>300
10e	H	Ph	A	6	30	CH_3CN	>300
10f	Me	Ph	A	4	82	CH_3CN	>300
10g	Ph	Ph	A	1	69	CH_3CN	>300
			B	6	15		
10h	4-$NO_2C_6H_4$	Ph	A	0.3	72	CH_3CN	>300

[a] Satisfactory analytical data (±0.4% for C, H, N, and Cl) were reported for all new compounds listed in the table (see supplementary material). [b] For spectral data, see the supplementary material. [c] Method A, from **3** and R^1CHO; method B, from **3** and R^1CO-CH_2CO_2Et.

to understand the reaction.

The cyclization, 6′ to 7 in Scheme I, seems to be a fast reaction, and attempts to isolate **6′** failed. A similar cyclization by the addition of an urea moiety to the intramolecular cyano group has been reported in the preparation of 3-alkyl-5-cyanocytosine from 3-alkylureidomethylenemalononitrile.[12]

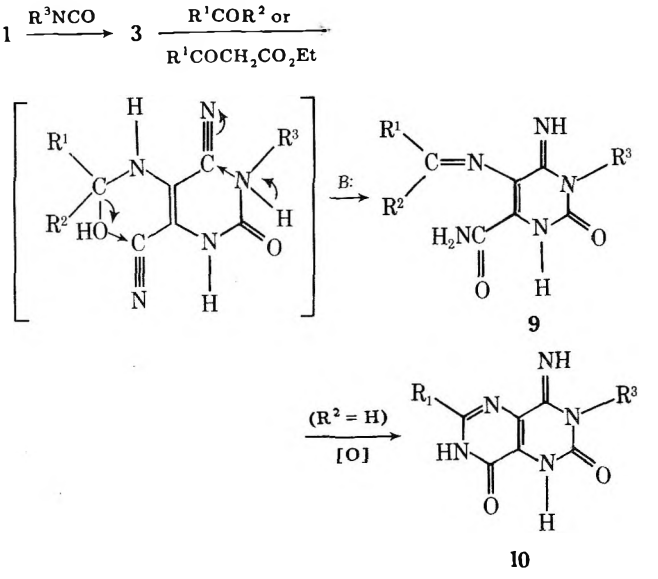
It was expected from Scheme I that cytosine **7** would also be obtained by the reversed reaction sequence: reaction of **1** and R^3NCO to give **3** followed by condensation with R^1COR^2. However, the reactions of **3** with ketones did not afford **7**, but instead the corresponding 6-carboxamides (**8a,b**) as shown in Table II. This reaction will be discussed in the next section.

Pyrimido[5,4-*d*]pyrimidines (Table III). The reaction of urea derivatives **3a–d** and aldehydes in the presence of triethylamine gave 3,6-disubstituted 4-aminopyrimido[5,4-*d*]pyrimidine-2,8-diols (**10a–h**) as colorless high-melting crystals. The structure of **10a–h** is consistent with their IR and mass spectra, which are characteristic with strong peaks attributed to the loss of $R^1C(=NH)NHCHO$ from the molecular ion (the spectroscopic data are presented in the supplement of Table III in the supplementary material). Their NMR spectra indicate the presence of three NH protons (exchangeable), one on the external nitrogen, for **10c** at δ 11.3, and two on the ring, for **10c** at δ 8.0 and 7.8. The structure **10** is confirmed by both the above-mentioned results that the hydration of **7a** gives **10g** and that the reaction of **3** and ketone gives **9**. The compound corresponding to **9a,b** is probably the precursor of **10** when R^2 is H.

The reaction to afford **10** proceeds smoothly at room temperature in an alcohol solvent, and the products are separated gradually as precipitates. An aqueous solution of aldehyde can be used as the reactant: formaline for **10a** and a 90% solution of *acetaldehyde for* **10b** *and* **10f**. *Using ethyl acylacetate* (method B) instead of aldehyde (method A) gave the same product **10**. The use of ethyl acylacetate had been developed for the preparation of imidazoles in a previous study[1] to introduce an RC≤ component by elimination of ethyl acetate. In the present study, however, imidazole formation giving rise to purine derivatives by cyclization with the 4-imino group is not observed, but further investigation under modified conditions is being undertaken.

Yamada and his co-workers[13] reported the formation of 4,8-diaminopyrimido[5,4-*d*]pyrimidine from hydrogen cyanide and formamidine in anhydrous liquid ammonia, and they explained the result by reaction of 2 mol of formamidine and diaminofumaronitrile, a postulated intermediate. Since the formation of **1** in their system was proved, the present study indicates another possibility of the mechanism, this being that the pyrimidopyrimidine resulted from an *N,N′*-bis(aminomethylene) derivative of **1** by a trans cyclization.

Scheme II



By the successive reaction **1** → **2** → **7** (Scheme I), one of the nitrile groups of **1** is left unchanged. Hydration of the C-6 nitrile group of **7** did not occur under the mild conditions used in the present synthesis. On the other hand, no nitrile compound was isolated by the reaction of reversed sequence, (**1** → **3**) → **9** or **10**, although the same type of trans cyclization occurred under closely similar reaction conditions. The nitrile group seems to be hydrated along with the carbonyl condensation. Thus, a mechanism involving intramolecular transfer of a water molecule is proposed as illustrated in Scheme II.

Oxidative cyclization of **9** into **10** occurs presumably by atmospheric oxygen. Oxidation during the workup of a *cis*-2,3-dihydropyrazine derivative into the corresponding pyrazine has been reported.[14]

Experimental Section

NMR spectra were determined using Me_2SO-d_6 solutions in a Varian HA-100 spectrometer, infrared (IR) spectra by KBr discs on a Hitachi EPR-G3 Infracord spectrometer, and mass spectra on a Hitachi RMU-6E mass spectrometer. All melting points were measured on a Yanagimoto MP-21 micro hot-stage apparatus and were corrected.

Diaminomaleonitrile (DAMN, 1) was purchased from the Nippon Soda Co., Ltd. (grade A; 98% purity). DAMN Schiff bases (**2a**,[9a] **2b**,[3] **2c**, **2d**,[9b] **2e**,[9c] and **2f**[1]) were prepared from 1 and aldehydes or benzophenone. *N*-Benzyl derivatives of 1 were prepared by the sodium borohydride reduction[3] of **2a–c**: ***N*-(4-chlorobenzyl)diaminomaleonitrile (4b)**, mp 130–131 °C dec (recrystallized from benzene), was prepared in a solvent mixture of methanol (50 mL), tetrahydrofuran (75 mL), and dimethyl sulfoxide (40 mL) from **2b** (9.2 g) and sodium borohydride (14.0 g) in 94% yield; ***N*-(4-methoxybenzyl)-diaminomaleonitrile (4c)**, mp 137–138 °C dec (recrystallized from benzene), was similarly prepared from **2c** in 96% yield.

General Procedure for DAMN Urea Derivatives 3a–e and 5a–c (Table I). A mixture of isocyanate (0.09 mol), 1 or **4a–c** (0.03 mol), and acetonitrile (50 mL) was stirred at room temperature for 24 h. The reaction mixture was then chilled and filtered to yield a solid product, which was washed with cold acetonitrile. When the reaction was carried out in other solvents than acetonitrile, such as tetrahydrofuran, major parts of the reactants were recovered unchanged.

***N'*-Methylurea Derivative of *N*-(4-Chlorobenzylidene)diaminomaleonitrile (6a).** Three drops of triethylamine were added to a mixture of 3.0 g of **2b**, 4.8 g of methyl isocyanate, and 50 mL of acetone. The reaction mixture was warmed gently at about 40–50 °C until precipitates separated (within few minutes) and then stirred at room temperature. After 15 min the solid product was collected by filtration and washed with acetone to give 2.8 g of a yellow-white powder. Recrystallization gave colorless needles (see Table I). Its NMR spectrum showed an azomethine proton at δ 7.50.

General Procedure for 3-Substituted 5-Alkylideneamino-6-cyanocytosines (7a–c; Table II). Compounds **7a**, **7c**, and **7d** were obtained by the same procedure described for **6a** at the temperature indicated in Table II from the corresponding isocyanate (R^3NCO) and **2a**, **2c**, and **2f**, respectively. Compound **7b** was obtained by the method using acetonitrile instead of acetone. A compound identical with **7b**, confirmed by its melting point and IR spectrum, was obtained by the following two methods. (1) A mixture of 0.29 g of **5b**, 0.3 g of activated manganese dioxide, and 5 mL of dimethylformamide was kept at about 70 °C for 4 h with occasionally shaking. Then the solid was removed by filtration and washed with a small quantity of dimethylformamide. The filtrate and washing were gathered and diluted by water to give 0.1 g of the product. (2) **6a** was dissolved in a 10% aqueous solution of NaOH and then neutralized with acetic acid to give **7b** as a white precipitate.

Reduction of 7 with $NaBH_4$. To an ice-cooled mixture of 1.0 g of **7a** and 25 mL of tetrahydrofuran was added 1.0 g of sodium borohydride portionwise. On stirring, **7** gradually dissolved into the solution which turned yellow to red-brown. Then the reaction mixture was poured into 300 mL of ice water. Filtration and washing with water gave 0.85 g of **8a** as a yellow powder (see Table II). By the same treatment **7b** gave **8b**.

Hydrolysis of 7. A mixture of 0.3 g of **7a**, 2 mL of hydrogen peroxide, and 10 mL of acetic acid was stirred at room temperature for 4 days. After neutralization with ammonium hydroxide, 0.1 g of a solid product was obtained in which a small amount of **7a** was included, as investigated by its IR spectrum. Recrystallization from a large volume of acetonitrile gave a compound identical in all respects with **10g** (see later). By the following treatments **7a** was recovered unchanged: (1) stirring with aqueous ammonia (28%) at room temperature for 2 h; (2) stirring with $NaOCH_3$ in methanol at room temperature for 16 h; (3) on heating at 60–80 °C with a catalytic amount of *p*-toluenesulfonic acid in dimethylformamide for 2 h.

5-Isopropylideneamino-3-phenylcytosine-6-carboxamide (9a) was prepared similarly by stirring a mixture of 1.0 g of **3e**, 1 mL of triethylamine, and 30 mL of acetone. Filtration and washing with acetone gave the product **9a** as a white powder: NMR δ 1.34 (s, 6, CH_3), 7.47 (m, 5), 7.5 (broad, 2, NH). Other spectral data are shown in the supplement of Table II (see supplementary material).

The treatment of 0.83 g of **3a**, 0.9 g of *p*-nitroacetophenone, and 20 mL of methanol gave **9b** as a yellow powder (Table II).

General Procedure for 3,6-Disubstituted 4-Aminopyrimido[5,4-*d*]pyrimidine-2,8-diol (10; Table III). Method A. Triethylamine was added to a mixture of **3** (0.01 mol), aldehyde (0.02 mol), and 80–100 mL of methanol or ethanol, and the reaction mixture was stirred for the length of time indicated in Table III. Filtration gave the first crop, and an additional crop was obtained from the filtrate after allowing it to stand for several hours. The ratio of triethylamine was varied from a catalytic amount (a few drops) to an equimolecular quantity (0.01 mol), but no substantial effect on the yield was observed. The addition of the base was carried out under cooling when aqueous solutions of aldehydes were used since a rapid decomposition was observed on heating **3** with water.

Method B. The above procedure was repeated using ethyl acylacetate (ethyl acetoacetate for **10a** and ethyl benzoacetate for **10g**) instead of aldehyde (acetaldehyde for **10a** and benzaldehyde for **10g**). The reaction proceeded in a similar manner, and identical products were obtained.

Registry No.—**1**, 1187-42-4; **2a**, 56029-18-6; **2b**, 51802-11-0; **2c**, 59574-37-7; **2f**, 55752-09-5; **3a**, 66483-01-0; **3b**, 66483-00-9; **3c**, 66482-99-3; **3d**, 66482-98-2; **3e**, 51802-29-0; **4a**, 51802-03-0; **4b**, 66551-64-2; **4c**, 66482-86-8; **5a**, 66483-02-1; **5b**, 66482-97-1; **5c**, 66482-96-0; **6a**, 66483-10-1; **7a**, 66483-09-8; **7b**, 66483-08-7; **7c**, 66483-07-6; **7d**, 66483-06-5; **8a**, 66483-05-4; **8b**, 66483-04-3; **9a**, 66483-03-2; **9b**, 66482-95-9; **10a**, 66482-94-8; **10b**, 66482-93-7; **10c**, 66482-92-6; **10d**, 66482-91-5; **10e**, 66482-90-4; **10f**, 66482-89-1; **10g**, 66482-88-0; **10h**, 66482-87-9; PhNCO, 103-71-9; *i*-Pr-NCO, 1795-48-8; BuNCO, 111-36-4; MeCHO, 75-07-0; PhCHO, 100-52-7; 2-furancarboxaldehyde, 98-01-1; HCHO, 50-00-0; 4-$NO_2C_6H_4$-CHO, 555-16-8; $MeCOCH_2CO_2Et$, 141-97-9; $PhCOCH_2CO_2Et$, 94-02-0.

Supplementary Material Available: Spectral and analytical data (5 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Par: 2: Y. Ohtsuka, *J. Org. Chem.*, **41**, 629 (1976).
(2) (a) Y. Ohtsuka, *J. Org. Chem.*, **41**, 713 (1976); (b) W. A. Sheppard and O. W. Webster, *J. Am. Chem. Soc.*, **95**, 2695 (1973).
(3) R. W. Begland, D. R. Hartter, F. N. Jones, D. J. Sam, W. A. Sheppard, O. W. Webster, and F. J. Weigert, *J. Org. Chem.*, **39**, 2341 (1974).
(4) F. D. Popp, *J. Heterocycl. Chem.*, **11**, 79 (1974).
(5) J. P. Ferris and F. R. Antonucci, *J. Am. Chem. Soc.*, **96**, 2010 (1974).
(6) T. H. Koch and R. M. Rodehorst, *J. Am. Chem. Soc.*, **96**, 6707 (1974).
(7) E. Ciganek, W. J. Linn, and O. W. Webster in "The Chemistry of the Cyano Group", Z. Rappoport, Ed., Interscience, New York, N.Y., 1970, p 508.
(8) R. W. Begland, U.S. Patents 3 912 724 and 3 914 276 (1975).
(9) (a) P. S. Robertson and J. Vaughan, *J. Am. Chem. Soc.*, **80**, 2691 (1958); (b) L. E. Hinkel, G. O. Richards, and O. Thomas, *J. Chem. Soc.*, 1432 (1937); (c) K. Onoda, *Nippon Nogei Kagaku Kaishi*, **36**, 255 (1962).
(10) These data did not give clear enough information to distinguish structure **7** from the tautomeric 4-amino structure. The ^{13}C NMR spectrum [in Me_2SO-d_6 with $Cr(AcAc)_3$] of **7b** showed two equivalent carbons at 112.9 ppm (downfield from Me_4Si) and one at 119.1 ppm for C-4, C-5, and C-6, assigned by the aid of a partial decoupling experiment and comparison with the spectrum of **2b**. The C-4 carbon of cytosine (predominant amino form) was observed at a much lower field at 171.0 ppm: M. P. Schweizer, E. B. Barta, J. T. Witkowski, and R. K. Robins, *J. Am. Chem. Soc.*, **95**, 3770 (1973). This difference suggests that structure **7** is preferable, and the reactivity of **7**, especially the lack of reactivity of the 4 substituent, seems to support this conclusion
(11) O. W. Webster, D. R. Hartter, R. W. Begland, W. A. Sheppard, and A. Cairncross, *J. Org. Chem.*, **37**, 4133 (1972).
(12) B. B. Kehm and C. W. Whitehead, "Organic Syntheses", Collect. Vol. 4, Wiley, New York, N.Y., 1967, p 515.
(13) Y. Yamada, I. Izumi, I. Kumashiro, and T. Takenishi, *Bull. Chem. Soc. Jpn.*, **42**, 1454 (1969).
(14) A. Padwa, M. Dharan, J. Smolanoff, and S. I. Wetmore, Jr., *J. Am. Chem. Soc.*, **95**, 1954 (1973).

Notes

Formation of Cyclic Disulfide Cation Radicals in the Electron Impact Induced Fragmentation of Mesocyclic Dithioethers

W. Kenneth Musker,* Barry V. Gorewit, Patricia B. Roush, and Thomas L. Wolford

Department of Chemistry, University of California, Davis, Davis, California 95616

Received January 9, 1978

Recently, we reported[1] that long-lived cation radicals are formed at room temperature in acetonitrile when certain mesocyclic dithioethers are treated with one-electron oxidizing agents such as NO^+ or Cu^{2+}. The enhanced stability of these cation radicals derived from mesocyclic dithioethers is attributed to an interaction between the transannular thioether group and the oxidized thioether to give a ring-fused system with an S–S bond. Because of this unusual behavior, we decided to investigate the mass spectra of mesocyclic dithioethers to determine if a similar transannular interaction gives fragmentation products containing S–S bonds.

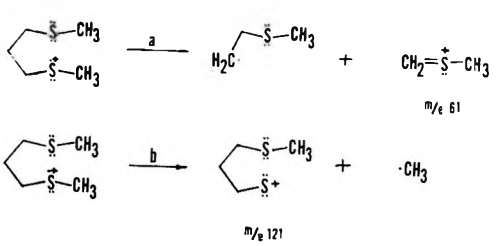
The compounds examined are 1,4-dithiane (1,4-DT), 1,4-dithiacycloheptane (1,4-DTCH), 1,5-dithiacyclooctane (1,5-DTCO), 1,4-dithiacyclooctane (1,4-DTCO), 1,5-dithiacyclononane (1,5-DTCN), 1,4-dithiacyclononane (1,4-DTCN), 1,6-dithiacyclodecane (1,6-DTCD), 2,5-dithiahexane (2,5-DTH), 2,6-dithiaheptane (2,6-DTHP), 2,7-dithiaoctane (2,7-DTO), and 2,8-dithianonane (2,8-DTN).

Results and Discussion

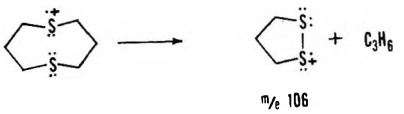
The mass spectra of most thioethers are similar to those of ethers. Normally, cleavage occurs either between the sulfur–carbon bond or the α,β carbon–carbon bond.[2] For example, the mass spectrum of 2,6-dithiaheptane (Scheme I) exhibits strong peaks at *m/e* 121 and 61. However, mesocyclic dithioethers exhibit intense peaks at *m/e* 106 when five-membered ring (1,2-dithiolane) and at *m/e* 120 when six-membered ring (1,2-dithiane) cation radicals can be formed by a transannular interaction. In Scheme II, the formation of the 1,2-dithiolane cation radical from 1,5-dithiacyclooctane is illustrated. This cation radical dominates the spectrum and is more than twice as intense as the parent. A similar decomposition to give the *m/e* 106 peak can be seen in both 1,5-dithiacyclononane and 1,4-dithiacycloheptane where a trimethylene chain also spans the two thioether groups.

The 1,2-dithiane cation radical forms when a tetramethylene chain spans the two thioether groups. In 1,5-dithiacyclononane, both 1,2-dithiolane and 1,2-dithiane cation radicals are observed (Scheme III), whereas 1,6-dithiacyclodecane and

Scheme I. Cleavage of 2,6-Dithiaheptane: (a) α,β C–C Cleavage; (b) S–C Cleavage



Scheme II. Cleavage of 1,5-Dithiacyclooctane



1,4-dithiacyclooctane give only the 1,2-dithiane cation radical. Subsequent cleavage of the 1,2-dithiane cation radical gives an intense peak at *m/e* 55 which is identical with that reported in the fragmentation of 1,2-dithiane itself.[3]

1,2-Dithiolane and 1,2-dithiane radical cations are also observed in the mass spectra of macrocyclic tetrathioethers, where a trimethylene chain (1,5,9,13-tetrathiacyclohexadecane) or a tetramethylene chain (1,6,11,16-tetrathiacycloeicosane), respectively, spans two sulfur atoms.

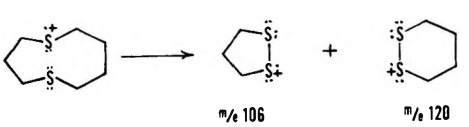
Only a weak peak due to a four-membered ring cyclic disulfide cation radical (*m/e* 92) is observed when a dimethylene bridge spans the two thioether groups (i.e., in 1,4-dithiacyclooctane, 1,4-dithiacycloheptane, and 1,4-dithiane). Apparently, the strain involved in forming a four-membered ring is so large that alternative cleavage modes predominate. To determine whether cation radicals with ring size greater than six form when the two thioether groups are separated by five methylene groups, 1,4-dithiacyclononane was examined. No seven-membered ring formation was observed as evidenced by the lack of a peak at *m/e* 134.

As part of a study of the photochemistry of dithioketals, Willett[4] also examined the mass spectra of a series of bicyclic dithioethers in which the two sulfur atoms are separated by two and three methylene groups. He reported that the 1,2-dithiolane cation radical and the 1,2-dithiacyclobutane cation radical are formed when the distance between the two sulfur atoms is relatively short. For example, he showed that in the two isomeric 2,6-dithiabicyclo[5.3.0]decanes, the cis isomer exhibits a more intense peak at *m/e* 106 than the trans isomer. However, when he examined the spectrum of 2,6-dithiabicyclo[5.3.1]undecane, a molecule in which the distance between the two sulfur atoms is longer, no peak appeared at *m/e* 106.[4]

These results suggest that an interaction between the two sulfur atoms must occur prior to any bond breaking process in order to produce cyclic disulfide cation radicals.

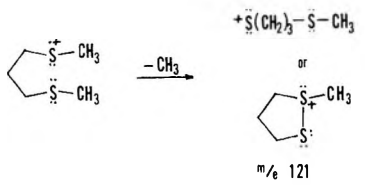
In 1,5-dithiacyclooctane a small peak is observed at *m/e* 74. Since this peak is at one-half the molecular weight of 1,5-dithiacyclooctane, the possibility that this peak is due to the dication of 1,5-dithiacyclooctane was considered.[5] However, since the relative intensity of the peak at *m/e* 74 did not change at different ionizing voltages, this peak is probably due to a normal fragmentation path of simple thioethers. A series of peaks at 45–47, 59–61, 73–75, and 87–89 are observed in the decomposition of thioethers when one, two, three, and four methylene groups are originally present on the sulfur atom. Thus the strong peak at *m/e* 88 in 1,6-dithiacyclodecane, one-half its molecular weight, and the small peaks at *m/e* 74

Scheme III. Cleavage of 1,5-Dithiacyclononane



0022-3263/78/1943-3235$01.00/0

Scheme IV. Cleavage of 2,6-Dithiaheptane



in 1,4-dithiacyclooctane and at *m/e* 60 in 1,4-dithiane are most likely due to fragments in this series rather than to the dications. To further support the belief that no dicationic species are formed in any of these dithioethers, it is noted that there is *no peak* at *m/e* 81 in the spectrum of 1,5-dithiacyclononane or 1,4-dithiacyclononane or at *m/e* 67 in 1,4-dithiacycloheptane.

The mass spectra of some acyclic dithioethers were obtained by Shuttleworth,[6] who reported relatively intense peaks at *m/e* 121 in 2,6-dithiaheptane (Scheme IV) and *m/e* 135 in 2,7-dithiaoctane corresponding to loss of a CH_3 group from the cation radical. However, the intensity of the peaks at *m/e* 107 in 2,5-dithiahexane and at *m/e* 149 in 2,8-dithianonane, which are attributed to the loss of one CH_3 group from the parent, were lower. Budzikewicz, Djerassi, and Williams[2] suggested that the *m/e* 121 peak in 2,6-dithiaheptane might be due to a cyclic ion rather than to a linear ion. In view of our results on mesocyclic dithioethers, the formation of cyclic ions in 2,6-dithiaheptane and 2,7-dithiaoctane appears more plausible. Since we did not observe either four-membered or seven-membered ring formation in mesocyclic systems in which two thioether sulfurs were bridged by two and five methylene groups, the rather low intensity of the peaks at *m/e* 107 and 149 in the mass spectrum of 2,5-dithiahexane and 2,8-dithianonane, respectively, are expected.

Experimental Section

The mass spectra were run on a CE 21-104. The 1,4-dithiane was purchased from the Aldrich Chemical Co., Inc., and was sublimed before use. 1,4-Dithiacycloheptane,[7] 1,5-dithiacyclooctane,[8] 1,4-dithiacyclooctane,[9] 1,5-dithiacyclononane,[9] 1,6-dithiacyclodecane,[10] 2,5-dithiahexane,[11] 2,6-dithiaheptane,[12] and 2,7-dithiaoctane[12] were synthesized following reported procedures.

1,4-Dithiacyclononane. Into a 3-neck 2-L Morton flask fitted with overhead stirrer, condenser, and adaptor for syringe pump was added 1 L of absolute ethanol. With stirring, 12 g (0.52 g-atom) of freshly cut sodium was added under nitrogen. The solution was heated to 50 °C and 21 mL (0.25 mol) of 1,2-ethanedithiol diluted to 100 mL with absolute ethanol and 57.5 g (0.25 mol) of 1,5-dibromopentane diluted to 100 mL with absolute ethanol were added simultaneously by a syringe pump at a rate of 0.30 mL/min. The mixture was refluxed for 0.5 h and then concentrated under vacuum. Water was added to the remaining thick oil, and the mixture was extracted three times with dichloromethane. The combined organic phase was dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was distilled under vacuum to give 0.24 g (0.6%) of 1,4-dithiacyclononane: bp 65–67 °C (0.3 mm); mp 59–60 °C; ^1H NMR (CCl_4) δ 2.8 (m, 8, CH_2-S), 1.9 (m, 6, —CH_2—); ^{13}C NMR ($CDCl_3$) δ 34.8, 33.5, 27.9, 24.5.

Registry No.—1,4-DT, 505-29-3; 1,4-DTCH, 6008-55-5; 1,5-DTCO, 6572-95-8; 1,4-DTCO, 6572-94-7; 1,5-DTCN, 6573-47-3; 1,6-DTCD, 51472-64-1; 2,5-DTH, 6628-18-8; 2,6-DTHP, 24949-35-7; 2,7-DTO, 15394-33-9; 2,8-DTN, 54410-63-8; 1,2-dithiolane cation radical, 66609-63-0; 1,2-dithiane cation radical, 56587-33-8.

Supplementary Material Available: Bar graphs showing the mass spectra of all the dithioethers are presented (5 pages). Ordering information is given on any current masthead page.

References and Notes

(1) W. K. Musker and T. L. Wolford, *J. Am. Chem. Soc.*, **98**, 3055 (1976).
(2) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectra of Organic Compounds", Holden-Day, San Francisco, Calif., 1967, p 276.
(3) J. H. Bowie, S.-O. Lawesson, J. Ø. Madsen, C. Nolde, G. Schroll, and D. H. Williams, *J. Chem. Soc. B*, 946 (1966).
(4) (a) J. D. Willett, Ph.D. Thesis, Massachusetts Institute of Technology, 1965. (b) J. D. Willett, J. R. Grunwell, and G. A. Berchtold, *J. Org. Chem.*, **33**, 2297 (1968). The thesis was brought to our attention by a referee. Willett appears to have made the first observations and conclusions concerning this type of fragmentation process.
(5) W. K. Musker and P. B. Roush, *J. Am. Chem. Soc.*, **98**, 6745 (1976).
(6) T. L. Shuttleworth, *Appl. Spectrosc.*, **18**, 78 (1964).
(7) N. B. Tucker and E. E. Reid, *J. Am. Chem. Soc.*, **55**, 775 (1933).
(8) J. R. Meadow and E. E. Reid, *J. Am. Chem. Soc.*, **56**, 2177 (1934).
(9) P. B. Roush, Ph.D. Thesis, University of California, Davis, Davis, Calif.
(10) L. A. Ochrymowycz, C.-P. Mak, and J. D. Michna, *J. Org. Chem.*, **39**, 2074 (1974).
(11) G. T. Morgan and W. Ledbury, *J. Chem. Soc.*, **121**, 2882 (1922).
(12) C. M. Hull and T. W. Borgar, *J. Org. Chem.*, **40**, 3152 (1975); M. Protiva, J. O. Jilek, and O. Exner, *Chem. Listy*, **47**, 580 (1953); *Chem. Abstr.*, **49**, 155 (1955).

Mechanism of Oxidation of Alkylaromatic Compounds by Metal Ions. 4. Cerium(IV) Pyridinium Chloride. A Novel Reagent for Side-Chain Oxidation of Highly Substituted Methylbenzenes[1]

Silvana Maini and Luigi Mandolini*

Centro C.N.R. di Studio sui Meccanismi di Reazione, Istituto di Chimica Organica, Università di Roma, 00185 Roma, Italy

Cesare Rol

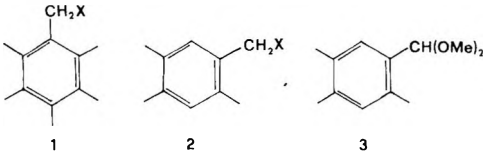
Dipartimento di Chimica, Università, 06100 Perugia, Italy

Received November 14, 1977

Several reports on oxidation reactions of methylbenzenes by Ce(IV) compounds are available in the recent literature.[2] We have shown that ceric ammonium nitrate (CAN) in oxygen-free AcOH leads to a mixture of side-chain acetoxylated and nitrooxylated products.[2] In view of the general interest of reactions leading to side-chain functionalization of alkyl aromatic compounds, we have investigated the behavior of a different oxidizing system, namely ceric pyridinium chloride $(C_5H_6N)_2CeCl_6$ (referred to as CPC), in either MeOH or EtOH solution. We now wish to report on a product study of the oxidation by this reagent of some highly substituted methylbenzenes, namely, hexamethylbenzene (HMB), durene (DUR), and mesitylene (MES).

The oxidation reactions were carried out under reflux in a nitrogen atmosphere with 2 mol of oxidant per mol of hydrocarbon. The results (Table I) show that with either HMB or DUR fair to good yields of side-chain chlorinated and/or alkoxylated products are formed. In contrast, MES does not seem to be reactive enough as to compete with the "spontaneous" reduction of CPC in boiling MeOH.[3] Because of its low reactivity, the oxidation of MES in EtOH solution was not attempted. Interestingly, both the oxidation reaction and the "spontaneous" reduction of CPC are at least two orders of magnitude faster in MeOH than in EtOH. This phenomenon might be related to different structures of the dissolved Ce(IV) species in the two solvents, possibly due to varying extents of displacement of loosely bound chloro ligands by solvent molecules (vide infra).

A dramatic change in the reaction mixture composition was observed when oxygen was bubbled through the solution during the oxidation of DUR in MeOH. 2,4,5-Trimethylbenzaldehyde, mp 38.5–40 °C,[4] was isolated in 65% yield. It was in fact detected in the ^1H-NMR spectrum of the crude reaction product mostly as its dimethyl acetal **3**.[5] The latter was also



1 2 3

Table I. Products Obtained in the Reaction of Some Methylbenzenes with CPC (1:2 mol ratio)

Substrate	Registry no.	Solvent	Time, h[a]	Products(s) (isolated yield, %)[b,n]
HMB	87-85-4	MeOH	ca. 0.05[c]	1, X = Cl (36);[d] X = OMe (38)[e]
DUR	95-93-2	MeOH	0.5	2,[f] X = Cl (35);[g] X = OMe (40)[h]
MES	108-67-8	MeOH	1.5	None
HMB		EtOH	3	1, X = OEt (75)[i]
DUR		EtOH	48[l]	2, X = OEt (47)[m]

[a] Time required at reflux temperature for a complete reduction of Ce(IV) to Ce(III), unless otherwise stated. [b] As based on starting hydrocarbon. Varying amounts of the latter were recovered in all cases thus leading to a nearly quantitative material balance. [c] The reaction was apparently controlled by the dissolution of HMB, which is sparingly soluble in MeOH at room temperature. [d] Mp 81–82 °C. See H. Hart and J. L. Relly, *Tetrahedron Lett.*, 143 (1977). [e] Mp 58–60 °C; ^{1}H NMR (CCl_4) δ 4.3 (s, 2 H, CH_2O), 3.2 (s, 3 H, OCH_3), 2.0–2.3 (m, 15 H, $ArCH_3$). [f] The absence of both chlorodurene and methoxydurene was checked by GLC analysis of the crude material (comparison with authentic samples). [g] ^{1}H NMR (CCl_4) singlets at δ 7.0 (1 H, ArH), 6.9 (1 H, ArH), 4.5 (2 H, CH_2Cl), 2.35 (3 H, $ArCH_3$), 2.2 (6 H, $ArCH_3$). [h] ^{1}H NMR (CCl_4) singlets at δ 6.9 (1 H, ArH), 6.75 (1 H, ArH), 4.3 (2 H, CH_2O), 3.2 (3 H, OCH_3), 2.15 (broad, 9 H, $ArCH_3$). [i] Bp 114 °C (0.6 mmHg), mp 28 °C. See I. I. Lapkin and R. C. Mukhina, *Zh. Obshch. Khim.*, 31, 4001 (1961); *Chem. Abstr.*, 57, 9710a. [l] Reduction of Ce(IV) was not complete. [m] The ^{1}H-NMR spectrum (CCl_4) was similar to that of 2, X = OCH_3, with the sole difference that the OCH_3 signal was replaced by that of OCH_2CH_3. [n] Registry No.—1 (X = Cl), 484-65-1; 1 (X = OMe), 20145-50-0; 2 (X = Cl), 10340-77-9; 2 (X = OMe), 18237-72-4; 1 (X = OEt), 65915-91-5; 2 (X = OEt), 65915-92-6.

formed besides 2, X = Cl and OMe, in runs where nitrogen was either contaminated or omitted.

The oxidation of either HMB or DUR with CPC is characterized by a remarkable specificity. Exclusion of oxygen allows selective oxidation to the alcohol level. Furthermore, only one out of the several methyl groups is attacked, and no nuclear substitution occurs when nuclear positions are available. The reaction is of synthetic value, in that it allows side-chain methoxylation and ethoxylation in fair to good yields by means of a simple one-step procedure. In the former case a prolonged boiling of the reaction mixture is required after the reduction of CPC is complete, in order to solvolyze any chloromethyl derivative. In EtOH solution, the reaction time is such as to allow complete solvolysis of any side-chain chlorinated material possibly formed.

In order to check whether all the methyl ether was produced by methanolysis of the corresponding chloride, the side-chain methoxylation to chlorination ratio was determined at the very early stages of the oxidation reaction of DUR. The experiment was carried out at room temperature for experimental convenience, since at this temperature methanolysis of 2, X = Cl, was slow (ca. 5% reaction after 90 min). Samples of the reaction mixture were taken at intervals, quenched with Fe^{2+}/MeOH, worked-up, and analyzed by GLC (Figure 1). Thus, a significant fraction, namely 0.25 of the oxidation reaction, led to direct side-chain methoxylation. The extent of side-chain methoxylation was reduced, although not completely suppressed, by addition of a large excess of LiCl.

The oxidation of polymethylbenzenes by CPC in MeOH bears striking similarities with the oxidation by CAN in AcOH, not only with respect to reaction products[1] either in the absence or in the presence of oxygen, but also to substrate selectivity leading in both reactions to the reactivity order HMB ≫ DUR ≫ MES.[6] The last point is noteworthy, since the observed pattern is inconsistent with a free-radical attack on the benzylic CH bond, for which a low substrate selectivity should be expected,[7] as well as with an electrophilic attack of molecular chlorine, possibly formed by oxidation of chloride ions by Ce(IV),[8] for which the reactivity order MES ≫ DUR is expected.[9] The intervention of molecular chlorine is further ruled out by the absence of chlorodurene in the reaction products. Rather, it seems more likely that CPC reacts via an electron-transfer mechanism (eq 1) as suggested for the reaction with CAN in AcOH,[1,6] for which the high substrate selectivity observed was related to the donor abilities of the hydrocarbons, as measured by the transition energies $h\nu_{CT}$ of their charge-transfer complexes with tetracyanoethylene.[6]

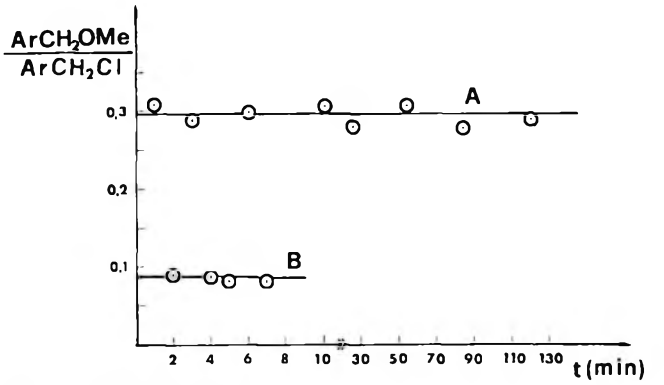


Figure 1. Side-chain methoxylation to side-chain chlorination molar ratio as a function of time for the reaction of DUR (0.03 M) with CPC (0.03 M) in MeOH at 19 °C (curve A). Curve B with added 1 M LiCl.

$$ArCH_3 + Ce(IV) \rightleftarrows ArCH_3^{+}\cdot + Ce(III) \quad (1a)$$

$$ArCH_3^{+}\cdot \rightarrow ArCH_2\cdot + H^+ \quad (1b)$$

$$ArCH_2\cdot + Ce(IV) \rightarrow \text{products} \quad (1c)$$

As to the mechanism for the conversion of the benzyl radicals to products, some information can be obtained from the data reported in Figure 1. A stepwise mechanism (eq 2), ac-

$$ArCH_2\cdot \xrightarrow{Ce(IV)} ArCH_2^{+} \begin{cases} \xrightarrow{Cl^-} ArCH_2Cl \\ \xrightarrow{MeOH} ArCH_2OMe \end{cases} \quad (2)$$

cording to which Ce(IV) oxidizes $ArCH_2\cdot$ to $ArCH_2^+$, which in turn is diverted into products by a competition between the solvent and free-chloride ions, seems unlikely in view of the fact that (i) the ratio of methoxylation to chlorination is remarkably constant with time and (ii) the large amount of added Cl^- ions, actually much greater than any amount possibly present at the early stages of the reaction, does not completely suppress the formation of the methoxy derivative. Rather, a ligand transfer mechanism[1,10] (eq 3) seems to ra-

$$ArCH_2\cdot + Ce^{IV}(Cl)_n(OMe)_{4-n} \rightarrow \begin{matrix} ArCH_2Cl \\ ArCH_2OMe \end{matrix} \quad (3)$$

tionalize the results better. This hypothesis requires that, in addition to chloro ligands, Ce(IV) possesses some methoxy

ligands, which does not seem unlikely in view of the well-known ability of Ce(IV) to complex alcohols and alkoxides.[11,12] The two reaction products would thus be formed by one-step, competing ligand-transfer reactions, with no benzyl cations involved as intermediates. The observed effect of added chloride ions could be explained as due to an increase of the ratio of chloro ligands to methoxy ligands, thus leading to a reduced ratio of methoxylation to chlorination.

Experimental Section

Most techniques and apparatus were as previously reported.[1] MeOH (Erba RS, water content 0.05%) and EtOH (Erba RSE, 99.9% pure) were used as received. The aromatic substrates (reagent grade chemicals) were purified by standard methods. CPC was prepared in good yield according to a literature method.[11]

General Oxidation Procedure. A solution of CPC (6.4 g, 12 mmol) in either MeOH or EtOH (150 mL) was flushed with nitrogen at room temperature (15 min), the proper methylbenzene (6 mmol) was added, and the resulting mixture was brought to boil by immersion in a preheated oil bath. After the red-orange color of Ce(IV) faded, the solution was rapidly cooled and poured into light petroleum that was thoroughly washed with water and dried (Na_2SO_4). The crude material obtained after removal of the solvent was eluted on acid-washed silica gel with $CHCl_3$/light petroleum 1:1. All isolated compounds were checked by GLC and found to be at least 99% pure.

Acknowledgments. The C.N.R. financial support is greatly acknowledged for the part of the work carried out at the University of Perugia. Thanks are also due to Professors E. Baciocchi and G. Illuminati for stimulating discussions.

Registry No.—3, 65915-93-7; CPC, 40888-83-3.

References and Notes

(1) Part 3: E. Baciocchi, C. Rol, and L. Mandolini, *J. Org. Chem.*, **42**, 3682 (1977).
(2) See ref 1 and references cited therein.
(3) When no aromatic substrate was present, reduction of CPC in boiling MeOH was complete in ca. 1 h. In EtOH, however, refluxing for 48 h gave no appreciable change in color.
(4) K. Awers and A. Köckritz, *Justus Liebigs Ann. Chem.*, **352**, 310 (1907).
(5) The ^{1}H-NMR signals due to the $CH(OCH_3)_2$ grouping were shown (CCl_4) as singlets at δ 5.3 (1 H) and 3.15 (6 H).
(6) E. Baciocchi, L. Mandolini, and C. Rol, *Tetrahedron Lett.*, 3343 (1976).
(7) G. A. Russel in "Free Radicals", Vol. I, J. K. Kochi, Ed., Wiley, New York, N.Y., 1973, p 275.
(8) Formation of molecular chlorine was actually observed from CPC in boiling MeCN, as shown by the fact that a stream of N_2 passed through the solution oxidized iodide ion to iodine. When carried out in the case of MeOH, the test was negative.
(9) E. Baciocchi and G. Illuminati, *Prog. Phys. Org. Chem.*, **5**, 1 (1967).
(10) W. S. Trahanovsky and J. Cramer, *J. Org. Chem.*, **36**, 1890 (1971).
(11) D. C. Bradley, A. K. Chatterjee, and W. Wardlaw, *J. Chem. Soc.*, 2260 (1956).
(12) D. Benson, "Mechanism of Oxidation by Metal Ions", Elsevier, Amsterdam, 1976, p 46.

Reaction of Singlet Oxygen with Enamino Lactones. Conversion of Lactones to α-Keto Lactones

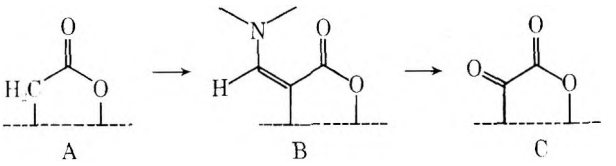
Harry H. Wasserman* and Jeffrey L. Ives

Department of Chemistry, Yale University, New Haven, Connecticut 06520

Received February 21, 1978

We have recently reported[1] a novel method for the conversion of ketones to α-diketones utilizing the facile cleavage of intermediate enamino ketones with singlet oxygen. The mildness and selectivity of this synthetic sequence prompted us to investigate its application to other carbonyl systems. We now report an extension of this procedure to the conversion of lactones to α-keto lactones.

Previous syntheses of α-keto lactones have generally been limited to the condensation of α-keto acids or esters with aldehydes followed by lactonization to α-keto-γ-butyrolactones.[2-5] These methods are often accompanied by side reactions such as dehydration of the intermediate γ-hydroxy-α-keto acids.[5] In our procedure, the α-keto lactones (both five- and six-membered cases) are formed *directly* from the parent lactones by a two-step process which, as outlined below, should have general applicability. The method involves conversion of the lactone A to the enamino lactone B by treatment with tris(dimethylamino)methane followed by oxidative cleavage of the enamine double bond with singlet oxygen to form the α-keto lactone C or its enol tautomer.



A B C

Our initial attempts to form the enamino intermediate B employed alkoxybis(dimethylamino)methane reagents along the lines of our earlier investigation on the oxidation of ketones to α-diketones.[1] Under these conditions, however, conversion to B was slow and often incomplete. We therefore used the more reactive DMF derivative, tris(dimethylamino)methane,[6] as recently reported by Martin and Moore[7] for the preparation of α-enamino butyrolactones.

Table I summarizes the systems studied, reaction conditions, and yields. All of the lactones (**1–6**) reacted readily with tris(dimethylamino)methane to yield the α-enamino derivatives (**7–12**). The second stage oxidative cleavage under conditions of dye-sensitized photooxygenation gave the desired α-keto lactones (**13–18**) in the yields shown. In all cases investigated, the α-keto lactones exist either exclusively or primarily in their enol forms.

Current interest in the preparation of α-methylene lactones[3] prompted us to explore the reaction of α-keto lactones **16** and **18** with phosphoranes under a large variety of reaction conditions[9] (temperature, solvent, reaction time, and method of ylide generation). Thus far, we have been unsuccessful in effecting a Wittig condensation with these systems. Under all conditions studied, the relatively acidic enol was rapidly and irreversibly deprotonated by the ylide to give, upon workup, only polymeric material, starting keto lactone, and traces of triphenylphosphine oxide.

We are currently studying further extensions of this synthetic sequence for the preparation of other α-keto carbonyl systems.

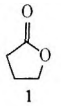
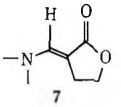
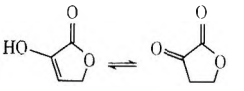
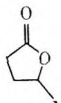
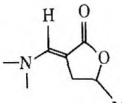
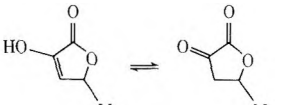
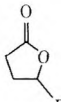
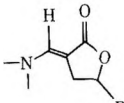
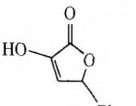
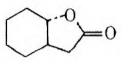
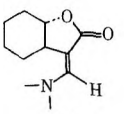
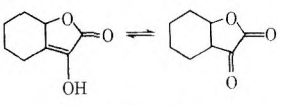
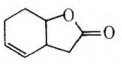
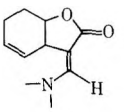
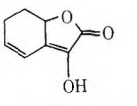
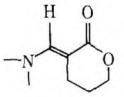
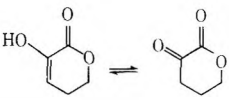
Experimental Section

Melting points were obtained in a Melt-Temp apparatus and are uncorrected. Infrared spectra were recorded in chloroform or neat using a Perkin-Elmer 700A spectrometer. NMR spectra were obtained with either a Perkin-Elmer R-32 90-MHz instrument or a Bruker 270-MHz instrument using tetramethylsilane as an internal standard. Mass spectra were recorded on a Hitachi RMU-6 spectrometer operated at 70 eV. Elemental analyses were performed by Dr. Robert Rittner, Olin Laboratories, New Haven, Conn.

Tris(dimethylamino)methane.[6] A mixture of 94.0 g (1.30 mol) of dimethylformamide and 57.0 g (0.53 mol) of dimethylcarbamyl chloride was heated at 120 °C under nitrogen for 24 h. The mixture was cooled to room temperature, and the resulting white crystals were filtered and washed several times with 100-mL portions of DMF and dried under vacuum for 48 h. A solution of 0.12 mol of lithium dimethylamide was prepared by adding 54 mL of a 2.2 M *n*-BuLi–hexane solution to a −78 °C solution of excess dimethylamine in 500 mL of THF followed by warming to 0 °C for 30 min. The solution was again cooled to −78 °C, and 13.5 g (0.10 mol) of the DMF–dimethylcarbamyl chloride adduct was added through Gooch tubing. The resulting slurry was stirred at room temperature for 18 h. Removal of solvent by distillation followed by vacuum distillation gave 7.4 g (51%) of the desired tris(dimethylamino)methane: bp 48 °C (12 mm) [lit.[6] bp 40–43 °C (12 mm)]; IR (neat) 3000–2700, 1475, 1450, 1345 cm^{-1}; NMR ($CDCl_3$) δ 3.05 (s, 1 H), 2.31 (s, 18 H); MS *m/e* 102, 44, 43.

0022-3263/78/1943-3238$01.00/0

Table I. Conversion of Lactones to α-Keto Lactones

Lactone		Enamino lactone		Keto lactone[c]
 1	a, 48 h, 90%	 7	b, 86%	 13 (>95% enol)
 2	a, 48 h, 90%	 8	b, 86%	 14 (>95% enol)
 3	a, 24 h, 87%	 9	b, 65%	 15
 4	a, 72 h, 86%	 10	b, 86%	 16 (90% enol)
 5	a, 60 h, 87%	 11	b, 72%	 17
 6	a, 30 h, 86%	 12	b, 72%	 18 (56% enol)

[a] Reaction of the lactone with 1.5 equiv of tris(dimethylamino)methane at 70 °C. [b] Photooxygenation of the enamino lactone in methylene chloride at −78 °C using 5 mg of bis(acenapthalene)thiophene and a Sylvania DWY 650-W lamp operated at 70 V followed by column chromatography on silica gel. [c] A mixture of keto and enol forms. The ratio of tautomers was determined by 90- and 270-MHz NMR spectroscopy in $CDCl_3$ at 25 °C.

α-(Dimethylaminomethylene)-γ-butyrolactone (7). A mixture of 0.35 g (4.0 mmol) of γ-butyrolactone and 0.79 g (5.4 mmol) of tris(dimethylamino)methane was heated under nitrogen with stirring at 70 °C for 48 h. The crude product was dried under vacuum for 2 h and crystallized from ether to give 0.53 g (90%) of **7**: mp 97–99 °C; IR ($CHCl_3$) 1710, 1620–1640 cm^{-1}; NMR ($CDCl_3$) δ 7.15 (t, 1 H), 4.25 (t, 2 H), 3.06 (m, 2 H), 3.04 (s, 6 H).

Anal. Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.69; H, 7.85; N, 10.10.

α-(Dimethylaminomethylene)-γ-valerolactone (8). A mixture of 0.67 g (6.7 mmol) of γ-valerolactone (**2**) and 1.40 g (9.75 mmol) of tris(dimethylamino)methane was heated under nitrogen with stirring at 70 °C for 48 h. The crude product was dried under vacuum and crystallized from ether to give 0.94 g (90%) of **8**: mp 54–55 °C; IR ($CHCl_3$) 1710, 1620, 1340, 1300 cm^{-1}; NMR ($CDCl_3$) δ 7.10 (t, 1 H), 4.52 (m, 1 H), 3.02 (s, 6 H), 3.0 (dd, 2 H), 1.30 (d, 3 H).

Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.70; H, 8.32; N, 9.20.

α-(Dimethylaminomethylene)-γ-phenyl-γ-butyrolactone (9). A mixture of 0.48 g (3.0 mmol) of γ-phenyl-γ-butyrolactone (**3**) and 0.65 g (4.5 mmol) of tris(dimethylamino)methane was heated at 70 °C under nitrogen with stirring for 24 h. The crude yellow solid was dried under vacuum and recrystallized from ether/ethyl acetate (4:1) to give 0.57 g (87%) of **9**: mp 145–147 °C; IR ($CHCl_3$) 1715, 1625, 1320 cm^{-1}; NMR ($CDCl_3$) δ 7.33 (s, 5 H), 7.17 (t, 1 H), 5.35 (dd, 1 H), 3.60 (dd, 1 H), 2.98 (s, 6 H), 2.90 (dd, 1 H).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.86; H, 6.85; N, 6.51.

***trans*-2-(Dimethylaminomethylene)-2-(2-hydroxycyclohexyl)acetic Acid Lactone (10).** A mixture of 1.60 g (11.4 mmol) of lactone **4** and 1.84 g (12.7 mmol) of tris(dimethylamino)methane was heated under nitrogen with stirring at 70 °C. After 48 h the crude product was crystallized from ether/pentane (4:1) to give 1.90 g (86%) of enamino lactone **10**: mp 76–78 °C; IR ($CHCl_3$) 1715, 1620, 1440, 1290 cm^{-1}; NMR ($CDCl_3$) δ 7.15 (d, 1 H), 3.50 (bm, 1 H), 3.00 (s, 6 H), 3.0–0.70 (bm, 9 H).

Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.60; H, 8.69; N, 7.20.

***cis*-2-(Dimethylaminomethylene)-2-(2-hydroxycyclohex-5-enyl)acetic Acid Lactone (11).** A mixture of 0.60 g (4.34 mmol) of lactone **5** and 0.93 g (6.44 mmol) of tris(dimethylamino)methane was heated under nitrogen with stirring at 70 °C for 60 h. The crude product was crystallized from ether/acetone (20:1) to give 0.73 g (87%) of enamino lactone **11**: mp 100–102 °C; IR ($CHCl_3$) 1710, 1620, 1280, 1190 cm^{-1}; NMR ($CDCl_3$) δ 7.14 (s, 1 H), 5.80 (m, 1 H), 5.50 (m, 1 H), 4.62 (m, 1 H), 3.69 (m, 1 H), 3.04 (s, 6 H), 2.5–1.5 (m, 4 H).

Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 65.65; H, 7.44; N, 7.00.

α-(Dimethylaminomethylene)-δ-valerolactone (12). A mixture of 0.40 g (4.0 mmol) of lactone **6** and 0.87 g (6.0 mmol) of tris(dimethylamino)methane was heated at 70 °C under nitrogen with stirring for 30 h. The crude product was crystallized from ether/pentane (5:1) to give 0.53 g (86%) of enamino lactone **12**: mp 59–60 °C; IR ($CHCl_3$) 1675, 1575, 1440, 1390 cm^{-1}; NMR ($CDCl_3$) δ 7.52 (s, 1 H), 4.20 (t, 2 H), 3.10 (s, 6 H), 2.67 (p, 2 H), 1.85 (t, 2 H).

Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.87; H, 8.28; N, 9.05.

General Photooxygenation Procedure. A solution of 3–5 mmol of enamino lactone and 5 mg of bis(acenaphthalene)thiophene (BANT) in 150 mL of dry methylene chloride was photooxygenated at −78 °C using a constant circulating oxygen supply and a Sylvania DWY 650-W lamp operated externally through Pyrex at 70 V. The uptake of oxygen was rapid and ceased after 30 min and 1.2 equiv of oxygen. The irradation was stopped, and the reaction mixture was allowed to warm slowly to room temperature. The mixture was concentrated and column chromatographed on silica gel using 2% acetone in methylene chloride to give the corresponding α-keto lactone.

α-Keto-γ-butyrolactone (13): 86%; IR ($CHCl_3$) 3600–2900, 1760 cm^{-1}; NMR ($CDCl_3$) δ 6.95 (s, 1 H), 4.75 (s, 1 H), 2.95 (m, 2 H); DNP derivative, mp 219–220 °C (lit.[5] mp 218 °C).

Anal. Calcd for $C_{10}H_8N_4O_6$: C, 42.87; H, 2.88; N, 20.00. Found: C, 42.68; H, 2.90; N, 19.83.

α-Keto-γ-valerolactone (14): 68%; mp 71–73 °C (lit.[5] mp 70–73 °C); IR ($CHCl_3$) 3500, 3300, 1760, 1400, 1320 cm^{-1}; NMR ($CDCl_3$) δ 6.65 (bs, 1 H), 6.27 (d, 1 H), 5.08 (m, 1 H), 3.0 (m), 2.25 (m), 1.42 (d, 3 H); MS *m/e* 114 (M^+), 69, 57, 44.

Anal. Calcd for $C_5H_6O_3$: C, 52.63; H, 5.30. Found: C, 52.19; H, 4.98.

α-Keto-γ-phenyl-γ-butyrolactone (15): 66%; IR ($CHCl_3$) 3500, 3350, 1765, 1500 cm^{-1}; NMR ($CDCl_3$) δ 7.30 (bs, 5 H), 6.29 (d, 1 H), 5.82 (d, 1 H); DNP derivative, mp 115–117 °C.

Anal. Calcd for $C_{16}H_{12}N_4O_6$: C, 53.94; H, 3.39; N, 15.72. Found: C, 54.28; H, 3.60; N, 15.96.

α-Keto Lactone 16: 86%; mp 98–101 °C (lit.[3] mp 99–110 °C); IR ($CHCl_3$) 3500, 3300, 1750 cm^{-1}; NMR ($CDCl_3$) δ 6.55 (bs, 1 H), 4.58 (m, 1 H), 3.00 (m, 2 H), 2.6–1.0 (m, 6 H); MS *m/e* 154 (M^+), 110, 97, 80, 79.

α-Keto Lactone 17: 72%; mp 93–96 °C: IR ($CHCl_3$) 3500, 3300, 1750, 1690, 1600 cm^{-1}; NMR ($CDCl_3$) δ 6.55 (d, 1 H), 6.08 (m, 1 H), 5.87 (dd, 1 H), 2.71–1.4 (m, 4 H).

Anal. Calcd for $C_8H_8O_3$: C, 63.15; H, 5.30. Found: C, 62.80; H, 5.04.

α-Keto-δ-valerolactone (18): 72%; IR ($CHCl_3$) 3450, 1765–1700 cm^{-1}; NMR ($CDCl_3$) δ 5.95 (t, 1 H), 5.75 (bs, 1 H), 4.60 (t, 2 H), 4.45 (t, 2 H), 2.87 (t, 2 H), 2.50 (m, 2 H); MS *m/e* 114 (M^+), 69, 57, 56, 41.

Acknowledgment. This work was supported by N.I.H. Grant GM-13854.

Registry No.—**1**, 96-48-0; **2**, 108-29-2; **3**, 1008-76-0; **4**, 27345-71-7; **5**, 34896-02-1; **6**, 542-28-9; **7**, 34009-40-0; **8**, 62527-57-5; **9**, 66516-03-8; **10**, 66516-02-7; **11**, 66516-01-6; **12**, 66516-00-5; **13**, 25409-36-3; **13** DNP, 3777-94-4; **14**, 21053-73-6; **15**, 19252-20-1; **15** DNP, 66515-98-8; **16**, 66515-99-9; **17**, 66516-05-0; **18**, 66516-04-9; tris(dimethylamino)-methane, 5762-56-1; dimethylformamide, 68-12-2; dimethylcarbamyl chloride, 79-44-7.

References and Notes

(1) H. H. Wasserman and J. L. Ives, *J. Am. Chem. Soc.*, **98**, 7868 (1976).
(2) K. H. Meyer, *Justus Liebigs Ann. Chem.*, **398**, 49 (1913).
(3) P. A. Plattner and L. M. Jamplosky, *Helv. Chim. Acta*, **26**, 687 (1943).
(4) H. Schintz and M. Hinder, *Helv. Chim. Acta*, **30**, 1349 (1947).
(5) C. H. Wermuth, *Bull. Soc. Chim. Fr.*, 1435 (1966), and references cited therein.
(6) H. Bredereck, F. Effenberger, and T. Brendle, *Angew. Chem., Int. Ed. Engl.*, **5**, 132 (1966); H. Weingarten and N. K. Edelman, *J. Org. Chem.*, **32**, 3293 (1967); H. Bredereck, F. Effenberger, T. Brendle, and H. Muffler, *Chem. Ber.*, **101**, 1885 (1968).
(7) S. F. Martin and D. R. Moore, *Tetrahedron Lett.*, 4459 (1976).
(8) For recent reviews on the synthesis of α-methylene lactones, see R. B. Gammill, C. A. Wilson, and T. A. Bryson, *Synthetic Commun.*, **5**, 245 (1975), and P. Grieco, *Synthesis*, 67 (1975).
(9) For example, see A. Maercker, *Org. React.*, **14**, 270 (1965); G. Wittig and U. Schollkopf, "Organic Synthesis", Collect. Vol. 5, Wiley, New York, N.Y., 1973, p 751; R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963); H. O. House and G. H. Rasmusson, *ibid.*, **26**, 4728 (1961).

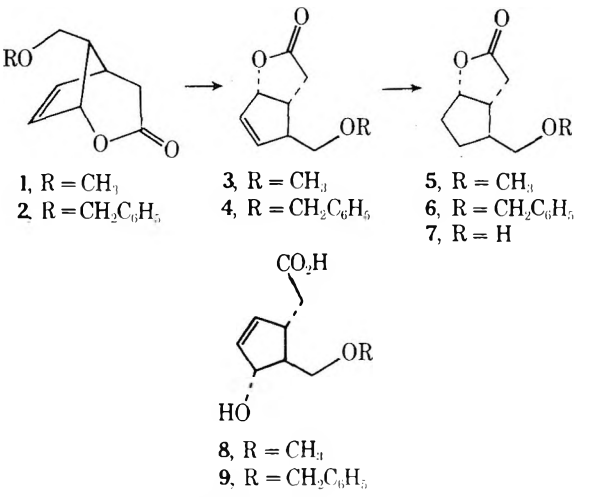
An Efficient Route to Intermediates for the Synthesis of 11-Deoxyprostaglandins

Jasjit S. Bindra* and Alex Grodski

Central Research, Pfizer Inc., Groton, Connecticut 06340

Received March 2, 1978

The benzyloxy bicyclic lactone **2** is an important starting material for the preparation of the unsaturated lactone **4**, an intermediate for the synthesis of A prostaglandins[1] and the lactone alcohol **7**. The latter is a key intermediate for the synthesis of pharmacologically interesting 11-deoxyprostaglandins.[2] Since the existing route from the bicyclic lactone **2** to **4** and thence to **7** involves several steps,[3-5] we have developed a simple one-step transformation of **2** to **4** involving a cationic rearrangement cyclization sequence. Compound **4** can be transformed into **7** in two additional steps, thus providing a convenient approach to 11-deoxyprostaglandins. A corresponding sequence from **1**, the methyl ether analogue of **2**, to **7** has also been developed.



1, R = CH_3
2, R = $CH_2C_6H_5$
3, R = CH_3
4, R = $CH_2C_6H_5$
5, R = CH_3
6, R = $CH_2C_6H_5$
7, R = H
8, R = CH_3
9, R = $CH_2C_6H_5$

Treatment of the lactone methyl ether **1** or the benzyl ether **2** with concentrated sulfuric acid in an aprotic solvent at room temperature for 12 h smoothly afforded in ca. 90% yield the rearranged lactones **3** and **4**. The rearrangement was effected in similar yields with *p*-toluenesulfonic acid or boron trifluoride etherate as catalysts. Alternatively, the optically active lactones **3** and **4** were obtained directly from the resolved intermediates **8** and **9** by treatment with concentrated H_2SO_4 as described above. Catalytic hydrogenation of **3** over 5% Rh/alumina gave the saturated ether **5**, which was demethylated using BBr_3 to furnish the desired alcohol **7** in 77% overall yield. However, catalytic hydrogenation and debenzylation of the benzyl ether **4** to provide **7** in 90% overall yield were best effected sequentially over 5% Rh/alumina[4] (to give **6**) followed by 5% Pd/C in ethyl acetate. Contrary to an earlier report, there was no evidence of hydrogenolysis of the allylic hydroxyl group in **4**.[3,6]

The three-step sequence of **2** to **7** or alternatively **9** to **7** (if optically active material is desired) constitutes the preferred route for intermediates for the preparation of 11-deoxyprostaglandins.

Experimental Section[7]

Preparation of Methyl Ether Lactone 3. A solution of 5.26 g (15 mmol) of the lactone **1** in 30 mL of Et_2O was treated with 0.3 mL of concentrated H_2SO_4, and the mixture was stirred under a nitrogen atmosphere overnight at room temperature. The reaction mixture was neutralized (pH 8) with saturated sodium bicarbonate solution, the Et_2O layer was separated, and the aqueous layer was further extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated to a crude oil weighing 2.4 g (95% yield). The product was purified by chromatography on silica gel (Baker) using CH_2Cl_2 followed by CH_2Cl_2/EtOAc (9:1) as eluent to furnish **3**: 2.2 g (87% yield); mp 50–51 °C; IR ($CHCl_3$) 1779 cm^{-1}; NMR ($CDCl_3$) δ 2.0–3.1 (4 H, m), 3.25 (3 H, s, $-OCH_3$), 3.2–3.4 (2 H, m, $-CH_2O$), 5.45 (1 H, m, –CHOCO), and 5.94 (2 H, m, olefinic); TLC R_f 0.5 (EtOAc).

Reduction of the Methyl Ether Lactone 3 to 5. A solution of 1.8 g (10.7 mmol) of unsaturated lactone methyl ether **3** in 20 mL of THF and 0.2 g of 5% rhodium on alumina was hydrogenated at 25 °C and atmospheric pressure until absorption ceased (15 min). The reaction mixture was filtered through Celite and evaporated to yield an oil weighing 1.8 g (100% yield). The oil was chromatographed on silica gel (Baker) eluting with CH_2Cl_2 followed by CH_2Cl_2/EtOAc (4:1) to afford **5** as a colorless oil: 1.76 g (96.0% yield); IR 1779 cm^{-1}; NMR ($CDCl_3$) δ 1.2–3.0 (8 H, m), 3.35 (2 H, d, J = 6 Hz, $-CH_2O-$), 3.38 (3 H, s, $-OCH_3$), and 5.00 (1 H, br, –CHOCO); TLC R_f 0.25 (3:1 C_6H_6/EtOAc).

Preparation of Benzyl Ether Lactone 4. Following the procedure described for the preparation of **3**, the lactone **2** or the corresponding hydroxy acid (+)-**9** was converted to **4** (91% yield), a pale yellow oil, identical in all respects with a sample prepared by the method of Corey and Snider.[4] Optically active material had $[\alpha]^{27}_D$ +214° (c 1.0, $CHCl_3$).

0022-3263/78/1943-3240$01.00/0

Reduction of the Benzyl Ether Lactone 4 to 6. Following the procedure described for the preparation of **5**, the double bond in benzyl ether **4** was selectively reduced over 5% Pd/C to furnish the saturated benzyl ether **6** in 97% yield: bp 150–155 °C (0.5 mm); IR ($CHCl_3$) 1776 cm^{-1}; NMR ($CDCl_3$) δ 3.4 (2 H, d, J = 6 Hz, $-CH_2O-$), 4.54 (2 H, br, $-OCH_2Ph$), 4.9 (1 H, m, –CHOCO), and 7.3 (5 H, s, C_6H_5); TLC R_f 0.55 (1:1 C_6H_6/ether).

Preparation of Lactone Alcohol 7: (a) From the Methyl Ether 5. A solution of 0.17 g (1 mmol) of lactone methyl ether **5** in 5 mL of CH_2Cl_2 was stirred at −78 °C under a nitrogen atmosphere. To this solution was added 0.5 mL (5.5 mmol) of BBr_3, and the resulting white slurry was brought rapidly to 0 °C. After completion of the reaction (5.5 h), 2 mL of ether was added dropwise and the mixture was stirred for 5 min and then added to a stirred slurry of 2.3 g of $NaHCO_3$ in 12 mL of saturated sodium potassium tartrate solution. The organic layer was separated and the water layer extracted with CH_2Cl_2. The combined organic extracts were washed with saturated sodium potassium tartrate and dried (Na_2SO_4). The crude product, weighing 154 mg, was purified by chromatography on silica gel (Baker) eluting with CH_2Cl_2 followed by CH_2Cl_2/EtOAc (9:1). Evaporation of the combined fractions gave pure **7** (121 mg, 77% yield): bp 135–138 °C (0.1 mm); IR ($CHCl_3$) 1770 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.3–2.9 (8 H, m), 3.05 (1 H, s, OH), 3.60 (2 H, d, J = 6 Hz, $-CH_2O-$), and 5.00 (1 H, br, –CHOCO); TLC R_f 0.3 (EtOAc). Optically active material had $[\alpha]^{27}_D$ −26.1° (c 1, $CHCl_3$).

(b) From the Benzyl Ether 6. A 52-g amount of the benzyl ether **6**, dissolved in 400 mL of EtOAc containing 0.5 mL of concentrated HCl, was hydrogenated over 10% Pd/C (4 g) at room temperature and pressure. After hydrogen absorption had ceased (1 h), workup followed by distillation gave 33 g of **7** (98% yield), identical in all respects with the material prepared above.

Acknowledgment. The authors wish to thank Drs. H.-J. Hess and E. J. Corey for helpful discussions.

Registry No.—**1**, 52578-42-4; **2**, 50889-56-0; **3**, 39673-26-2; **4**, 35761-79-6; **5**, 66748-93-4; **6**, 54382-69-3; **7**, 43119-34-2; (+)-**9**, 41787-51-3.

References and Notes

(1) E. J. Corey and P. A. Grieco, *Tetrahedron Lett.*, 107 (1972).
(2) For a detailed review of the chemistry and biology of 11-deoxyprostaglandins, see J. S. Bindra and R. Bindra, "Prostaglandin Synthesis", Academic Press, New York, N.Y., 1977, Chapter 20.
(3) P. Crabbé and A. Guzmán, *Tetrahedron Lett.*, 115 (1972).
(4) E. J. Corey and B. B. Snider, *J. Org. Chem.*, **39**, 256 (1974).
(5) S. Ranganathan, D. Ranganathan, and R. Iyengar, *Tetrahedron*, **32**, 961 (1976).
(6) P. Crabbé, A. Cervantes, and A. Guzmán, *Tetrahedron Lett.*, 1123 (1972).
(7) Melting points (uncorrected) were taken with a Thomas-Hoover capillary apparatus. NMR spectra were recorded on Varian A-60 and T-60 spectrometers with Me_4Si as an internal standard. IR spectra were determined with a Perkin-Elmer Model 21 spectrometer.

The *E* Isomer of Acetophenone Iminoxy, an Overlooked Radical

Adri Mackor

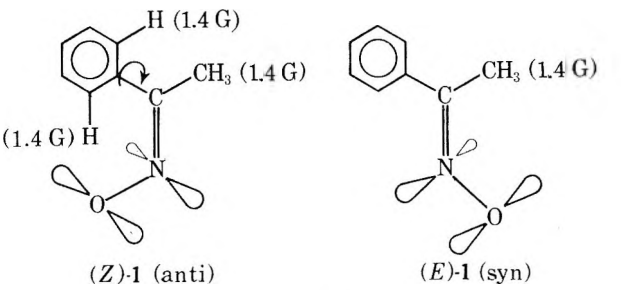
Contribution from the Institute for Organic Chemistry TNO, 3502 JA Utrecht, The Netherlands

Received April 21, 1978

The acetophenone iminoxy radical has been observed by ESR spectroscopy during oxidation of acetophenone oxime in a number of studies: in a flow system[1] with ceric salts, in static systems with lead tetraacetate in benzene[2,3] or methylene chloride,[4,5a] and by other methods.[5b]

It is a transient radical which rapidly disappears after its generation at ambient temperatures, giving rise to diamagnetic products[3] and secondary radicals of the nitroxide type as noted by several authors. The latter radicals are readily distinguished from the iminoxy radical by their lower nitrogen hyperfine splitting constants (hfsc): a_N(iminoxy) ≃ 31 G; a_N(nitroxide) ≤ 16 G.

In these studies only one iminoxy radical was detected, and



(*Z*)-1 (anti) (*E*)-1 (syn)

it was established by Gilbert and Norman[5a] to be the *Z* isomer [(*Z*)-1] in which a characteristic 1.4 G coupling with both ortho hydrogens is present due to interaction of the rapidly rotating phenyl group with the unpaired electron which is contained in a σ-type orbital.[6a] This orbital is derived from an oxygen p orbital and the nitrogen nonbonding sp^2 orbital which are in the C=N–O plane. The spin density in iminoxy radicals is almost evenly distributed over nitrogen and oxygen. The C=N–O angle has been calculated to be 139°, and thus it is larger than in the parent oxime.[6b] It is rather surprising that for the iminoxy radical only the *Z* form has been found so far, while for the oxime the *E* form strongly predominates (≃95% in the equilibrium mixture; the isolation of the *Z* isomer has only recently been accomplished[7,8,9]). Apparently, in **1** the *E* → *Z* isomerization is a very rapid process and (*Z*)-**1** is the thermodynamically more stable isomer.

Z/*E* isomerization in iminoxy radicals leading to an equilibrated mixture of two radicals with separate ESR signals has been observed frequently.[10] The same situation exists in a number of para- or meta-substituted acetophenone iminoxy radicals.[11,12] It therefore seemed desirable to confirm the previous assignment of the ESR signal of the acetophenone iminoxy radical to exclusively (*Z*)-**1** with the aid of the compounds perdeuterated either in the methyl or phenyl group.

Experimental Section

(*E*)-Acetophenone oxime was characterized by its melting point (58–59 °C) and NMR spectrum. In addition to a correct melting point, the α,α,α-trideuterated compound was found to contain a methyl group with >95% deuterium content by NMR spectroscopy and ≥98% by mass spectrometry; the pentadeuteriophenyl oxime had 97.5 (NMR) and 98% (MS) deuterium content. NMR spectra were taken on Varian A-60 and HA-100 spectrometers. Mass spectra were run on an AEI-MS-902 mass spectrometer.[13] ESR spectra were taken on a Varian E-4 spectrometer with a variable temperature accessory. The hfsc are uncorrected, but they can be compared with those obtained with the same instrument for the perylene radical cation[14] in 98% sulfuric acid at 20 °C (found: 4.10, 3.10, and 0.45 G). Values of g were measured with respect to solid DPPH (taken as g = 2.0036).

Results and Discussion

We have previously analyzed the ESR spectra of aromatic iminoxy radicals in more detail than was done before[15,16] using *tert*-butyl peroxalate[17] (TBPO) as a convenient thermal source of *tert*-butoxy radicals in apolar solvents at ambient temperature, which in turn generate iminoxy radicals from the oximes.

This method enabled us to maintain a steady state of acetophenone iminoxy radicals for periods up to hours and to study them at leisure under high resolution. In addition to the previously reported a_N = 1.4 G (5 H, CH_3 and ortho H's), the spectra of (*Z*)-**1** contain a small para H coupling (a_H^p = 0.56 G), indicating the presence of some unpaired spin density in the aromatic π-electron system. The coupling is removed by para substituents like OCH_3 (Figure 1). To explain the unpaired π-spin density in (*Z*)-**1** and in other aromatic iminoxy radicals in which the oxygen atom and the phenyl group are in a *Z* position, the author has proposed a $\sigma \rightarrow \pi$ spin polarization mechanism at nitrogen and/or oxygen and a distri-

0022-3263/78/1943-3241$01.00/0

Table I. ESR Spectral Parameters of Acetophenone Iminoxy Radicals[a]

Radical	Temp, °C	Z isomer a_N	Z isomer a_H	Z isomer Other $a_{H(D)}$	Z isomer g value	E isomer a_N	E isomer a_H	E isomer Other $a_{H(D)}$	E isomer g value
1	25	31.44	1.39 (5 H)	0.56 (p-H)	2.0059	Obscured by Z isomer			
2[b]	−30	31.5	c	c	c	31.1	–	c	c
2	20	31.40	1.44 (2 H)	$a_D \sim 0.24$	2.0058	31.00	–	–	2.0064
2	38	31.3	c	c	c	30.9	–	c	c
2[d]	38	31.6	~1.5 (2 H)	c	c	31.1	–	c	c
2[e]	25	31.4	1.44 (2 H)	$a_D \sim 0.24$	2.0057	31.0	–	–	2.0065
3	20	31.40	1.37 (3 H)	–	2.0059	31.12	1.40 (3 H)	$a_D \sim 0.25$	2.0066

[a] Obtained by oxidation of the oxime with TBPO (in CS_2 unless stated otherwise). Hfsc are given in gauss. [b] With lead tetraacetate as an oxidant. [c] Not recorded. [d] In methylene chloride. [e] In benzene.

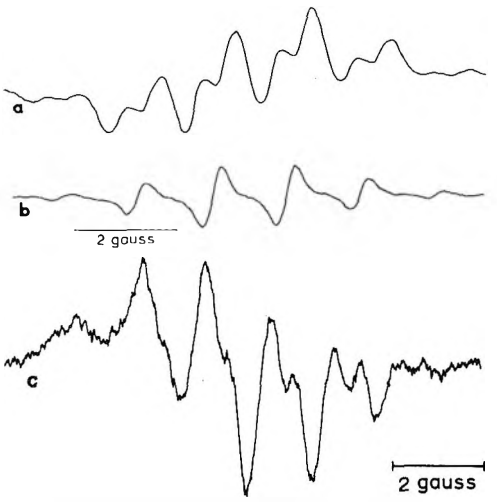


Figure 1. ESR spectra of the low-field nitrogen groups of (a) acetophenone iminoxy (1) and (b) p-methoxyacetophenone iminoxy radicals (in CS_2 at 40 °C) and (c) the high-field nitrogen group of acetophenone iminoxy (1) (in CS_2 at 10 °C).

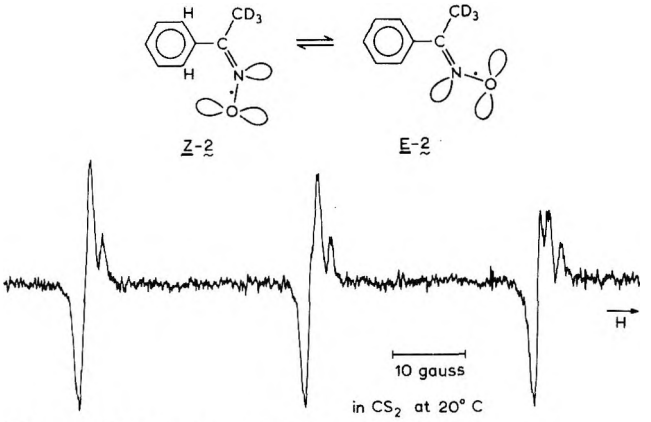


Figure 2. ESR spectrum of compound 2.

bution of the unpaired π-electron density over the entire π-electron system, as expected for a π radical.[15,16]

At first sight, the spectrum of 1 in the temperature range from 20–40 °C does not show evidence for the presence of the E isomer. However, this evidence was obtained from a study of the α,α,α-trideuterated compound $C_6H_5C(CD_3)=NO\cdot$ (2). The ESR spectrum reproducibly showed the presence of two iminoxy radicals 2 in comparable amounts with different a_N and g values and line widths (Figure 2). Only one of these radicals shows the expected hfsc of ~1.4 G with presumably the two ortho hydrogens, and therefore it is assigned structure (Z)-2 (cf. Table I). The other radical which slightly predominates in the spectrum gives a single broad line in each nitrogen group of lines (Figures 2 and 3). The same results were obtained when TBPO as a hydrogen abstracting agent was replaced by lead tetraacetate; at −30 °C a mixture was ob-

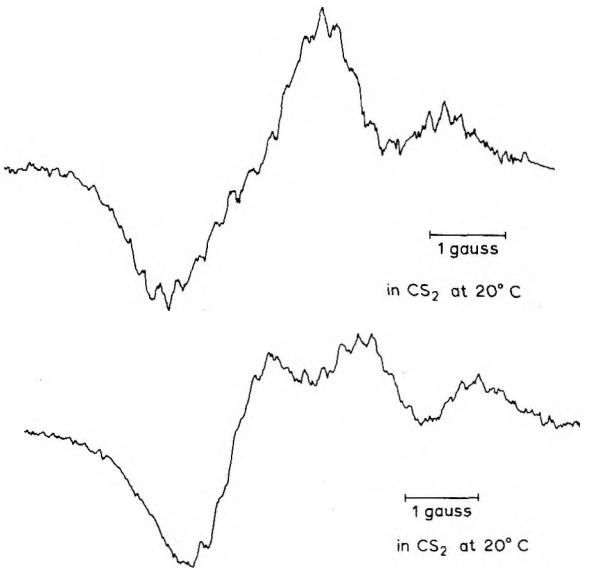


Figure 3. Enlarged ESR spectra of the low-field (top) and high-field (bottom) nitrogen groups of radical 2.

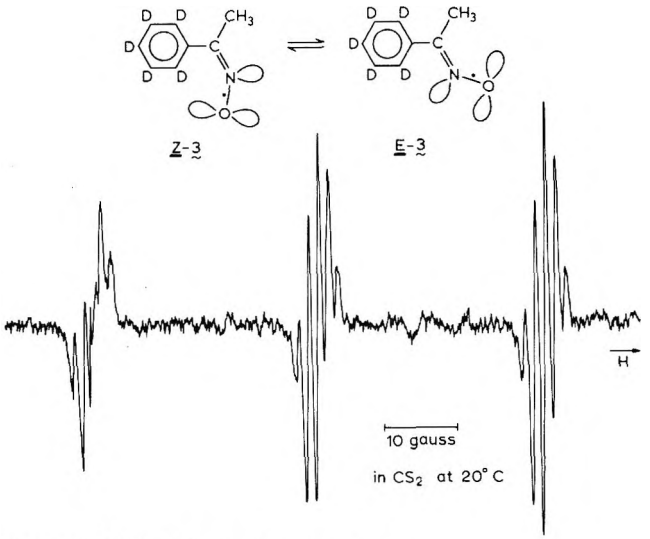


Figure 4. ESR spectrum of compound 3.

served in which the second radical predominates more strongly. Replacing CS_2 as a solvent by methylene chloride or benzene had no effect on the appearance of the second radical.

It is therefore concluded not only that a Z/E equilibrium mixture of 2 is formed upon oxidation of the oxime but that the so far unknown E isomer is even slightly predominating, at least in acetophenone iminoxy with a trideuterated methyl group under our conditions.

The spectrum of the pentadeuteriophenyl compound $C_6D_5C(CH_3)=N-O\cdot$ (3) supports this conclusion (Figure 4).

Figure 5. ESR spectrum of the low-field nitrogen group of **3**.

Although the asymmetry of the three nitrogen groups of lines is less obvious than in **2**, the shape, number of hf lines, and overall width of each group are sufficiently different to allow an unambiguous interpretation. Again the mixture contains at least 50% of the *E* isomer of **3**. In the low-field nitrogen group all 8 lines of the two overlapping 1:3:3:1 quartet splittings of the methyl group can be recognized (Figure 5). The results for **1**, **2**, and **3** are presented in Table I.

Conclusions

From these consistent results with deuteration either in the side chain or in the aromatic nucleus, we are forced to conclude that **1** also exists, at least 50%, as its *E* isomer. Formerly, this isomer was not recognized due to the fact that its spectrum strongly coincides with and is obscured by that of (*Z*)-**1**. Both radicals possess a methyl group hfsc of ~1.4 G, as is found in acetone iminoxy;[5] in (*Z*)-**1** the aromatic ortho hydrogens have only a slightly different hfsc. The *E* isomer of **1** will give rise to a 1:3:3:1 quartet in each nitrogen line, possibly broadened by unresolved hfsc from aromatic hydrogen atoms and appearing on the low-field side of each nitrogen line of (*Z*)-**1**. Since in **2** and **3** the spectra of *E* and *Z* isomers are best separated in the high-field nitrogen group, the *E* isomer of **1** is also expected to show up most clearly in this part of the spectrum. Indeed, the high-field nitrogen group of **1** is asymmetric and it contains broadened and intensified lines on its low-field side, supporting the correctness of the foregoing conclusions (Figure 1c). Moreover, it appears that the *E* radical is slightly favored over the *Z* form, especially at low temperatures. An increase in the *Z*/*E* ratio from parent oxime to radical is consistent with the larger C=N-O angle in the radical. However, this increase is less dramatic than believed formerly. The widespread acceptance in the literature of the strong preference of acetophenone iminoxy radical for the *Z* configuration and further conclusions, which are based on this incorrect assumption, will have to be reconsidered accordingly. These results stress again that great care has to be exercised when interpreting partially resolved ESR spectra of iminoxy radicals.[18]

Acknowledgment. The author is deeply obliged to his colleagues at the Universities of Amsterdam and Utrecht for discussion and practical help, especially to Mr. A. V. E. George for extensive assistance and to Mr. L. C. J. van der Laan and Dr. P. C. Vijfhuizen for supplying samples of oximes with recently established purity.

Registry No.—(*Z*)-**1**, 66538-90-7; (*Z*)-**2**, 66538-91-8; (*Z*)-**3**, 66538-92-9; (*E*)-**1**, 66538-95-2; (*E*)-**2**, 66538-93-0; (*E*)-**3**, 66538-94-1.

References and Notes

(1) J. R. Thomas, *J. Am. Chem. Soc.*, **86**, 1446 (1964).
(2) M. Bethoux, H. Lemaire, and A. Rassat, *Bull. Soc. Chim. Fr.*, 1985 (1964).
(3) J. L. Brokenshire, J. R. Roberts, and K. U. Ingold, *J. Am. Chem. Soc.*, **94**, 7040 (1972).
(4) J. W. Lown, *J. Chem. Soc. B*, 644 (1966).
(5) (a) B. C. Gilbert and R. O. C. Norman, *J. Chem. Soc. B*, 123 (1968); (b) B. C. Gilbert, V. Malatesta, and R. O. C. Norman, *J. Am. Chem. Soc.*, **93**, 3290 (1971).
(6) (a) S. F. Nelson, *Free Radicals 1973*, **2**, 562 (1973); (b) W. M. Fox and M. C. R. Symons, *J. Chem. Soc. A*, 1503 (1966).
(7) R. F. Rekker and J. U. Veenland, *Recl. Trav. Chim. Pays-Bas*, **78**, 739 (1959).
(8) G. J. Karabatsos and R. A. Taller, *Tetrahedron*, **24**, 3347 (1968).
(9) J. H. Smith and E. T. Kaiser, *J. Org. Chem.*, **39**, 728 (1974).
(10) T. S. Dobashi, D. R. Parker, and E. J. Grubbs, *J. Am. Chem. Soc.*, **99**, 5382 (1977).
(11) In view of this conclusion, it is difficult to understand the general validity of the following statement made by Dondoni et al.,[12] who, after drawing an analogy between acetophenone oximes and benzohydroximoyl chlorides (ArC(Cl)=NOH), conclude that the latter compounds give iminoxy radicals with an anti configuration. "This constitutes evidence for the same configurational assignment for the radical as for its precursor since, considering that only **one** isomer has been observed for both radical and precursor, it seems unlikely that the stability of syn and anti forms is completely reversed in the two cases."
(12) A. Dondoni, G. F. Pedulli, and G. Barbaro, *J. Org. Chem.*, **37**, 3564 (1972).
(13) P. C. Vijfhuizen, H. van der Schee, and J. K. Terlouw, *Org. Mass Spectrom.*, **11**, 1198 (1976).
(14) J. P. Colpa and J. R. Bolton, *Mol. Phys.*, **6**, 273 (1963).
(15) (a) A. Mackor, Ph.D. Thesis, University of Amsterdam, 1968; cited in ref 16; (b) A. Mackor, manuscript in preparation.
(16) M. F. Chiu, B. C. Gilbert, and B. T. Sutcliffe, *J. Phys. Chem.*, **76**, 553 (1972).
(17) P. D. Bartlett, E. P. Benzing, and R. E. Pincock, *J. Am. Chem. Soc.*, **82**, 1762 (1960).
(18) G. A. Russell and A. Mackor, *J. Am. Chem. Soc.*, **96**, 145 (1974).

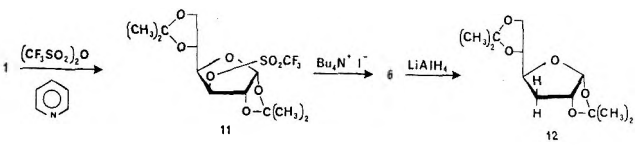
Communications

A New Synthesis of Deoxyiodo Sugars

Summary: Reaction of tetrabutylammonium iodide with carbohydrates containing the trifluoromethanesulfonate (triflate) group has been found to be a very effective means for synthesis of deoxyiodo sugars.

Sir: Deoxyhalogeno sugars are among the most versatile intermediates in carbohydrate synthesis. These compounds have been used in the formation of a variety of substances, including anhydro, aminodeoxy, deoxy, epoxy, and unsaturated sugars.[1] Although several types of reaction have been useful in synthesizing halogenated carbohydrates, displacement processes generally have been the most effective. Many displacement reactions, however, have been subject to one or more of the following limitations: (a) destructively vigorous reaction conditions; (b) inability to effect displacement in some instances (particularly when the leaving group is on a secondary carbon); (c) competing elimination reactions; (d) molecular rearrangements. The purpose of this communication is to report a procedure for the synthesis of deoxyiodo sugars which overcomes many of these limitations by using the remarkably reactive trifluoromethanesulfonate (triflate) leaving group in combination with tetrabutylammonium iodide. This combination has produced substitution in high yield without competition from elimination or rearrangement in each of the molecular systems upon which it has been attempted.

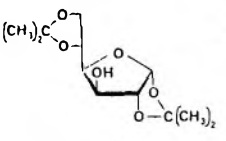
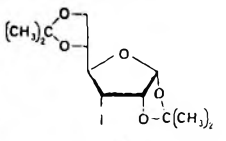
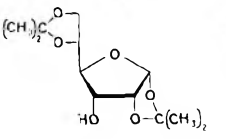
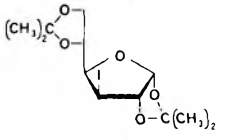
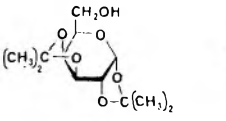
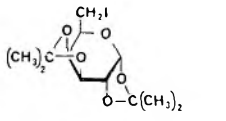
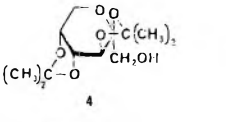
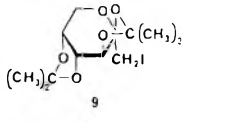
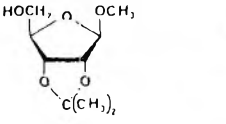
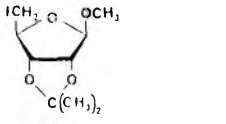
Five partially protected monosaccharides (**1**–**5**) have been converted into their corresponding iodides (**6**–**10**) via triflate displacement (Table I). The procedure for this conversion is illustrated by a description of the preparation of 3-deoxy-3-iodo-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**6**). Triflic anhydride[2] (1.68 g, 6.0 mmol) in 20 mL of dichloromethane was added to a solution of 0.52 g (6.5 mmol) of pyridine in 100 mL of dichloromethane maintained at −15 °C. To this solution was added 1.0 g (3.8 mmol) of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose[3] (**1**) in 50 mL of dichloromethane and



11 12

the reaction mixture was stirred for 1.5 h at −15 °C before being poured into 200 mL of 5% sodium bicarbonate solution. The organic layer was separated and dried (anhydrous sodium sulfate) and the solvent was distilled to give a quantitative yield of 1,2:5,6-di-*O*-isopropylidene-3-*O*-triflyl-α-D-glucofuranose[4] (**11**). The triflate **11** was dissolved in 50 mL of benzene, 3.7 g (10 mmol) of tetrabutylammonium iodide[5] was added, and the reaction mixture was refluxed for 18 h. The cooled solution was washed with 50-mL portions of water, 5% sodium bisulfite, saturated sodium bicarbonate, and water and dried over anhydrous sodium sulfate, and the solvent was distilled to leave 1.24 g of noncrystalline material which was homogeneous by TLC and GC analyses. The chemical ionization mass spectrum of this material had an intense parent peak at *m/e* 371 and the ^{1}H NMR spectrum (60 MHz, $CDCl_3$) had absorptions at δ 5.72 (d, 1 H, J = 3 Hz), 4.50 (t, 1 H, J = 3 Hz), 4.33–3.50 (m, 4 H), 1.57 (s, 3 H), 1.33 (s, 3 H), and 1.23 (s, 6 H). This information suggested structure **6** for the reaction product and excluded **7** (C-3 epimer of **6**), a compound with a quite different ^{1}H NMR spectrum.[6,7] This suggested assignment was confirmed by reduction of the reaction product with lithium aluminum hydride in refluxing ether to 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose (**12**). The iodides **7**–**10** were prepared in the same manner as **6** and compared to independently obtained samples (see Table I for yields and references).

Table I

reactant	product	yield	reference
 1	 6	87%	none
 2	 7	84%	7
 3	 8	94%	3
 4	 9	99%	15
 5	 10	65%	16

The synthesis of **6** from **1** is a significant example of the triflate displacement process because it occurs without rearrangement or elimination. This type of reactivity stands in contrast to other attempts to halogenate **1** via displacement processes; in fact, neither compound **6** nor the corresponding fluoro, chloro, and bromo derivatives previously have been reported. Attempts to synthesize these compounds invariably have led to rearrangement or elimination reactions;[8–14] thus, in addition to being a convenient and relatively mild reaction sequence, triflate displacement has a distinct advantage over other substitution reactions.

We are planning to extend this reaction sequence to other carbohydrate systems and to use it to introduce other halogens.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this research.

References and Notes

(1) Excellent reviews on syntheses and reactions of halogenated carbohydrates have been published: (a) W. A. Szarek, *Adv. Carbohydr. Chem. Biochem.*,

0022-3263/78/1943-3244$01.00/0

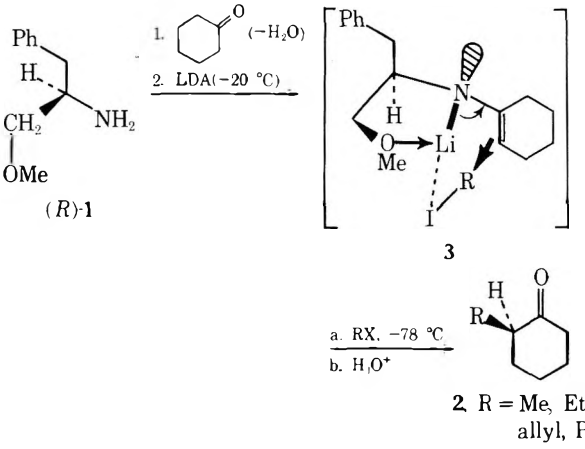
28, 225 (1973); S. Hanessian, *Adv. Chem. Ser.*, **No. 74,** 159 (1968); J. E. G. Barnett, *Adv. Carbohydr. Chem.*, **22,** 177 (1967).
(2) M. Fieser and L. F. Fieser, "Reagents for Organic Synthesis", Vol. 4, Wiley, New York, N.Y., 1974, p 533.
(3) Pfanstiehl Laboratories, Waukegan, Ill.
(4) (a) L. D. Hall and D. C. Miller, *Carbohydr. Res.*, **40,** C1 (1975); (b) L. D. Hall and D. C. Miller, *ibid.*, **47,** 229 (1976). The procedure for triflate formation used in the present study is a modification of that employed by Hall and Miller.
(5) Aldrich Chemical Company, Inc., Milwaukee, Wisc.
(6) R. H. Bell, D. Horton, D. M. Williams, and E. Winter-Mihaly, *Carbohydr. Res.*, **58,** 109 (1977).
(7) D. M. Brown and G. H. Jones, *J. Chem. Soc. C*, 252 (1967).
(8) (a) J. S. Brimacombe, A. B. Foster, R. Hems, J. H. Westwood, and L. D. Hall, *Can. J. Chem.*, **48,** 3946 (1970); (b) A. B. Foster, R. Hems, and J. M. Webber, *Carbohydr. Res.*, **5,** 292 (1967).
(9) (a) S. Hanessian and N. R. Plessas, *J. Org. Chem.*, **34,** 2163 (1969); (b) S. Hanessian, *Methods Carbohydr. Chem.*, **6,** 190 (1972).
(10) S. Hanessian, M. M. Ponpipom, and P. Lavallee, *Carbohydr. Res.*, **24,** 45 (1972).
(11) C. R. Haylock, L. D. Melton, K. N. Slessor, and A. S. Tracey, *Carbohydr. Res.*, **16,** 375 (1971).
(12) A. Zamojski, W. A. Szarek, and J. K. N. Jones, *Carbohydr. Res.*, **26,** 208 (1973).
(13) D. C. C. Smith, *J. Chem. Soc.*, 1244 (1956).
(14) E. Hardegger, G. Zanetti, and K. Steiner, *Helv. Chim. Acta*, **46,** 282 (1963).
(15) K. James and S. J. Angyal, *Aust. J. Chem.*, **25,** 1967 (1972).
(16) H. M. Kissman and B. R. Baker, *J. Am. Chem. Soc.*, **79,** 5534 (1957).

Roger W. Binkley,* David G. Hehemann
Department of Chemistry
Cleveland State University
Cleveland, Ohio 44115
Received March 24, 1978

Asymmetric Alkylation of Acyclic Ketones via Chiral Metallo Enamines. Effect of Kinetic vs. Thermodynamic Metalations

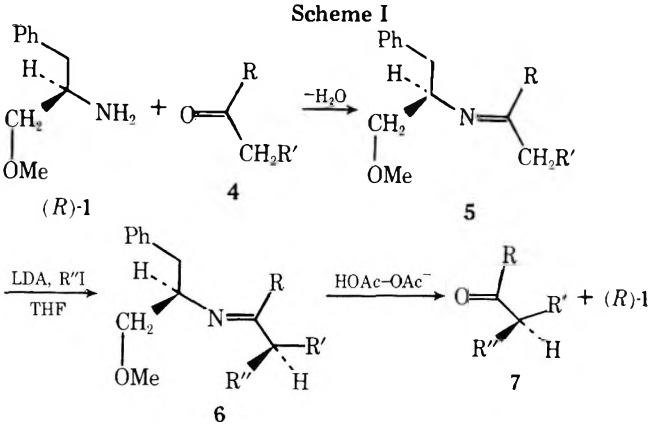
Summary: Chiral imines of acyclic ketones have been metalated and alkylated to afford α-alkyl ketones in 20–98% ee after equilibration of the metallo enamines.

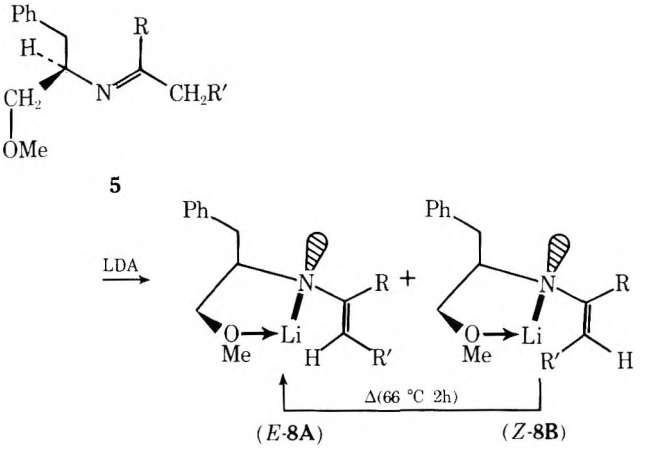
Sir: We recently described an asymmetric synthesis of 2-alkylcyclohexanones (**2**) via the chiral methoxyamine **1**.[1] The process was based upon the premise that the intermediate metallo enamine **3** would exist as a rigid five-membered ring through chelation of the methoxyl group with the lithium cation, providing favorable topological features for specific sites of alkylation. In order to account for the configurations



obtained, it was suggested that the alkyl halide may approach from the front side of the cyclohexene moiety, leading to 2-alkylcyclohexanones in high enantiomeric purity.[2] It seemed reasonable that this rigid metallo enamine should also provide α-alkyl ketones of high enantiomeric purity in the acyclic series. We now report that the conditions utilized above with acyclic ketones gave very poor results with regard to enantioselective alkylation, but a minor modification of the experimental procedure led to α-alkyl ketones **7** in generally high enantiomeric purity (Table I) within the constraints of certain structural features (vide infra). When the reaction conditions utilized for **2** (LDA, −20 °C; R″I, −78 °C) were employed for the acyclic imines **5,** alkylation occurred with no difficulty, furnishing **6** (Scheme I). However, hydrolysis to the ketones **7** gave products in 3–44% enantiomeric excess (Table I, % ee's in parentheses). The possibility that the lithiated enamines were kinetically formed as mixtures of *E* and *Z* isomers (**8A, 8B**), a situation not possible in the cyclohexene system **3,** was therefore considered. When the lithio enamines, formed at −20 °C, were heated to reflux (THF) prior to alkylation, and the alkyl halide was added after cooling at −78 °C (first three entires, Table I), the ketones were obtained in 76–98% ee! In the case where R (in **4** or **5**) was phenyl or benzyl (last four entries, Table I), the % ee of the ketones **7** was less dramatically affected. Thus, the kinetic or the thermodynamic ratio of lithio enamines **8** is dependent upon the bulk of the substituents present. It may, therefore, be assumed that metalation of **5** produces **8A** and **8B** kinetically; however, heating **8** (**A, B**) allows equilibration which favors the most stable lithio enamine. The relative size of the three substituents

Scheme I

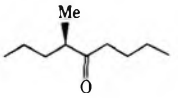
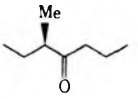
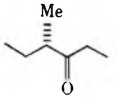
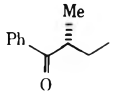
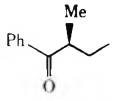
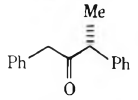
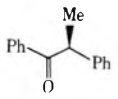




about the double bond will dictate whether the thermodynamic ratio of enamines is very different from the kinetic ratio.[3] As seen from the table, the progression of high % ee to a relatively lower one follows the increasing size of substituents on the ketone or lithio enamine **8**. Larger groups, such as phenyl, may decrease the thermodynamic stability of the *E* relative to the *Z* isomer, resulting in ketones of lower enantiomeric purity. In the last entry of Table I, two phenyl groups are present in **8** and from the absolute configuration of the ketone isolated, we may assume that the (*Z*)-enamine is slightly favored (60:40) to give 20% ee with an *S* configuration. The previous conditions for generating lithio enamines (~−20 °C) were obviously insufficient to effect their equilibration

0022-3263/78/1943-3245$01.00/0

Table I. Formation of Chiral α-Alkyl Ketones (7)

4			α-alkyl ketones				
R	R′	R″I	7	Yield, %	$[\alpha]^{25}_D$	% ee[a]	configuration
n-Bu	*n*-Pr	MeI		75	−12.8° (2.6, Et_2O)	88 (435)	*R*[b]
n-Pr	Et	MeI		84	−17.1° (2.0, Et_2O)	98 (43)	*R*[c]
Et	Me	EtI		48[e]	+24.3° (2.9, Et_2O)	76 (3)	*S*[d]
Ph	Et	MeI		77[g]	−15.3° (5.6, Et_2O)	35	*R*[f]
Ph	Me	EtI		80[g]	+23.5° (5.4, Et_2O)	53 (44)	*S*[f]
$PhCH_2$	Ph	MeI		90[g]	−12.0° (4.3, PhH)	41 (25)	*R*[h,i]
Ph	Ph	MeI		88[g]	+51.4° (1.5, EtOH)	20	*S*[j]

[a] Values of % ee in parentheses are those obtained prior to heating 8 for 2 h. [b] Percent enantiomeric excess determined by chiral shift reagent, tris[3-(heptafluoro-1-hydroxybutylidene)-*d*-camphorato]europium(III), purchased from Aldrich. [c] Rotation based on 17.5° (1.8, ether) for pure ketone: D. Seebach, V. Ehrig and M. Teschner, *Justus Liebigs Ann. Chem.*, 1357 (1976). Chiral shift reagent, as in *b*, confirmed enantiomeric purity. [d] F. Nerdel and E. Henkel, *Chem. Ber.*, **86**, 1002 (1953). [e] Low yield due to partial loss of material during solvent evaporation. [f] D. Seebach, D. Steinmuller, and F. Demuth, *Angew, Chem., Int. Ed. Engl.*, **7**, 620 (1968). [g] Contains unalkylated ketone, $[\alpha]_D$ values are extrapolated after known mixtures were prepared to validate such extrapolations. The amount of unalkylated ketone in each case varied from 7 to 30% and the $[\alpha]_D$ varied linearly. [h] See ref 2a. [i] Absolute configuration determined by Baeyer–Villiger oxidation of **7** to α-methylbenzyl alcohol of the *R* configuration. [j] Based on $[\alpha]_D$ +252° (1.4, ethanol) reported by O. Cervinka and L. Hub, *Collect. Czech. Chem. Commun.*, **33**, 1911 (1968).

and they remain in their kinetic ratio until the solution is heated to reflux. An operationally useful mechanism for the alkylation, consistent with the absolute configuration of all the ketones produced, indicates that the alkyl iodide approaches the *E* isomer from the front side of the π system, analogous to **3**, aligning both molecules enroute to the transition state. Although other mechanistic alternatives may be invoked,[2b] it is feasible to utilize the current scheme in order to predict the correct stereochemistry of the products.

A typical procedure for (*R*)-(−)-3-methyl-4-heptanone follows. A mixture of 10 g (60.6 mmol) of **1**,[4] 8.3 g (73 mmol) of 4-heptanone, and 100 mL of benzene was treated with 1–2 drops of trifluoroacetic acid and heated to reflux with azeotropic removal of water. The benzene solution was shaken with powdered sodium bicarbonate, dried, and distilled to give the imine **5** (R = *n*-Pr; R′ = Et): bp 85–88 °C (0.02 Torr); 13.8 g (85%); $[\alpha]^{25}_D$ +53.0° (4.76, MeOH). A solution of 21 mmol of lithium diisopropylamide in 40 mL of THF was treated at −20 °C with 20 mmol of **5** dissolved in 20 mL of THF. The solution was stirred (−20 °C) for 1 h and then heated at reflux for 2 h. After cooling to −78 °C, a solution of 21 mmol of methyl iodide in 20 mL of THF was added over 5 min and the reaction mixture stirred at −78 °C for 4 h. The mixture was quenched with 2 mL of methanol and partitioned between ether (75 mL) and water (75 mL). The aqueous phase was extracted (2×) with ether and the combined organic extracts were washed successively with water and brine. The solvents were evaporated and the crude imine **6** was directly dissolved in 75 mL of pentane and shaken for 30 min with 80 mL of acetic acid–sodium acetate buffer.[6] Separation of the layers, concentration, and distillation gave (*R*)-(−)-3-methyl-4-heptanone (85%), $[\alpha]_D$ −17.1° (c 2.0, Et_2O), 98% ee.[7]

Further studies to extend the scope of this asymmetric alkylation to other carbonyl compounds are under investigation.[8]

Acknowledgment. The authors express their gratitude to the National Science Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support.

References and Notes

(1) A. I. Meyers, D. R. Williams, and M. Druelinger. *J. Am. Chem. Soc.*, **98**, 3032 (1976).
(2) Additional successes involving asymmetric ketone alkylation have since been reported: (a) D. Enders and H. Eichenauer, *Angew. Chem., Int. Ed. Engl.*, **15**, 549 (1976); (b) J. K. Whitesell and M. A. Whitesell, *J. Org. Chem.*, **42**, 377 (1977).
(3) The kinetic ratio of **8A** to **8B** appears to be sensitive (as it should be) to highly hindered bases. Thus, lithium 2,2,6,6-tetramethylpiperide at −20 °C was treated with the imine of 3-pentanone **5** (R = Et, R′ = Me) and without heating to reflux (nonequilibrating conditions) gave, after alkylation with ethyl iodide, ethyl *sec*-butyl ketone (third entry in Table I) in 69% ee.
(4) Preparation of (*R*)-(+)-**1** was accomplished by BH_3·Me_2S reduction[5] of (*R*)-*C*-phenylalanine (G. D. Searle) to (*R*)-phenylalaninol [88%, $[\alpha]_D$ +24.5° (1.2, EtOH)] and treatment with KH–MeI to **1** [75%, $[\alpha]_D$ +14.4° (5.0, PhH)].
(5) C. F. Lane, U.S. Patent (to Aldrich) 3 935 280.
(6) G. R. Kieczykowski, R. H. Schlessinger, and R. B. Salsky, *Tetrahedron Lett.*, 597 (1976) have described a useful buffer so ution for the hydrolysis of imines.
(7) The sensitivity of these ketones to racemization has been determined and found to be completely stable to VPC (150 °C), the sodium acetate–acetic acid buffer solution used in the hydrolysis of **6** even after 24 h contact, and storage at room temperature for at least 4 weeks. The racemization under

any of these conditions was <1%.

(8) A study involving asymmetric alkylation of aldehydes via their chiral imines has been performed and appears to depend upon different parameters than that reported here [A. I. Meyers, G. S. Poindexter, and Z. Brich, *J. Org. Chem.*, **43**, 892 (1978)].

A. I. Meyers,* Donald R. Williams
Department of Chemistry, Colorado State University
Fort Collins, Colorado 80523
Received May 2, 1978

Novel Oligomers of Propyne: Tetramethylcyclooctatetraenes and (*Z*)-2,4-Dimethyl-1,3-heptadien-5-yne

Summary: Propyne has been catalytically oligomerized to produce novel cyclic tetramers, a linear trimer, and cyclic trimers.

Sir: Numerous organometallic compounds are known to catalyze the oligomerization of propyne to mixtures of 1,2,4- and 1,3,5-trimethylbenzene.[1] We wish to report that the black, nickel-containing substances prepared by the co-condensation[2] of nickel atoms and alkynes are active, homogeneous catalysts for the oligomerization of terminal acetylenes under very mild conditions, in some cases producing novel oligomers.[3] In the case of propyne, the new oligomers are: 1,3,5,7-tetramethylcyclooctatetraene (I), 1,2,4,6-tetramethylcyclooctatetraene (II), 1,2,4,7-tetramethylcyclooctatetraene (III), and (*Z*)-2,4-dimethyl-1,3-heptadien-5-yne (IV), a linear trimer; the first named compound was prepared earlier by photolysis of 2,4-dimethylcoumalin.[7]

For the purpose of this study, oligomerization reactions were conducted in sealed tubes at 60 °C in dioxane solvent in the presence of 10 g of liquid propyne employing the soluble, black Ni–propyne co-condensation product as catalyst. Propyne and other alkynes such as acetylene, phenylacetylene, and 2-methyl-3-butyn-2-ol can also be cyclotetramerized at room temperature and 1 atm pressure. In a typical sealed tube reaction, 0.1 g of nickel catalyst dissolved in 5 mL of dry, air-free dioxane will oligomerize 4–6 g of propyne monomer in 20 h. The distribution of products is given in Table I.

For the purpose of structural characterization of particular isomers, the oligomer mixture was reacted with tetracyanoethylene (TCNE) in ether–dioxane solution at 18 °C under nitrogen, using TCNE as the limiting reagent, giving a brown-red solution which becomes almost colorless in about 3 min. Removal of solvent and unreacted oligomers under vacuum at room temperature and sublimation of the white residue at 75 °C (10^{-2} Torr) yields two products, a tetramer–TCNE adduct (*m/e* 288) and a trimer–TCNE adduct (*m/e* 248). The adducts can be separated by vacuum thermal gradient sublimation, yielding a white tetramer–TCNE adduct (mp 184–186 °C dec) (V) and a white trimer–TCNE adduct (mp 86–87 °C) (VI).

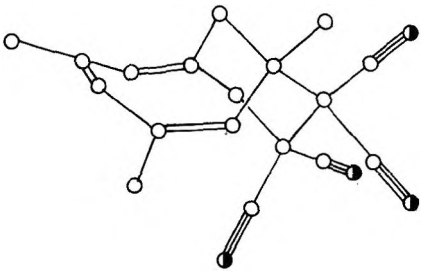
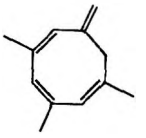


Figure 1. Perspective view of 3,5,7-trimethyl-8,8,9,9-tetracyanobicyclo[5.3.1]undeca-1,3,5-triene (hydrogen atoms omitted for clarity).

Definitive structural information about V was obtained from an X-ray crystal structure analysis on crystals grown from ether solution. The structure of V is shown in Figure 1.[4]

Consideration of the structure of V reveals it to be the 8 + 2 cycloaddition product of TCNE with the hydrocarbon (VII), an exocyclic methylene isomer of 1,3,5,7-tetramethylcyclooctatetraene (I). We believe that VII arises from I during

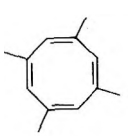
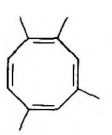
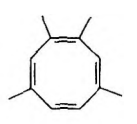
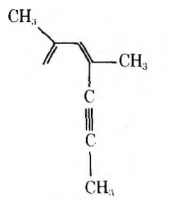
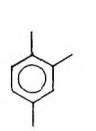
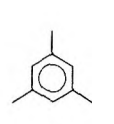


VII

the course of the reaction by means of an isomerization of I mediated by TCNE radical anion[5] and the inherent stability of the radical cation of I compared to radical cations of other isomers of tetramethylcyclooctatetraene.[6] Other information supporting the presence of I rather than VII in the oligomer mixture includes: (1) the absence of *exo*-methylene and allylic methylene resonances in ^1H and ^{13}C NMR spectra of tetramer mixtures; (2) the presence of ^{13}C NMR resonances attributable to I at 23.9, 125.7, and 140.8 ppm vs. Me_4Si in $DCCl_3$ from tetramer mixtures distilled from the trimer; (3) the decrease of a sharp ^1H NMR methyl resonance at δ 1.66 from within the methyl resonance envelope after reaction with TCNE, compared to the methyl resonance of δ 1.68 reported for pure I;[7] (4) in reactions requiring 40 h at 20 °C Criegee et al.[8] prepared TCNE adducts of three isomeric tetramethylcyclooctatetraenes (none of which was I). All adducts were 4 + 2 cycloaddition products of the bicyclo form of the olefin. Because our adduct is formed in 3 min, we believe a route other than that observed by Criegee is involved.

After reaction with TCNE, unreacted tetramer eluted from 10% $AgNO_3$ on silica gel with 20:1 pentane–ether proved to

Table I. Oligomers of Propyne

oligomer	 I	 II	 III	 IV		
mol % oligomer produced	10[a]	30[a]	15[a]	34[b]	6[b]	5[b]

[a] Integration of ^1H NMR shows 55% tetramer; amounts of individual isomers are estimated from GC/MS data. Tetramer mixtures show an asymmetric vinyl resonance centered at δ 5.40 and asymmetric methyl resonances centered at δ 1.70 vs. Me_4Si in CS_2 solution. [b] Integration of ^1H NMR.

0022-3263/78/1943-3247$01.00/0

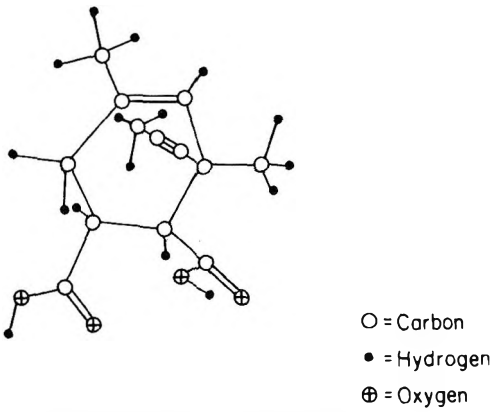


Figure 2. Perspective view of 3,5-dimethyl-*trans*-3-(1-propynyl)-4-cyclohexene-*cis*-1,2-dicarboxylic acid.

be primarily one isomer, assigned structure II based on ^{13}C NMR resonances at 21.7, 21.9, 23.5, 23.7, 125.9, 126.2, 128.4, 128.5, 138.4, 139.1, 140.6, and 141.2 ppm. Material not chromatographed from $AgNO_3$ proved to be a mixture of primarily two isomers, compound II and another isomer, assigned structure III based on ^{13}C NMR resonances at 21.6, 23.9, 125.8, 128.8, 138.7, and 140.7 ppm.

Repeated attempts to obtain crystals of the trimer–TCNE adduct (VI) suitable for X-ray analysis proved fruitless. Thus, reaction of trimer mixtures with excess maleic anhydride in dioxane–acetone for 4 h at 60 °C produces a trimer–maleic anhydride adduct (VIII) (*m/e* 218) almost quantitatively. After thermal gradient vacuum sublimation to separate excess maleic anhydride, VIII unfortunately proved to be a colorless, viscous liquid which could not be crystallized. Treatment of VIII with H_2O at 80 °C for 30 min produced an almost quantitative yield of the trimer–"maleic acid" adduct (IX) (*m/e* 236) which after sublimation at 125 °C (10^{-2} Torr) and recrystallization from ether–hexane gave white crystals (mp 197–198 °C) suitable for X-ray analysis.

The results of the X-ray structural analysis of IX are shown in Figure 2.[9]

Analysis of this adduct by standard Woodward–Hoffmann rules for Diels–Alder adducts[10,11] shows the trimer to be (*Z*)-2,4-dimethyl-1,3-heptadien-5-yne (IV) rather than the other possible isomeric arrangement about the 4 position. Compound IV exhibits the following NMR spectra: ^1H in dioxane, slightly broad vinyl resonances at δ 6.05, 5.01, and 4.87, and sharp methyl resonances at δ 1.92 and 1.87, with relative areas 1:1:1:6:3; ^{13}C, in $DCCl_3$, sp^3 resonances at 4.5, 21.2, and 26.0, sp resonances at 80.6 and 92.2, sp^2 resonances at 116.6, 117.6, 136.1, and 142.5 ppm vs. Me_4Si. The other trimers, 1,2,4- and 1,3,5-trimethylbenzene, were identified from reference ^1H and ^{13}C NMR spectra.

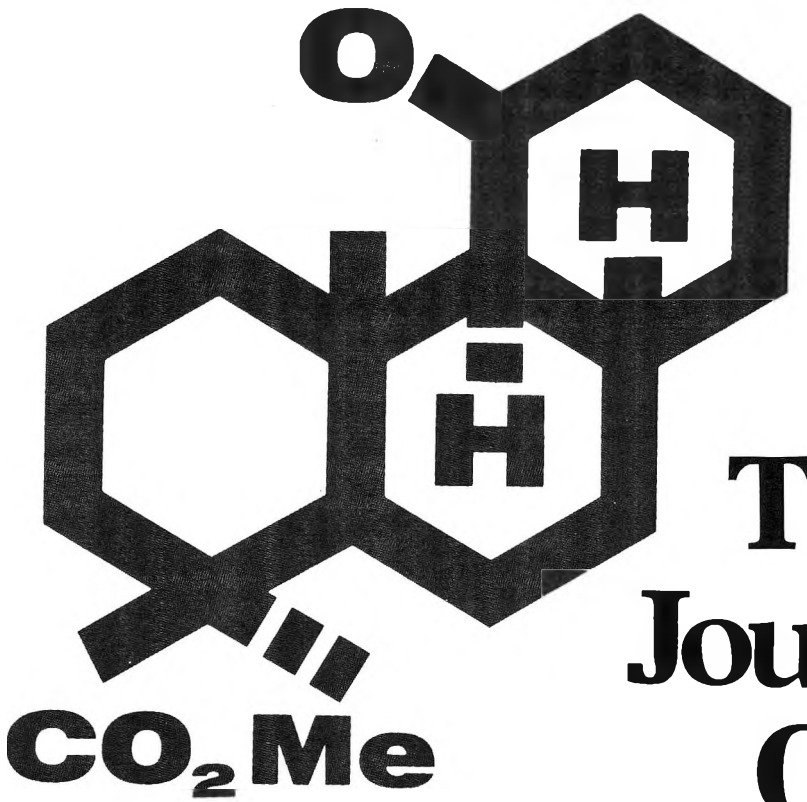
Additionally, the same nickel catalysts used for propyne oligomerization will reduce benzene to cyclohexane and methyl benzoate to methyl cyclohexylcarboxylate at room temperature and 2 atm hydrogen pressure in ether solution.

Acknowledgments. We thank the Robert A. Welch Foundation and the National Science Foundation for generous support of this program. In addition, the National Science Foundation is acknowledged for providing a portion of the funds for the purchase of the NMR equipment employed by us (Grant No. GP-41570), and for the purchase of the Syntex $P2_1$ diffractometer (Grant No. GP-37028). Finally, stimulating discussions covering various aspects of this work with B. A. Shoulders, J. C. Gilbert, N. L. Bauld, P. E. Riley, and R. E. Davis are acknowledged.

References and Notes

(1) (a) M. L. H. Green, J. Knight, L. C. Mitchard, G. G. Roberts, and W. E. Silverthorn, *J. Chem. Soc., Chem. Commun.*, 987 (1972); (b) A. F. Donda and G. Moretti, *J. Org. Chem.*, **31**, 985 (1966); (c) R. Tsumura and N. Hagihara, *Bull. Chem. Soc. Jpn.*, **37**, 1889 (1964); (d) L. S. Meriwether, E. C. Colthup, G. W. Kennerly, and R. N. Reusch, *J. Org. Chem.*, **26**, 5515 (1961); (e) E. F. Lutz, *J. Am. Chem. Soc.*, **83**, 2551 (1961).
(2) V. Graves and J. J. Lagowski, *Inorg. Chem.*, **15**, 577 (1976).
(3) L. H. Simons and J. J. Lagowski, "Reaction of Alkynes with Transition Metal Atoms", in "Fundamental Research in Homogeneous Catalysis", Vol. 2, M. Tsutsui, Ed., Plenum Press, New York, N.Y., 1978.
(4) P. E. Riley and R. E. Davis, private communications.
(5) Z. Rappoport, Ed., "The Chemistry of the Cyano Group", Interscience, New York, N.Y., 1970.
(6) N. L. Bauld, private communication.
(7) P. de Mayo and R. W. Yip, *Proc. Chem. Soc.*, 84 (1964).
(8) R. Criegee, W. Eberius, and H. A. Brune, *Chem. Ber.*, **101**, 94 (1968).
(9) P. E. Riley and R. E. Davis, private communications.
(10) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Academic Press, Weinheim, W. Germany, 1970.
(11) R. Hoffmann and R. B. Woodward, *Acc. Chem. Res.*, **1**, 17 (1968).

Leslie H. Simons, Joseph J. Lagowski*
Department of Chemistry
University of Texas at Austin
Austin, Texas 78712
Received February 21, 1978



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 **1978**
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.	All Other Countries
ACS Member*	☐ $26.00	☐ $36.00
Nonmember	☐ $104.00	☐ $114.00

Bill me ☐ Bill company ☐ Payment enclosed ☐

Air freight rates available on request.

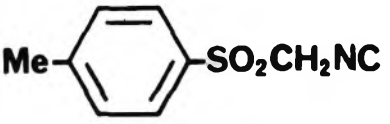
Name _____

Street _____ Home ☐ Business ☐

City _____ State _____ Zip _____

Journal subscriptions start in January '78.
Allow 60 days for your first copy to be mailed.
*NOTE: Subscriptions at ACS member rates are for personal use only.

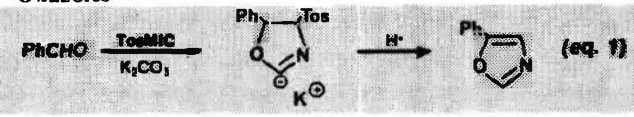
TosMIC



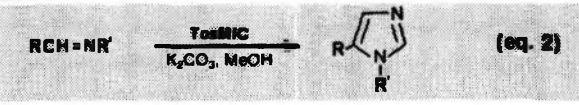
★ One-carbon elongation of ketones to acids, nitriles, etc.
★ Synthesis of 5-membered heterocycles, α-hydroxyaldehydes, etc.

Tosylmethyl isocyanide (TosMIC) has been used extensively for the synthesis of diverse *5-membered heterocyclic systems*. Some representative examples are shown in equations 1-4.

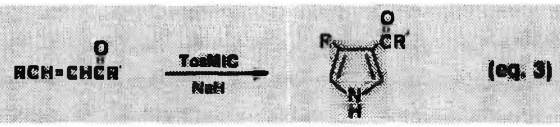
Oxazoles[1]



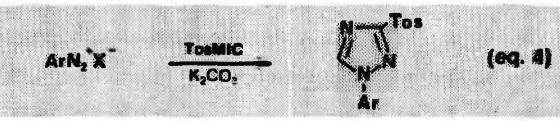
Imidazoles[2]



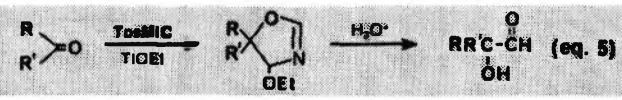
Pyrroles[3]



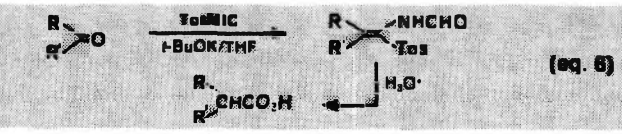
1,2,4-Triazoles[4]



4-Ethoxyoxazolines[5] are formed by the reaction of **TosMIC** with ketones in the presence of thallous ethoxide; acid hydrolysis affords *α-hydroxyaldehydes* (eq. 5).[6] Reac-

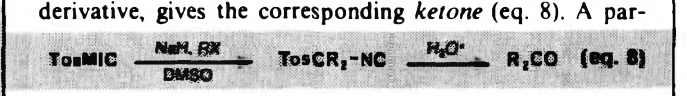


tion of a ketone with the conjugate base of **TosMIC** in THF gives the corresponding 1-formylamino-1-tosylalkene. Subsequent hydrolysis affords the *carboxylic acid* (eq. 6).[7] The

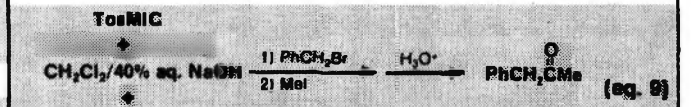


same reaction performed in dimethoxyethane/*t*-butanol gives nitriles (eq. 7).[8]

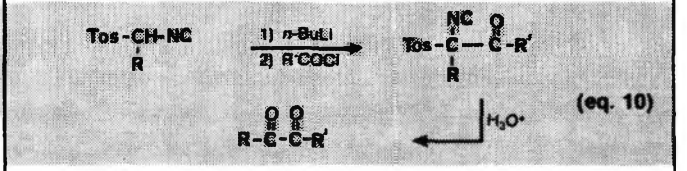
Recent developments in the use of **TosMIC** as a synthetic reagent have focused on its properties as a masked formaldehyde equivalent with *umpolung* of normal carbonyl reactivity. Thus, dialkylation of the conjugate base of **TosMIC**, followed by hydrolysis of the resulting dialkyl derivative, gives the corresponding *ketone* (eq. 8). A par-



ticularly convenient one-pot synthesis of *unsymmetrical ketones* employs phase-transfer catalysis to achieve sequential dialkylation of **TosMIC** (eq. 9).[9]



Similarly, the conjugate base of monoalkylated **TosMIC** can be acylated to provide an acyclic product, which upon hydrolysis yields a *diketone* (eq. 10).[10]



References:

1) A.M. van Leusen, B.E. Hoogenboom, and H. Siderius, *Tetrahedron Lett.*, 2369 (1972).
2) A.M. Van Leusen, J. Wildeman, and O.H. Oldenziel, *J. Org. Chem.*, **42**, 1153 (1977).
3) A.M. van Leusen, H. Siderius, B.E. Hoogenboom, and D. van Leusen, *Tetrahedron Lett.*, 5337 (1972).
4) A.M. van Leusen, B.E. Hoogenboom, and H.A. Houwing, *J. Org. Chem.*, **41**, 711 (1976).
5) O.H. Oldenziel and A.M. van Leusen, *Tetrahedron Lett.*, 163 (1974).
6) O.H. Oldenziel and A.M. van Leusen, *ibid.*, 167 (1974).
7) U. Schöllkopf, R. Schröder, and E. Blume, *Ann. Chem.*, **766**, 130 (1972); U. Schöllkopf and R. Schröder, *Angew. Chem., Int. Ed. Engl.*, **11**, 311 (1972).
8) O.H. Oldenziel and A.M. van Leusen, *Synth. Comm.*, **2**, 281 (1972); *Tetrahedron Lett.*, 1357 (1973); O.H. Oldenziel, D. van Leusen, and A.M. van Leusen, *J. Org. Chem.*, **42**, 3114 (1977).
9) O. Possel and A.M. van Leusen, *Tetrahedron Lett.*, 4229 (1977).
10) D. van Leusen and A.M. van Leusen, *ibid.*, 4233 (1977).

18,820-4 Tosylmethyl isocyanide (TosMIC)
5g $12.90; 25g $43.25

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