VOLUME 38 APRIL 20, 1973 NUMBER 8 JOCEAH

THE JOURNAL OF Organic Chemistry

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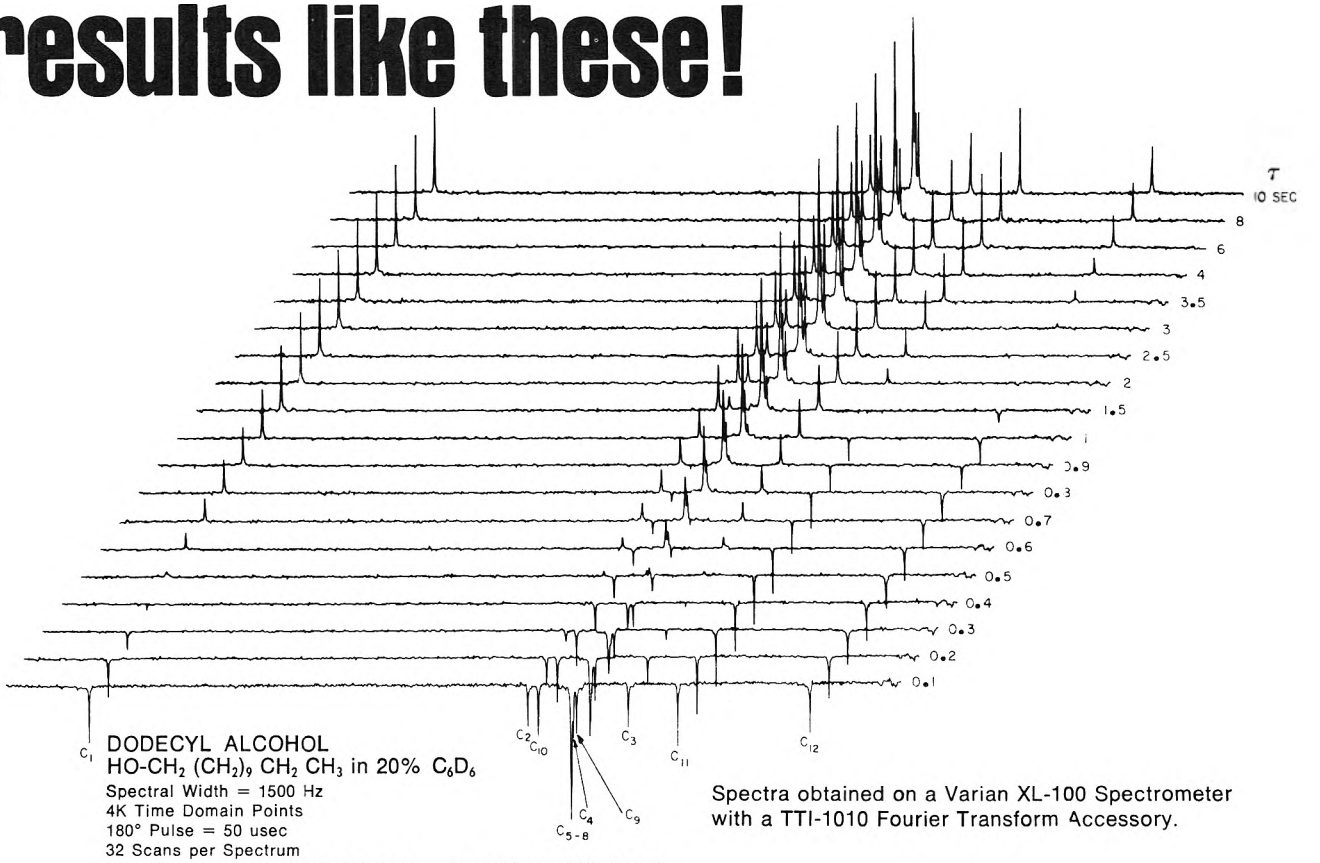

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180° Pulse = 50 usec
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After all spectra are obtained, they are processed all at once and displayed or plotted as shown. The spin-lattice relaxation times of each line can be estimated from the plots or calculated using a least squares treatment from the equation $A = A_0\ [1 - 2 \exp(-\tau/T_1)]$. This calculation is performed directly by the program upon command.

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1. R. L. Vold, J. S. Waugh, M. P. Klein, and D. E. Phelps, **J. Chem. Phys. 48**, 3831 (1968).
2. A. Allerhand, D. Doddrell, V. Glushko, D. W. Cochran, E. Wenkert, P. J. Lawson and F. Gurd, **J. Am. Chem. Soc. 93**, 544 (1971).

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THE JOURNAL OF Organic Chemistry

Published by the
AMERICAN CHEMICAL SOCIETY
1155 16th Street, N.W.
Washington, D.C. 20036

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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 Processing Department, American Chemical Society, 20th and Northampton Sts., Easton, Pa. 18042: Head, CHARLES R. BERTSCH; Production Editor, EILEEN SEGAL; Assistant Editor, FERN S. JACKSON; Editorial Assistant, ANDREW J. D'AMELIO.

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JOCEAH 38(8) 1439–1622 (1973)

THE JOURNAL OF Organic Chemistry®

VOLUME 38, NUMBER 8 APRIL 20, 1973

NOTES

COMMUNICATIONS

As a service to our readers, we bring to your attention a recent paper: "Nomenclature of Regular Single-Strand Organic Polymers," recommendations of the IUPAC Macromolecular Nomenclature Commission, reprinted in *Macromolecules*, **6**, 149 (1973).

AUTHOR INDEX

In papers with more than one author the name of the author to whom inquiries about the paper should be addressed is marked with an asterisk in the by-line.

THE JOURNAL OF Organic Chemistry®

VOLUME 38, NUMBER 8

APRIL 20, 1973

The Synthesis of Dicyclopenta[*ef*,*kl*]heptalene (Azupyrene). I. Routes to 1,6,7,8,9,9a-Hexahydro-2*H*-benzo[*c*,*d*]azulen-6-one[1,2]

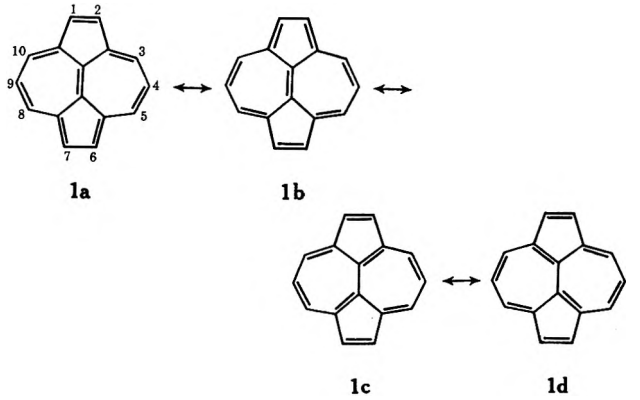
ARTHUR G. ANDERSON, JR.,*[3] GARY M. MASADA,[3,4] AND ANDREW F. MONTANA[3,5]

Department of Chemistry, University of Washington, Seattle, Washington 98195, and the Department of Chemistry, Seattle Pacific College, Seattle, Washington 98119

Received August 4, 1972

As the first phase in the synthesis of dicyclopenta[*ef*,*kl*]heptalene, four routes to 1,6,7,8,9,9a-hexahydro-2*H*-benzo[*c*,*d*]azulen-6-one (**19**) *via* the intermediate 4-(1-indanyl)butanoic acid (**3**) have been investigated: (i) *via* a Reformatsky reaction of 1-indanone with methyl 4-bromo-2-butenoate; (ii) *via* a Reformatsky reaction of 1-indanone with ethyl bromoacetate and subsequent chain lengthening by a malonic ester alkylation sequence; (iii) *via* reaction of 1-indanone with 3-methoxy-1-propylmagnesium chloride and subsequent chain lengthening by carbonation of a Grignard reagent; (iv) by reaction of sodio indene with 1-chloro-3-bromopropane and a subsequent Grignard carbonation sequence. Route iv proved to be the shortest, most adaptable to relatively large runs, and gave the best overall yields. The melting point of **3** in the literature was found to be incorrect. The acid-catalyzed cyclization of **3** or its acid chloride to **19** was accompanied by the formation of 1,2,3,4-tetrahydro-5*H*-fluoren-4-one (**20**).

The dicyclopenta[*ef*,*kl*]heptalene structure (**1**), for which we have proposed the common name azupyrene,[1] represents a cyclocondensed, conjugate-unsaturated, convex, nonalternant hydrocarbon having no benzenoid components. Two of the valence-bond resonance formulas (**1a**, **1b**) possess a 14-π-electron system peripheral to a central 2-π-electron moiety, whereas the other two noncharge-separated formulas (**1c**, **1d**) do



1a **1b**

1c **1d**

not. Azupyrene therefore provides a new, nonbenzenoid system for the further tests of structural theories of aromaticity, especially that of Platt[6,7a] wherein a stable (*i.e.*, $4n + 2$) π-electron "shell" will be separated from inner π electrons by circular nodes such that the two loci of unsaturation will consist of more or less discrete molecular orbitals. This concept, a modification of an earlier one based on the free-electron model.[7,8] has afforded an explanation of the aromatic character of benzenoid cyclocondensed hydrocarbons (*e.g.*, pyrene, coronene, and ovalene, for which extension of the Hückel rule has not been satisfactory), and of acepleiadylene (as contrasted with pleiadiene and acepleiadiene).[9]

The azupyrene structure is also symmetric[10] such that Craig's rules[11] may be formally applied to any of the Kekule structures with either of the two axes of symmetry. The result in each case is that $f + g$ is an even number and the valence-bond ground state is therefore predicted to be totally symmetric and, consequently, to have normal aromatic stability. A calculated value of 0.38 β has been determined for the specific delocalization energy per electron for azupy-

(1) A preliminary announcement of the synthesis has appeared: A. G. Anderson, Jr., A. A. MacDonald, and A. F. Montana, *J. Amer. Chem. Soc.*, **90**, 2993 (1968).

(2) Taken in part from the Ph.D. Theses of G. M. M. and A. F. M., University of Washington.

(3) University of Washington.

(4) NIH Predoctoral Fellow, 1968–1970.

(5) Seattle Pacific College.

(6) J. R. Platt, *J. Chem. Phys.*, **22**, 1448 (1954).

(7) (a) J. R. Platt, *ibid.*, **17**, 484 (1949); (b) W. T. Simpson, *ibid.*, **17**, 1218 (1949).

(8) N. S. Bayliss, *ibid.*, **16**, 287 (1948); H. Kuhn, *ibid.*, **16**, 840 (1948); F. D. Rice and E. Teller, "The Structure of Matter," Wiley, New York, N. Y., 1949, p 110.

(9) V. Boekelheide, W. E. Langeland, and C.-T. Liu, *J. Amer. Chem. Soc.*, **73**, 2432 (1951); V. Boekelheide and G. K. Vick, *ibid.*, **73**, 653 (1951).

(10) One other compound of this type is known: the isomeric pentaleno-[1,6,5-*def*]heptalene, which is less symmetrical. K. Hafner, R. Fleischer, and K. Fritz, *Angew. Chem., Int. Ed. Engl.*, **4**, 69 (1965).

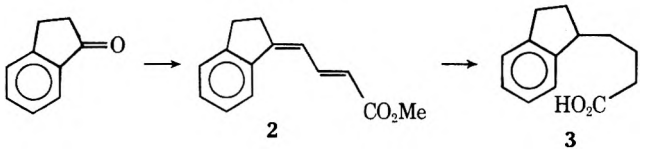
(11) D. P. Craig, *J. Chem. Soc.*, 3175 (1951); D. P. Craig and A. Macoll, *ibid.*, 964 (1949). Azupyrene may have an abnormal symmetry in this regard, however.[12]

rene[12] as compared to 0.41 β for pyrene, 0.38 β for anthracene, and 0.37 β for naphthalene.

The general route selected for the synthesis resolved into three quite distinct parts in the laboratory: (i) the preparation of 1,6,7,8,9,9a-hexahydro-2*H*-benzo[*c*,*d*]azulen-6-one (**19**), (ii) the preparation of 1,5,6,-6a,7,8,9,9a-octahydro-2*H*-indeno[5,4,3-*cde*]azulene, and (iii) the conversion of the octahydroindenoazulene to azupyrene. The present paper presents the results of the first part of the study.

Route 1. *Via* a Reformatsky Reaction of 1-Indanone and Methyl 4-Bromo-2-butenoate.—The first synthesis carried out was that shown in Scheme I. A Re-

SCHEME I

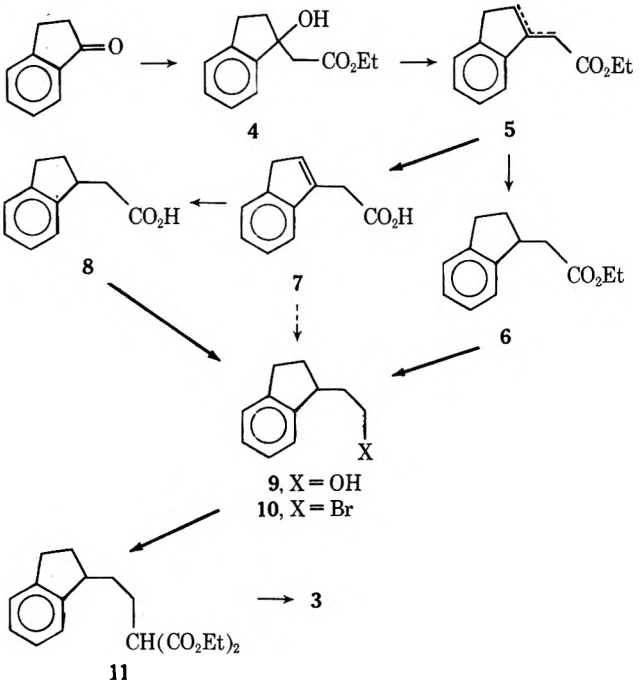


formatsky reaction involving 1-indanone and methyl 4-bromo-2-butenoate formed the hydroxy ester plus some dehydrated ester (**2**) and 2-(1-indanylidene)-1-indanone (the ketol condensation product from 1-indanone). Treatment of this mixture with hydrogen and W-6 Raney nickel gave incomplete reduction, and subsequent dehydration with potassium bisulfate, hydrogenation (platinum catalyst), and saponification gave **3** in only *ca.* 14% overall yield. It was then found that distillation of the crude Reformatsky product mixture in the presence of *p*-toluenesulfonic acid effected complete dehydration and the product thus formed could be converted to **3** in good (80%) yield (36–42% overall) by reduction (platinum catalyst) and hydrolysis. Thus, in practice, this route as developed involved just three operational steps with the isolation of but one intermediate (**2**). There were, however, two major disadvantages: it was difficult to carry out the Reformatsky reaction on larger than a 0.5 *M* scale, and extensive polymerization occurred if the acid-catalyzed dehydration was performed on more than 25 g.

Route 2. *Via* a Reformatsky Reaction of 1-Indanone and Ethyl Bromoacetate. Scheme II.—The product (**3**) obtained from route 1 melted at 72–73°, whereas von Braun, *et al.*,[13] had reported a value of 92°. Though our product and its amide derivative gave correct analyses, it was considered advisable to repeat the von Braun synthesis[13,14] to be certain that the products were indeed the same and to compare the two routes, since little yield data had been reported in the earlier work.

A Reformatsky reaction of 1-indanone with ethyl bromoacetate gave the hydroxy ester **4** (71%). Distillation of **4** in the presence of *p*-toluenesulfonic acid or treatment with thionyl chloride and pyridine gave incomplete dehydration, but heating with anhydrous formic acid gave $\geq$90% yields of the unsaturated ester **5**, the ultraviolet spectrum of which indicated the

SCHEME II



presence of a considerable fraction having the exocyclic double bond. Catalytic (platinum) reduction of **5** afforded **6** (93%). Reduction of **6** to **9** with lithium aluminum hydride (in place of sodium–alcohol) increased the yield in this step from 40% to 94%.

The alternative path of hydrolysis of the unsaturated ester **5** to the corresponding acid **7** and reduction of the latter to **9** was also examined. Unexpectedly,[15] reaction of **7** with lithium aluminum hydride gave incomplete reduction, but catalytic (platinum) hydrogenation gave **8** (72%) and subsequent hydride reduction formed **9** (79%). This path thus proved to be one step longer and to give lower yields.

Reaction of **9** with excess hydrogen bromide formed **10** (82%), which, upon treatment with sodiomalonic ester gave **11** (76%), and hydrolysis and then decarboxylation of **11** formed **3** (75%, 28% overall). The shorter and better path for this route involved seven operational steps with six isolated intermediates. It was judged to be inferior to Scheme I, as it also contained a Reformatsky reaction, for which large runs gave lower yields, and gave a lower overall yield. The product (**3**) obtained was identical with that from Scheme I; so the melting point reported[13] was incorrect.

Route 3. *Via* the Reaction of 1-Indanone with 3-Methoxy-1-propylmagnesium Chloride. Scheme III.—Smith and Sprung[16] had studied the use of 3-alkoxypropyl halides for the introduction of a three-carbon chain bearing a terminal functional group and found that methoxy was cleaved more readily than ethoxy. Accordingly, a Grignard reaction of 1-indanone and 3-methoxy-1-propylmagnesium chloride yielded 1-hydroxy-1-(3-methoxypropyl)indan (**12**) (41%), which after dehydration afforded 3-(3-methoxypropyl)indene (**13**) (63%). The assignment of the double bond position in **13** was based on comparison of the ultraviolet spectrum with those of 3-methyl-

(12) A. Rosowsky, H. Fleischer, S. T. Young, R. Partch, W. H. Sanders, Jr., and V. Boekelheide, *Tetrahedron*, **11**, 121 (1960); B. A. Hess, Jr., and L. J. Schaal, *J. Org. Chem.*, **36**, 3418 (1971), give 0.353 β for azupyrene.

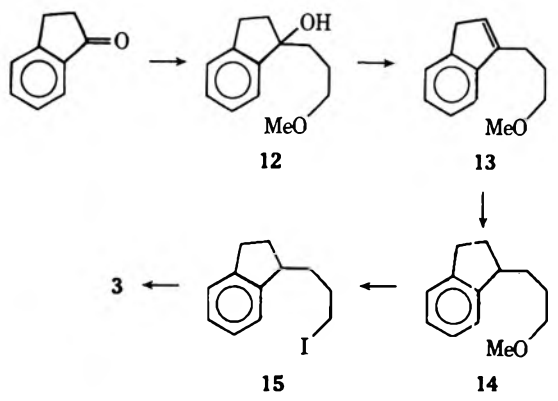
(13) J. von Braun and E. Rath, *Chem. Ber.*, **60B**, 1182 (1927).

(14) J. von Braun, E. Danziger, and Z. Koehler, *ibid.*, **50**, 56 (1917).

(15) R. F. Nystrom and W. B. Brown, *J. Amer. Chem. Soc.*, **69**, 2548 (1947), reported that $LiAlH_4$ effected the conversion of cinnamic acid to 3-phenyl-1-propanol.

(16) L. I. Smith and J. A. Sprung, *ibid.*, **65**, 1276 (1943).

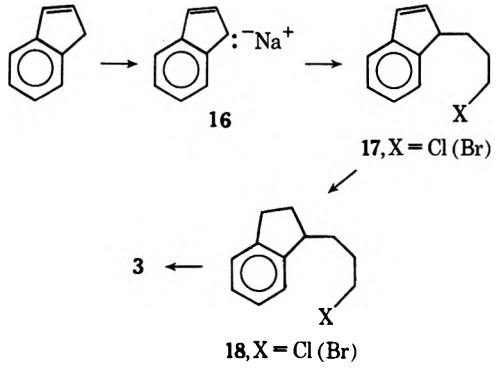
SCHEME III



indene and 3-indenylacetic acid (**7**). Catalytic (platinum) hydrogenation of **13** gave the saturated ether **14** (87%). Smith and Sprung[16] had found that sealed-tube reactions with hydrobromic acid gave much better yields than open-vessel reactions for the cleavage of similar ethers. However, the method of Stone and Schechter[17] using potassium iodide and phosphoric acid did not require sealed vessels and was found to be superior for the conversion of **14** to the iodide **15** (62%). Carbonation of the Grignard reagent from **15** gave **3** (52%, 8% overall). The low overall yield and the necessity of synthesizing the 3-methoxypropyl chloride (three steps from trimethylene glycol) made this route the least satisfactory.

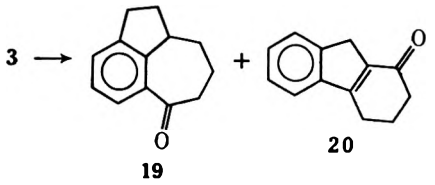
Route 4. *Via* **1-(3-Halopropyl)indene. Scheme IV.**—This route utilized relatively inexpensive, com-

SCHEME IV



mercially available reagents and it was hoped that the reactions involved would be adaptable to relatively large runs. In practice, the source and purity of the indene proved to be important[18] and, independent of this factor, the yields of **17** (obtained as a mixture of the chloride and bromide from the reaction of **16** with 1-chloro-3-bromopropane) varied considerably for reasons which could not be determined. Efforts to resolve these difficulties led to three procedures for the preparation of **16** and its conversion to **17**. One procedure required very pure indene, yet formed considerable by-product. The most satisfactory method (68%, 75% net) did not require such pure indene and gave little of the by-product. High yields (>90%) of **18** were obtained from **17** and carbonation of the Grignard reagent from **18** produced **3** (70–81%, 43–52% overall). This route involved three operation steps and the isolation of two intermediates (**17** and **18**). It was considered to be the best with respect to practical convenience, especially for relatively large runs, as well as for the overall yield despite the uncertainties with regard to the behavior of the indene.

von Braun and Rath[13] had reported a low (15%) yield for the inverse Friedel–Crafts cyclization of the acid chloride of **3** to **19** and noted that, in contrast,



this method gave good yields of 1-indanone and 1-tetralone. We have found that a high-dilution technique using carbon disulfide gives 45–52% yields. The convenience of the one-step ring closure with polyphosphoric acid was attractive, but with the commercial reagent yields of 30% or less were usually obtained, plus appreciable amounts of a by-product (**20**) which was also isolated from cyclization of the acid chloride in tetrachloroethane. The latter product was both unexpected and undesirable and its source was investigated. The ketone **19** was shown to be stable to polyphosphoric acid; so an impurity in **3** was suspected. A sample of **3** was converted to the methyl ester and the derivative was purified by preparative gas–liquid chromatography. Reaction of the pure acid **3** obtained from this ester with polyphosphoric acid, and of the acid chloride with aluminum chloride, gave **20** along with **19**. Thus **20** is formed from **3** and a likely intermediate is 4-(3-indenyl)butanoic acid,[19] formed *via* acid abstraction of hydride from the tertiary benzylic carbon.

The inconsistent results in the cyclizations with different batches of commercial polyphosphoric acid led to a study of the yield of **19** as a function of the composition of the reagent. It was found that the reaction was very sensitive to the percentage of P_2O_5 and that *ca.* 45% yields of **19** could be obtained with 80% P_2O_5 regent,[20] and this became the method of choice.

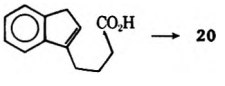
Experimental Section

Melting points were taken in capillary tubes using an aluminum block and are corrected. Boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 21 recording spectrophotometer using NaCl prisms and cells. Ultraviolet spectra were taken on a Cary Model 115 spectrophotom-

(17) H. Stone and H. Schecter, *J. Org. Chem.*, **15**, 491 (1950).

(18) Other workers have had similar experiences with indene: Professor H. Rapoport, University of California, Berkeley, personal communication, 1958.

(19) The action of an acid catalyst on 4-(3-indenyl)butanoic acid would lead to **20**; *cf.* F. H. Howell and D. A. H. Taylor, *J. Chem. Soc.*, 3011 (1957).



Other examples of acid-catalyzed formation of unsaturated ketones from alkenes and carboxylic acids are known: L. H. Rand and R. J. Dolinski, *J. Org. Chem.*, **31**, 3063, 4061 (1966); S. B. Kukari and S. Dev, *Tetrahedron*, **24**, 545 (1968).

(20) R. C. Gilmore and W. J. Horton, *J. Amer. Chem. Soc.*, **73**, 1411 (1951), found 79.8% P_2O_5 content optimum for the analogous cyclization of 4-(1,2,3,4-tetrahydro-1-naphthyl)butanoic acid. The high yields (92–94%) in this case may be due to the difference in reactivity of the position ortho to a six-membered rather than a five-membered ring.

eter. Elementary analyses were performed by B. Nist and C. H. Ludwig.

1-Indanone.—A modification of the method of Cope[21] was used. A mixture of 450 g (3.0 mol) of 3-phenylpropanoic acid and 450 g (3.8 mol) of thionyl chloride was refluxed for 2 hr. Distillation gave 471 g (94%) of 3-phenylpropanoyl chloride, bp 112–115° (15 mm) [lit.[22] bp 121–122° (22.5 mm)]. The acid chloride (168 g, 1 mol) was added rapidly (10 min) to a well-stirred suspension of 175 g (1.3 mol) of aluminum chloride in 400 ml of petroleum ether (bp 60–90°). The mixture was stirred for 15 min after HCl evolution had ceased and then a solution of 30 ml of concentrated hydrochloric acid in 1 l. of H_2O was cautiously added. Distillation of the residue from the washed (5% sodium bicarbonate), dried (magnesium sulfate), combined ethereal layers from the extraction of the mixture with four 200-ml portions of ether gave 106 g (80%) of 1-indanone, bp 88–90° (*ca.* 1 mm) [lit.[23] bp 125–126° (17 mm)].

4-(1-Indanyl)butanoic Acid (3) *Via* a Reformatsky Reaction of 1-Indanone and Methyl 4-Bromo-2-butenoate.—A mixture of 100 g of granular (20 mesh), purified[24] Zn, 225 ml of anhydrous benzene, and 5 g of $HgCl_2$ was stirred vigorously for 15 min under a N_2 atmosphere in a flask equipped with an efficient condenser with a drying tube and a stirrer which extended to the bottom of the flask. A solution of 66 g (0.5 mol) of 1-indanone, 90 g of methyl 4-bromo-2-butenoate, 75 ml of dry benzene, and 225 ml of dry ether and then an iodine crystal were added. The application of external heat started a vigorous exothermic reaction which was controlled by cooling (ice bath). After the reaction had been moderated (30 min), the mixture was heated and stirred under gentle reflux. Three additions of 30 g of methyl 4-bromo-2-butenoate, 50 g of Zn, and an iodine crystal were made at 90-min intervals. After an additional 3 hr, the mixture was cooled to room temperature and poured into a solution of 70 ml of glacial acetic acid and 500 ml of H_2O. The separated aqueous layer was extracted several times with ether, and the combined organic layer and ethereal extracts were washed with 10% ammonium hydroxide until the alkaline extracts were only slightly colored (6–8 times) and then with saturated NaCl solution. Removal of the solvents and unreacted starting materials by distillation at *ca.* 10 mm left a yellow oil which appeared to consist of methyl 4-[1-(1-hydroxy)indanyl]-2-butenoate (ir 3390 cm^{-1}), methyl 4-(1-indanylidene)-2-butenoate (**2**) [uv (ethanol) 243, 350, and 338 nm], and a small amount of 2-(1-indanylidene)-1-indanone.[25]

Rapid distillation of one-half of the yellow oil (*ca.* 25 g)[27] in the presence of 50 mg of *p*-toluenesulfonic acid from a pear-shaped flask and through an air-cooled tube gave 23.4 g (44% from 1-indanone) of **2** as a yellow oil: bp 125–145° (*ca.* 1 mm); uv (ethanol) 243 nm (log ϵ 3.95), 250 (3.92), and 338 (4.04); ir (neat) 1724 and 1628 cm^{-1}. The yields for four runs using 0.5–1 mol of indanone ranged from 41 to 58%; larger runs gave lower yields of the Reformatsky products.

A mixture of 12 g (0.056 mol) of **2**, 100 ml of absolute ethanol, and 0.1 g of prereduced PtO_2 in a Parr flask was treated with H_2 (3 atm). The uptake of H_2 ceased at the theoretical amount (0.11 mol) and the catalyst was removed by filtration. The filtrate was divided into two equal fractions and each half was diluted to 150 ml with ethanol and treated separately as follows. A solution of 6 g (0.107 mol) of KOH in 150 ml of H_2O was added to the alcoholic solution and the mixture was heated (reflux) for 3.5 hr under N_2. The alcohol was removed by distillation and the cooled alkaline solution was extracted with ether, treated with Norit, filtered, and acidified with 6 *N* hydrochloric acid. The tan crystals of crude **3** (4.6 g, 80% from **2**, 36–42% overall), mp 70–73°, after recrystallization from *n*-hexane gave colorless needles: mp 72–73°;[28] uv (ethanol) 260 nm (log ϵ 2.88), 266 (3.08), and 273 (3.14).

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.25; H, 7.79.

4-(1-Indanyl)butanamide.—One gram of **3** was refluxed with 5 ml of thionyl chloride for 30 min. The cooled mixture was poured into 15 ml of cold, concentrated ammonium hydroxide. Filtration separated the colorless precipitate, which after recrystallization from water melted at 95–96°.

Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43. Found: C, 76.92; H, 8.39.

4-(1-Indanyl)butanoic Acid (3) *Via* a Reformatsky Reaction of 1-Indanone and Ethyl Bromoacetate.[29]—A mixture of 200 g of purified,[24] granular (20 mesh) Zn, 10 g of $HgCl_2$, and 600 ml of dry benzene was stirred in the apparatus and as described for the above Reformatsky reaction. A solution of 132 g (1.0 mol) of 1-indanone, 280 ml of ethyl bromoacetate, and 500 ml of dry ether and then an iodine crystal were added with stirring and the reaction was initiated, controlled, and maintained as before. Two further additions of 100 g of Zn, 50 ml of ethyl bromoacetate, and an iodine crystal were made at 2-hr intervals. Reflux was continued for 2 hr after the last addition and then the cooled mixture was poured into 1 l. of 6 *N* sulfuric acid and worked up as described above to give 157 g (71%) of ethyl 2-[1-(1-hydroxy)-indanyl]acetate (**4**) as a light yellow oil, bp 120–125° (0.5 mm) [lit.[14] bp 180° (18 mm)].

The hydroxy ester **4** (20 g, 91 mmol) was heated (steam bath) with 115 ml of anhydrous formic acid for 15 min.[30] The cooled reaction mixture was taken up in 200 ml of H_2O and 100 ml of benzene and the separated aqueous layer was extracted with two 50-ml portions of ether. Removal of the solvents (distillation) from the combined, washed (5% $NaHCO_3$, H_2O), dried ($CaSO_4$) organic layers and distillation of the residue gave 16.7 g (90%) of the unsaturated ester **5**: bp 130–140° (2.5 mm) [lit.[14] bp 166–168° (10 mm)]; uv (ethanol) 226 nm (log ϵ 3.89), 232 (3.81), 263 (3.85), 271 (3.92), 278 (3.95), 290 (3.98), 308 (3.94), and 319 (sh, 3.89). Runs using 60 g of the hydroxy ester gave up to 96% yields.

A mixture of 22 g (0.11 mol) of the unsaturated ester **5**, 30 g (0.52 mol) of KOH, 500 ml of ethanol, and 600 ml of H_2O was heated under reflux for 3 hr and the alcohol was removed by distillation. The cooled red alkaline solution was extracted with ether, treated with Norit, and then acidified with concentrated hydrochloric acid. Recrystallization of the collected precipitate from *n*-hexane gave 15 g (79%) of the indenylacetic acid **7**, mp 87–94° (lit.[14] mp 85–86°) and 87–95° after a second recrystallization, as a mixture of needles and prisms, uv (ethanol) 254 nm (log ϵ 2.97) and 280 (2.3).

A Parr flask was charged with 19.5 g (0.11 mol) of the unsaturated acid **7**, 100 ml of absolute ethanol, 0.2 g of PtO_2, and H_2 (3 atm). After the H_2 uptake had ceased at the theoretical amount, the mixture was filtered and the solvent was removed under reduced pressure to give, after two recrystallizations from petroleum ether (bp 30–60°), 15.1 g (72%) of α-(1-indanyl)acetic acid (**8**), mp 58–61° (lit.[14] mp 60–61°).

A solution of 356 g (1.76 mol) of the unsaturated ester **5**, 350 ml of absolute ethanol, and 1 g of prereduced PtO_2 in a large Parr flask was treated with H_2 at 3 atm. After the H_2 uptake ceased, an additional 0.3 g of PtO_2 was added, whereupon H_2 uptake resumed. When the H_2 uptake again ceased a second portion of 0.3 g of PtO_2 was added. After the H_2 pressure became constant, the solution was decanted from the catalyst, the solvent was removed, and the residue was distilled to give 334 g (93%) of ethyl α-(1-indanyl)acetate (**6**), bp 93–95° (*ca.* 0.5 mm) or 124–125° (3 mm) [lit.[14] bp 149–150° (12 mm)]. The uv and ir spectra showed no absorption for nonbenzenoid C=C. Yields of 94–96% were obtained in smaller (*ca.* 0.2 mol) runs.

To a stirred solution of 4.75 g (0.125 mol) of $LiAlH_4$ in 180 ml of dry ether in a 1-l. three-necked flask equipped with a condenser with a drying tube, a mechanical stirrer, and a dropping funnel was added a solution of 15.1 g (86 mmol) of the saturated acid **8** in 150 ml of dry ether at a rate which caused gentle refluxing (45 min). The mixture was stirred for an additional 15 min and then cooled. H_2O (cautiously to decompose excess hydride) and then 150 ml of 10% sulfuric acid were added. The separated ethereal layer was washed with 5% $NaHCO_3$ and then saturated NaCl solutions and dried ($CaSO_4$). Removal of the solvent and

(21) A. C. Cope, *J. Amer. Chem. Soc.*, **72**, 3056 (1950).

(22) R. A. Pacaud and C. F. H. Allan, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 336.

(23) H. F. Greef, Ph.D. Thesis, University of Washington, 1951.

(24) J. von Braun and W. Eberlein, *Chem. Ber.*, **45**, 384 (1912).

(25) When the washed and dried organic layer and extracts from one run were allowed to stand for 2 months, light green crystals (*ca.* 4 g) separated. Recrystallization four times from benzene with the addition of Norit the first two times followed by sublimation and drying over P_2O_5 gave yellow needles, mp 144–144.4° (lit.[26] mp 142°).

(26) F. S. Kipping, *J. Chem. Soc.*, **65**, 480, 495 (1894).

(27) Larger batches gave lower yields.

(28) The melting point of 92° reported by J. von Braun and E. Rath[13] is incorrect.

(29) The procedures are in part modifications of those given by J. von Braun, *et al.*,[13,14] who reported little yield data.

(30) W. E. Bachmann and R. O. Edgerton, *J. Amer. Chem. Soc.*, **62**, 2970 (1940).

distillation of the residue gave 11 g (79%) of β-(1-indanyl)ethyl alcohol (9), bp 118–124° (6 mm) [lit.[14] bp 150–152° (11 mm)].

In the manner described for the above reduction of 8 except that the reaction mixture was stirred for 2 hr after completion of the addition, 370 g (1.81 mol) of ethyl α-(1-indanyl)acetate (6) was treated with 45 g (1.27 mol) of $LiAlH_4$ in 1.4 l. of dry ether. Hydrolysis was effected with 200 ml of H_2O and 1200 ml of 10% sulfuric acid. There was obtained 294 g (94%) of 9, bp 97–100° (0.5 mm).

In a 500-ml, three-necked flask equipped with a mechanical stirrer, a gas inlet tube reaching the bottom of the flask, a thermometer, and an exit tube connected through a trap into a tared flask containing H_2O was placed 267 g (1.78 mol) of the saturated alcohol 9. The flask was heated to 120° (oil bath), and dry HBr was added through the inlet tube. The exothermic reaction caused the temperature to rise to 130°. When excess HBr increased the weight of the tared flask (5 hr), the addition was stopped and the mixture was cooled to and then held at room temperature for 24 hr. The mixture was washed with 600 ml of 6 *M* sulfuric acid and the acid washings were extracted with two 300-ml portions of ether. Removal of the solvent from the combined, washed (two 300-ml portions of H_2O, 300 ml of 50% methyl alcohol, and 300 ml of saturated NaCl solution), dried ($MgSO_4$) organic layers and then distillation gave 398 g (82%) of β-(1-indanyl)ethyl bromide (10), bp 99–100 (1 mm) [lit.[13] bp 145–147° (16 mm)].

To a stirred, gently refluxing solution of sodiomalonic ester prepared from 44.5 g (1.95 g-atom) of Na, 1300 ml of dry ethanol, and 312 g (1.95 mol) of redistilled ethyl malonate in a 3-l. flask equipped with a condenser with a drying tube, a dropping funnel, and a mechanical stirrer was added 327 g (1.45 mol) of the above bromide 10 over a period of 3 hr, during which period NaBr precipitated. The mixture was refluxed for 10 hr and then allowed to stand at room temperature for 24 hr. Alcohol (*ca.* 1.2 l.) was removed by distillation, the mixture was cooled, and the NaBr was dissolved by adding 1 l. of H_2O. The layers were separated and the aqueous layer was extracted with four 300-ml portions of ether. Removal of the solvent from the combined, washed (saturated NaCl solution), and dried ($MgSO_4$) organic layers and then distillation gave 336 g (76%) of diethyl β-(1-indanyl)ethylmalonate (11), bp 143–145° (0.2 mm) [lit.[13] bp 212° (12 mm)].

To a solution of 240 g of KOH dissolved in 250 ml of H_2O in a flask fitted with a condenser was added 336 g (1.1 mol) of the above diester 11 and 400 ml of ethanol, and, after the initial vigorous reaction had subsided, the mixture was refluxed for 8 hr. The solvent was removed by distillation, and the cooled solution was acidified with concentrated hydrochloric acid. The collected, dried precipitate was heated in a flask at 160° (oil bath) until the evolution of CO_2 ceased (5 hr) and then cooled. Recrystallization of the crude acid from hexane gave 168 g (75% from 11 and *ca.* 28% from 1-indanone) of 4-(1-indanyl)butanoic acid (3) as colorless crystals, mp 72–73° [no depression on admixture with samples prepared *via* other routes (*vide supra* and *infra*)].

4-(1-Indanyl)butanoic Acid (3) *via* the Reaction of 1-Indanone with 3-Methoxy-1-propylmagnesium Chloride.—To a flame-dried flask equipped with a mechanical stirrer, a condenser with a drying tube, and a pressure-equalizing dropping funnel, and containing 8 g (0.33 g-atom) of Mg turnings and an iodine crystal, were added with stirring and under a N_2 atmosphere 75 ml of dry ether and a solution of 36.2 g (0.33 mol) of 3-methoxy-1-chloropropane[31] in 55 ml of dry ether, the latter at a rate to maintain gentle refluxing. The mixture was refluxed for 30 min after the addition was complete, then cooled to below 10°. A solution of 43 g (0.33 mol) of 1-indanone in 200 ml of dry ether was added slowly and the mixture was then refluxed for 1 hr. The cooled mixture was poured into a solution of 8 ml of concentrated sulfuric acid in 150 ml of ice water. The separated aqueous layer was extracted with ether. The solvent was removed from the combined, washed (5% $NaHCO_3$ and saturated NaCl solutions), dried ($CaSO_4$) organic layers and distillation of the residue gave 27.8 g (41%) of 1-hydroxy-1-(3-methoxypropyl)indan (12), bp 133–135° (1.5 mm), $n^{25.5}D$ 1.5320.

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.80; H, 8.61.

A mixture of 20 g (98 mmol) or the above alcohol 12 and 60 g of potassium pyrosulfate was heated at 155–160° (oil bath) for 1 hr. The cooled mixture was extracted with ether several times and the combined ethereal layers were dried ($MgSO_4$). Removal of the solvent and distillation of the residue gave 11.5 g (63%) of 3-(3-methoxypropyl)indene (13): bp 85–77° (0.3 mm); $n^{26.5}D$ 1.5423; uv (ethanol) 252 nm (log ε 4.02), 280 (2.94), and 290 (1.70).

Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.98; H, 8.74.

A suspension of 11 g (59 mmol) of the above unsaturated ether 13, and 0.1 g of prereduced PtO_2 in 100 ml of absolute ethanol was treated with H_2 at 30 psi in a Parr apparatus. After H_2 uptake ceased (2 hr), the mixture was filtered. Distillation of the filtrate gave 9.74 g (87%) of 1-(3-methoxypropyl)indan (14), bp 91–92° (0.3 mm), $n^{25.5}D$ 1.5215.

Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 81.96; H, 9.55.

A mixture of 8 g (42 mmol) of the above saturated ether 14, 18.74 g (0.113 mol) of KI, and 95% phosphoric acid (from 4.3 g of P_2O_5 and 33.1 ml of 85% phosphoric acid) was heated with vigorous stirring at 150° (oil bath) for 5 hr.[17] The cooled mixture was extracted with ether several times and the combined extracts were washed with 10% $NaHCO_3$ 10% $NaHSO_3$, and saturated NaCl solutions and then dried ($CaSO_4$). Removal of the solvent and distillation of the residue gave 12 g (62%) of 1-(3-iodopropyl)-indan (15), bp 100–105° (0.05 mm), $n^{25.5}D$ 1.5889.

Anal. Calcd for $C_{12}H_{15}I$: C, 50.37; H, 5.28. Found: C, 50.31; H, 5.40.

In an oven-dried flask equipped with a condenser with a drying tube, a mechanical stirrer, and a dropping funnel were placed 0.25 g (10.3 mg-atom) of Mg turnings and 5 ml of dry ether. A solution of 2.86 g (10 mmol) of the above iodide 15 in 10 ml of dry ether was added with stirring at a rate to maintain gentle refluxing (30 min) and the mixture then was refluxed for an additional 30 min. The mixture was cooled to 10–15° and poured over 5 g of powdered CO_2. After the excess CO_2 had evaporated, a solution of 2 ml of concentrated hydrochloric acid in 15 ml of H_2O was added. The separated aqueous layer was extracted with ether and the combined organic layers were extracted with two 10-ml portions of saturated $NaHCO_3$ solution. Acidification of the combined alkaline extracts with dilute hydrochloric acid, filtration, and drying of the collected precipitate gave 1.05 g (51.5%) of 4-(1-indanyl)butanoic acid (3), mp 71.5–72.5° [no depression on admixture with samples prepared *via* other routes (*vide supra*)].

4-(1-Indanyl)butanoic Acid (3) *Via* 1-(3-Halopropyl)indene (17). Method A.—To a stirred, refluxing suspension of 40 g (0.87 mol) of NaH (52%)–mineral oil in a solution of 350 g (2.22 mol) of 1-chloro-3-bromopropane and 2 l. of K-dried tetrahydrofuran under a N_2 atmosphere was added 80 g (0.69 mol) of indene[32] and the mixture was stirred under reflux for *ca.* 20 hr (including the time for indene addition). The cooled mixture was filtered and the filtrate was washed with 10% hydrochloric acid, 5% $NaHCO_3$, and saturated NaCl solutions. Distillation of the dried ($MgSO_4$) solution removed the solvent and unchanged indene and then afforded 83 g (62%) of 17, bp 120–130° (2 mm), which was indicated by analysis to be principally the chloro compound.[33] This material was converted to 18 as described below.

Method B.—A solution of 260 g (2.24 mol) of indene[34] in 200 ml of tetrahydrofuran was added over a 30-min period to a stirred, refluxing suspension of 90 g (2 mol) of NaH (53.2%)–mineral oil in 1 l. of K-dried tetrahydrofuran under a N_2 atmosphere. During the addition the mixture changed from green to red-violet. It was refluxed for 12 hr, diluted with 1 l. of tetrahydrofuran, and then added over a 15-hr period to a stirred, refluxing solution of 784 g (5 mol) of 1-chloro-3-bromopropene in 1 l. of tetrahydrofuran under a N_2 atmosphere. Work-up as described in A gave 209 g (54%) of 17, bp 120–130° (2 mm), as obtained in A.[35]

(31) Prepared in 51% yield by the method of R. L. Letsinger and A. W. Schnizer, *J. Org. Chem.*, **16**, 704 (1951), from 3-methoxy-1-propanol which was prepared in 65% yield by the method of L. I. Smith and J. A. Sprung.[16]

(32) Neville Chemical Co. or Rütgenswerke-Aktingesellschaft. These products were *ca.* 100% pure as shown by vpc analysis. Indene from Aldrich Chemical Co. or from Matheson was impure and unsatisfactory. The yield of product was independent of the rate of addition of the indene.

(33) This method gave inconsistent results (30–62% yields) from a large number of runs for reasons which were not apparent. Appreciable quantities (up to 20 g) of red oil were obtained as the distillation residue. The use of Na, $NaNH_2$, or LiH in place of NaH was less satisfactory.

(34) Matheson Scientific, Inc.

(35) Several runs gave yields of 37–54%. The reasons for the variation were not apparent.

Method C.—To a stirred, refluxing solution of 450 g (2.87 mol) of 1-chloro-3-bromopropane and 80 g of indene[36] in 2 l. of tetrahydrofuran (distilled from $LiAlH_4$) under a N_2 atmosphere was added 40 g (0.87 mol) of a NaH (52%)–mineral oil suspension in *ca.* 1 g portions over a period of 3–4 hr and reflux was then maintained for 10–12 hr. Work-up as described in A gave 91 g (68%) of **17**, bp 120–130° (2 mm), as obtained in A. The yield based on recovered indene was 75%. The product was converted to **18** as described below.

In a large Parr bomb 354 g (1.83 mol) of the unsaturated halide **17**, 500 ml of absolute ethanol, and 1 g of prereduced PtO_2 were treated with H_2 at 3-atm pressure until H_2 uptake ceased. An additional 0.2 g of PtO_2 was added. The theoretical amount (1.83 mol) of H_2 was taken up. Decantation of the solution from the catalyst and distillation gave 325 g (91%) of the corresponding 1-(3-halopropyl)indan (**18**), bp 97–100° (0.9 mm).[37] One-fourth of a solution of this product (327 g, 1.69 mol) in 100 ml of dry ether was added to 43 g (1.77 g-atoms) of Mg turnings[38] and 850 ml of dry ether under a N_2 atmosphere in a flask equipped with a stirrer, a condenser with a drying tube, and a dropping funnel. After the reaction had begun, the remaining solution was added at a rate to maintain gentle refluxing (*ca.* 90 min) and the mixture was refluxed for an additional 3 hr. The cooled mixture was poured, a little at a time and with stirring, onto excess freshly crushed Dry Ice in five 500-ml filter flasks. After the excess Dry Ice had evaporated, hydrolysis was effected with 1 l. of 5% hydrochloric acid. Ether (750 ml) was then added, the separated aqueous layer was extracted with 300 ml of ether, and the combined ethereal solutions were washed with water and then extracted with 10% aqueous KOH. Acidification of the alkaline extracts with concentrated hydrochloric acid formed an oil which solidified on standing. The crude product was dried *in vacuo* over P_2O_5 and then recrystallized from hexane to give 232–279 g (70–81%) of 4-(1-indanyl)butanoic acid (**3**), mp 71–73° (no depression on admixture with samples prepared *via* the other routes described above).

Cyclization of 4(1-Indanyl)butanoic Acid (3). Method A.—A mixture of 30 g (0.147 mol) of **3** and 30 g (0.25 mol) of thionyl chloride was refluxed for 1 hr and then distilled. The acid chloride of **3** (29 g, 89%) was collected at 116–118° (0.5 mm) [lit.[13] bp 172° (12 mm)].

A solution of 12.2 g (0.05 mol) of the acid chloride in 1 l. of anhydrous carbon disulfide was added over a 5-hr period to a stirred suspension of 9.5 g (0.07 mol) of powdered $AlCl_3$ in 1 l. of dry carbon disulfide and the mixture was then refluxed with stirring for 3 hr. Ice water (800 ml) was added cautiously to the deep red mixture, the carbon disulfide was removed by distillation (water bath), and the residual material was extracted with ether. Removal of the solvent from the combined, washed (6 *N* hydrochloric acid, 7% $NaHCO_3$, and then saturated NaCl), dried ($MgSO_4$) extracts and then distillation gave 4.97 g (52%) of 1,6,7,8,9,9a-hexahydro-2*H*-benzo[*c*,*d*]azulen-6-one (**19**), bp 110–112° (0.5 mm) [lit.[13] bp 172° (12 mm)].[39]

Anal. Calcd for $C_{13}H_{14}O$: C, 83.84; H, 7.58 Found: C, 83.55; H, 7.58.

Method B.—To polyphosphoric acid (79.8% in P_2O_5), prepared by the cautious, slow addition with swirling of 920 ml of 85% phosphoric acid to 1430 g of P_2O_5, maintained at 80–90° (water bath), was added 57.4 g (0.282 mol) of finely powdered **3** with swirling. This temperature and vigorous, frequent swirling were continued for 15 min, during which time the color of the mixture changed from orange to dark red-brown. The mixture was poured immediately onto 4 l. of crushed ice and stirred until the dark, viscous mass had completely hydrolyzed. The hydrolysate was divided into two equal portions, the volume of each was brought to 3 l. with H_2O, and the yellow suspensions which resulted were extracted with ether until the extracts were colorless. Removal of the solvent from the combined, washed (H_2O, saturated $NaHCO_3$, saturated NaCl), dried ($MgSO_4$) extracts left 48.4 g of amber oil which was chromatographed on acidic alumina (1.5 lb in a 5.5-cm diameter column). An oily forerun (4.73 g) was eluted with hexane, 10:1 hexane–ethyl acetate then removed **19** as a pale yellow oil, and finally 1,2,3,4-tetrahydro-5*H*-fluoren-4-one (**20**) was eluted with 1:1 hexane–ethyl acetate. Crystallization of **19** from methanol at −25° gave 24.2 g (46%) of colorless prisms: mp 40.0–41.5°; uv (cyclohexane) 243 nm (log ε 4.03), 291 (3.77), and 322 (sh, 1.95); ir (CCl_4) 1709 cm^{-1}.

Recrystallization of the yellow solid **20** from hexane gave 11.3 g (22%) as colorless plates: mp 106–106.5° (lit.[40] mp 104–106°); uv (cyclohexane) 225 nm (log ε 3.88), 232 (4.07), 238 (4.07), 290 (sh, 4.29), 296 (4.30), and 307 (sh, 4.16).

Anal. Calcd for $C_{13}H_{12}O$: C, 84.75; H, 6.57. Found: C, 84.77; H, 6.38.

Registry No.—**2**, 38425-60-4; **3**, 38425-61-5; **4**, 1620-02-6; **5**, 38386-68-4; **6**, 22339-45-3; **7**, 1620-00-4; **8**, 38425-65-9; **9**, 38425-66-0; **10**, 38434-35-4; **11**, 38434-36-5; **12**, 38434-37-6; **13**, 38434-38-7; **14**, 38434-39-8; **15**, 38434-40-1; **17** (X = Cl), 38521-62-9; **18** (X = Cl), 38434-41-2; **19**, 14528-87-1; **20**, 7235-16-7; 1-indanone, 83-33-0; 3-phenylpropanoic acid, 501-52-0; 3-phenylpropanoyl chloride, 645-45-4; methyl 4-bromo-2-butenoate, 1117-71-1; 4-(1-indanyl)butanamide, 38434-44-5; ethyl bromcacetate, 105-36-2; sodiomalonic ester, ethyl, 28290-06-4; 3-methoxy-1-chloropropane, 36215-07-3; 1-chloro-3-bromopropane, 109-70-6; indene, 95-13-6; 4-(1-indanyl)butanoic acid, chloride, 38434-46-7.

Acknowledgments.—This investigation was supported in part by grants from the National Science Foundation. The authors wish to thank Robert Hathaway, Ruth Ann Henrikson, Imadel James, and Gerald Klein for valuable assistance.

(36) Either pure indene[32] or 90% indene (Aldrich Chemical Co.) was satisfactory. This method also gave lower yields (43–60%) in some runs for reasons which could not be determined.

(37) In a large number of runs yields varied from 90 to 95%.

(38) Ground in a dry mortar and pestle just prior to using. The addition of ethyl- or methylmagnesium iodide was sometimes necessary to initiate the reaction.

(39) A procedure using tetrachloroethane as the solvent at room temperature gave 26–34% of **19** and *ca.* 9% of **20**, bp 120–125° (0.5 mm).

(40) A. G. Anderson, Jr., and S. Y. Wang, *J. Org. Chem.*, **19**, 277 (1954).

The Synthesis of Dicyclopenta[*ef*,*kl*]heptalene (Azupyrene). II. Routes from 1,6,7,8,9,9a-Hexahydro-2*H*-benzo[*c*,*d*]azulen-6-one and 5-Phenylpentanoic Acid[1,2]

ARTHUR G. ANDERSON, JR.,*[3] ANDREW F. MONTANA,[3,4]
ALAN A. MACDONALD,[3] AND GARY M. MASADA[3,5]

Department of Chemistry, University of Washington, Seattle, Washington 98195, and the Department of Chemistry, Seattle Pacific College, Seattle, Washington 98119

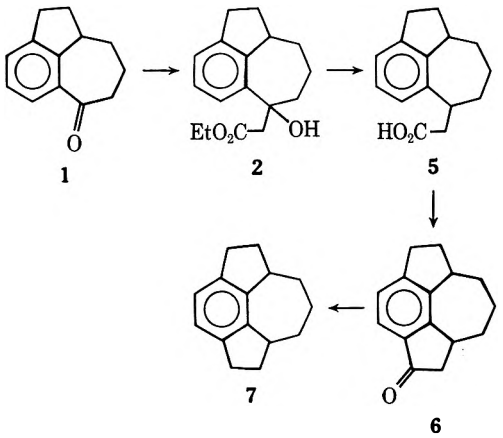
Received August 4, 1972

In the second phase of the synthesis of azupyrene, two routes *via* the intermediate 1,5,6,6a,7,8,9a-heptahydro-2*H*-indeno[5,4,3-*cde*]azulene (**7**) have been investigated: (i) from 1,6,7,8,9,9a-hexahydro-2*H*-benzo[*c*,*d*]azulen-6-one (**1**) as depicted in Schemes I, II, and III, and (ii) from 5-phenylpentanoic acid (**23**) as depicted in Scheme IV. The best route afforded **7** as the cis isomer (**19**) in *ca.* 43% overall yield from **1** and involved just three operational steps. This provided a seven-step synthesis of **19** from indene in 8–9% overall yield. Reaction of **19** with ethyl diazoacetate, saponification, and then concomitant decarboxylation and dehydrogenation formed azupyrene (3.8%).

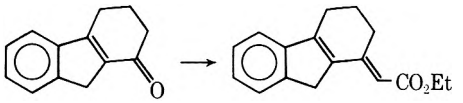
The previous paper[1] described the first phase in the synthesis of azupyrene: routes to 1,6,7,8,9,9a-hexahydro-2*H*-benzo[*c*,*d*]azulen-6-one (**1**). The present paper describes the synthesis of 1,5,6,6a,7,8,9,9a-octahydro-2*H*-indeno[5,4,3-*cde*]azulene (**7**) and its conversion to azupyrene (**25**). Two routes to **7** were investigated: (i) from **1** and (ii) from benzocycloheptene (**22**).

Route 1. From 1,6,7,8,9,9a-Hexahydro-2*H*-benzo[*c*,*d*]azulen-6-one (1).—The general plan of this route is shown in Scheme I. The initial objectives were the

SCHEME I

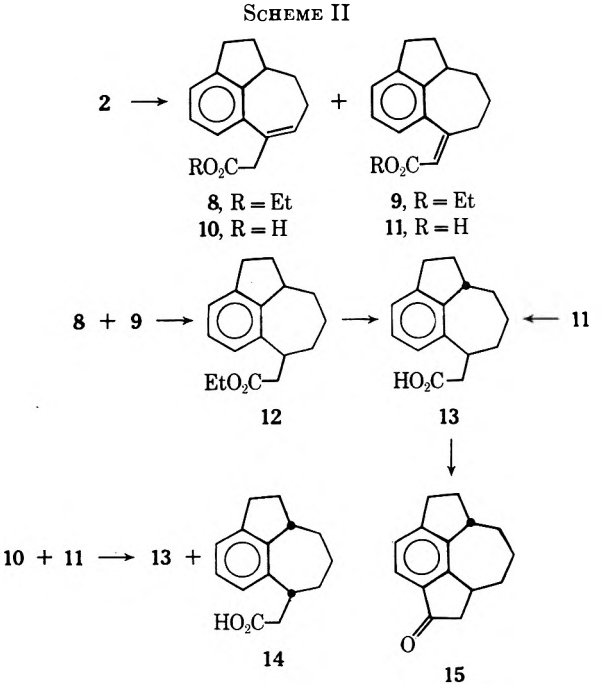


conversion of **1** to **2** (77%) by a Reformatsky reaction and then dehydration, hydrogenation, and hydrolysis to form **5**. Treatment of **2** with 6 *N* sulfuric acid effected hydrolysis but not dehydration, and distillation in the presence of *p*-toluenesulfonic acid gave incomplete loss of water. The stability of **2** is characteristic of Reformatsky esters derived from benzocyclohepten-1-ones.[6] Initially the Reformatsky reaction was carried out on impure **1** containing **3**[1] and the product consisted of a mixture of **2** and **4** which did not separate on distillation. The absorption spectrum of **4** led to the erroneous conclusion that the dehydration of **2** had occurred. Subsequently this difficulty was overcome by the chromatographic separation of **1** and **3**. Three methods were found to effect the



dehydration of **2**: (i) treatment with thionyl chloride and pyridine (84%); (ii) refluxing with *p*-toluenesulfonic acid in toluene (93%); and (iii) heating with anhydrous formic acid (97.5%). The infrared (two carbonyl peaks) and the nuclear magnetic resonance (vinylic singlet superimposed on a triplet) spectra of the dehydration product showed the presence of two species (**8** and **9**, Scheme II).[7] Hydrogenation of the

SCHEME II



mixture over platinum gave impure saturated ester **12**,[8] which after saponification afforded *ca.* 40% of

(1) Paper I: A. G. Anderson, Jr., G. M. Masada, and A. F. Montana, *J. Org. Chem.*, **38**, 1439 (1973).

(2) Taken in part from the Ph.D. Theses of A. F. M., A. A. M., and G. M. M., University of Washington.

(3) University of Washington.

(4) Seattle Pacific College.

(5) NIH Predoctoral Fellow, 1968–1970.

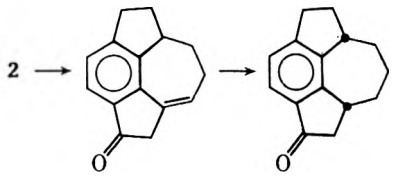
(6) R. C. Gilmore and W. J. Horton, *J. Amer. Chem. Soc.*, **73**, 1411 (1951); H. F. Greef, Ph.D. Thesis, University of Washington, 1951.

(7) Molecular models of **8–11** indicate that structures having the double bond in the endo position would be sterically less strained. The stabilization by conjugation in the exo-unsaturated structures is thus of comparable magnitude.

(8) The product also contained **9**, which reacted very slowly. Repeated hydrogenation of the mixture did not completely reduce this isomer.

13. A mixture of 13 and 14 (42%) was usually obtained when 8 and 9 were first converted to the unsaturated acids 10 and 11 and the latter mixture reduced. The proportion of isomers varied and some runs afforded very predominantly (*ca.* 90%) 11 (λ_{max} 269 nm). Hydrogenation of isolated 11 gave pure 13 (98%) and treatment of the latter with polyphosphoric acid (93%) or thionyl chloride and then aluminum chloride (55%) formed the trans tetracyclic ketone 15. The assignments of the structures for the isomers will be discussed later.

The reactions of Scheme II were not considered to be satisfactory. It was evident that hydrogenolysis of the benzylic hydroxyl group in 2 would avoid the problem of reduction of a mixture of 8 and 9 or 10 and 11 and also shorten the route by one step. Treatment of 2 with hydrogen and palladium or platinum catalysts, however, gave no reaction and attempted reduction by reaction with phosphorus and iodine in acetic acid[9] or with concentrated hydriodic acid in acetic acid[10] failed to give the desired transformation. The direct cyclization of 2, with the possibility of concomitant removal of the hydroxyl, was considered next. Gilmore had found that the yield of ketone was the same from the cyclization of 5-phenylpentanoic acid or its methyl ester with polyphosphoric acid.[11] Reaction of 2 with this reagent at 80–90° for but 5 min[12] effected cyclization and dehydration to give a single product (16), a rather unstable substance, in

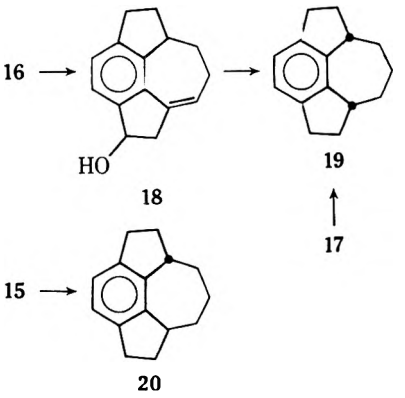


16 17

84% yield. The position of the carbon–carbon double bond in 16 was shown by the absorption spectra: a maximum at 247 nm, and pmr signals for a weakly split singlet at 2.92 (methylene adjacent to the carbonyl) and a triplet at 5.75 ppm (vinylic hydrogen). This intermediate, however, was inert to hydrogen in the presence of palladium on charcoal or platinum in ethanol, and platinum in acetic acid gave only 33% of 6 as the cis isomer (17). An attempted reduction with diborane using a method previously employed successfully on azulenic ketones[13] produced only yellow oils. Thus, although this new path eliminated the dehydration and ester hydrolysis steps, an alternative to the catalytic reduction was needed.

The existence of the Brown catalyst, supported platinum generated by the *in situ* reduction of platinum salts by borohydride,[14] led to the development of a new reaction sequence (Scheme III) wherein 16 was treated with excess sodium borohydride to reduce the carbonyl group. Decolorizing carbon and chloro-

SCHEME III

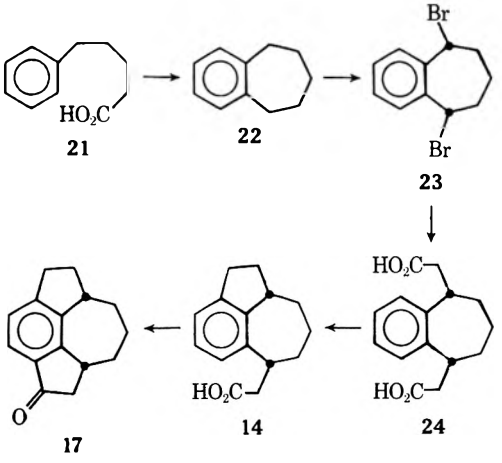


platinic acid were then added, any excess borohydride was destroyed, and the solution was brought to the required acidity with hydrochloric acid, and hydrogenative reduction of the carbon–carbon double bond and cleavage of the benzylic hydroxyl were all effected in one continuous operation to give 7 as the cis isomer (19) in 66% yield. The intermediate alcohol 18 could be isolated and was characterized. Pure 18 could be converted to 19 by hydrogenation with platinum in acetic acid, but in lower yield (56.5%). Wolff-Kishner reduction of 17 also gave, as expected, 19, whereas the trans isomer (20) was obtained from 15.

The best route from 1 to 7 now involved just three operational steps and gave an overall yield of the cis isomer (19) of *ca.* 43%. This made the overall yield from indene 8–9% for nine reactions and seven operational steps.

Route 2. From 5-Phenylpentanoic Acid (21) (Scheme IV).—An additional route to 7 patterned after

SCHEME IV



the synthesis of tetrahydropyracene from tetralin[15] was investigated concurrently with the above studies. The initial intermediate needed for this approach was 5-phenylpentanoic acid (21), and three methods of preparation were compared. The first, Doebner condensation of cinnamaldehyde with malonic acid to give 5-phenylpenta-2,4-dienoic acid and then reduction with Raney nickel alloy and base, gave 90–95% overall yields[16] but the product was sometimes ob-

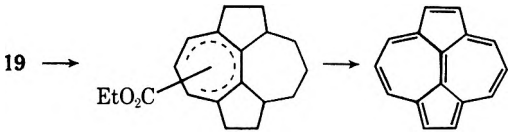
(9) C. S. Marvel, F. D. Hager, and E. C. Caudle, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1941, p 224.
(10) M. Orchin and L. Reggel, *J. Amer. Chem. Soc.*, **73**, 436 (1951).
(11) R. C. Gilmore, *ibid.*, **73**, 5879 (1951).
(12) No reaction occurred at lower temperatures, and longer times resulted in appreciable decomposition.
(13) A. G. Anderson, Jr. and R. D. Breazeale, *J. Org. Chem.*, **34**, 2375 (1969).
(14) H. C. Brown and C. A. Brown, *J. Amer. Chem. Soc.*, **84**, 2827 (1962); *Tetrahedron, Suppl. 8*, **22** (1), 149 (1966).
(15) A. G. Anderson, Jr., and R. G. Anderson, *J. Amer. Chem. Soc.*, **79**, 1197 (1957).
(16) A. G. Anderson, Jr., and S. Y. Wang, *J. Org. Chem.*, **19**, 277 (1954).

tained as an oil which was difficult to purify. The second, a Knoevenagel reaction of cinnamaldehyde with malonic ester followed by saponification, Raney nickel alloy–base reduction, and decarboxylation, gave *ca.* 50% overall yields and an oil product difficult to purify. The third, Friedel–Crafts reaction of benzene with glutaric anhydride and then Clemmensen reduction of the keto acid, gave *ca.* 80% of crystalline **21** and was considered to be the best.

Conversion of **21** to benzocycloheptene (**22**) was effected by Friedel–Crafts cyclization of the acid chloride from **21** and Clemmensen reduction of the resultant cyclic ketone in 60–70% overall yield. The bromination of tetralin with *N*-bromosuccinimide is vigorously exothermic.[15] In contrast, the reaction with **22** was very slow and heat, light, and azobisisobutyronitrile were needed to achieve a moderate rate. Molecular models showed that just two of the four benzylic hydrogens would be reactive and that these would be sterically less favorably oriented than the corresponding tetralin hydrogens.[17] Analysis of the product indicated it to be a mixture of **23** and the monobromo compound. Reaction of this material with sodiomalonic ester and then saponification gave a mixture of acids which was partially separated before thermal decarboxylation. The sequence afforded only 5% of the desired benzocycloheptene-1,5-diacetic acid (**24**). This route was therefore of no value for the synthesis of **7** but it provided pure samples of tricyclic acid **14** and tetracyclic ketone **17** which were isomers of those (**13** and **15**) obtained from the previous synthesis (Scheme II). Cyclization of **24** with polyphosphoric acid and then Clemmensen reduction[18] gave **14** (48%), and cyclization of the latter afforded **17** (60%).

The assignment of the stereochemistry to the trans (**13** and **15**) and cis (**14**, **17**, **24**) isomers was based on indirect evidence. Molecular models indicated that the two sterically less hindered benzylic positions on **22** and **23** were cis. The appreciably greater hindrance for a trans substituent made it seem likely that the malonic ester and, consequently, the acetic acid substituents would occupy the cis positions also. Models of the tetracyclic ketones (**15** and **17**) showed that the carbonyl of the cis isomer was slightly more nearly in the plane of the benzene ring than in the trans isomer. In agreement with this, the absorption maximum for **17** (264 nm) was at a longer wavelength than that (261 nm) for **15**. A similar difference (1705 and 1720 cm^{-1}) in the same direction was observed in the infrared spectra. Also, the more planar stuctures (**14**, **17**, and **24**) would be expected to have higher melting points than their isomers, and this was found to be so.

Conversion of 19 to Azupyrene (25).—The final phase of the synthesis was the conversion of **19** to azupyrene (**25**). Diazomethane was considered first for the ring-enlargement step, as dehydrogenation of the product would give azupyrene. Trial reactions were conducted on prehnitene (1,2,3,4-tetramethylbenzene) as a model system. Reactions of prehnitene with diazomethane, neat or in solution, catalyzed by cuprous ion,[19] bis(acetylacetonato)copper(II),[20] or cupric ion[21] gave low yields of cycloheptatriene product and a satisfactory separation of the mixture by liquid-phase column chromatography was not achieved. The use of diiodomethane or ethyl diiodoacetate with a zinc–copper couple, and of ethyl diiodoacetate with diethylzinc, were also unsatisfactory. Heating of prehnitene with ethyl diazoacetate[22] in the presence of bis(acetylacetonato)copper(II) or cupric ion gave mostly diethyl fumarate and diethyl maleate, but the reaction in the absence of a catalyst gave a separable ester fraction which exhibited pmr absorption for vinylic hydrogens. Treatment of **19** with the diazo ester gave two ester fractions which could be separated from unchanged hydrocarbon. That these were isomeric was indicated by the virtual identity of their nuclear magnetic resonance spectra and the fact that one became identical in all respects with the other upon standing.



25

Hydrolysis of the ester product afforded the corresponding acid. The low volatility of this substance made the use of a liquid-phase dehydrogenation method possible with methyl oleate as the solvent and hydrogen acceptor and a specially prepared palladium on carbon[23] as the catalyst. It was hoped that decarboxylation would occur concomitantly and a trail reaction with 1,2,3,6-tetrahydro-6-azuloic acid[24] was found to give azulene in 12% yield. Application of the procedure to the tetracyclic acid gave azupyrene (**25**; 3.8% from **19**) as thermally stable, bronze crystals.

The structure and aromatic character of **25** were confirmed by its spectra. The infrared spectrum showed absorption characteristic for aromatic CH and C=C, and a band at 1377 cm^{-1} very similar to that exhibited by azulene. The nuclear magnetic resonance spectrum showed a four-proton singlet, a four-proton doublet, and a two-proton triplet with a 1000-cycle sweep width, and with a 50-cycle sweep width eight lines of a characteristic AB_2 pattern were revealed. The value for the dimagnetic susceptibility of $\Lambda/\Lambda_{bz} = 3.9 \pm 0.3$ measured with a Faraday balance[25] was comparable with that (4.2 ± 0.1) obtained for pyrene.[26] The electron spin resonance spectrum of the 17-electron anion radical[27] showed the hyper-

(17) The configuration of the radical intermediate from benzocycloheptene would provide less resonance stabilization.

(18) Wolff–Kishner reduction of the intermediate keto acid gave poor yields.

(19) E. Muller, H. Fricke, and H. Kessler, *Tetrahedron Lett.*, 1501 (1963); 1525 (1964). E. Muller, B. Zech, R. Heischkeil, H. Fricke, and H. Suhr, *Justus Liebigs Ann. Chem.*, **662**, 38 (1963).

(20) H. Nozake, S. Moriuti, M. Yamabe, and R. Noyori, *Tetrahedron Lett.*, 59 (1966); S. Kida, *Bull. Chem. Soc. Jap.*, **29**, 805 (1956).

(21) D. O. Cowan, M. H. Couch, K. R. Kopecky, and G. S. Hammond, *J. Org. Chem.*, **29**, 1922 (1964).

(22) An excess of the diazo compound was used, in contrast to the usual excess of hydrocarbon, in all reactions with prehnitene and **19**, since it was not feasible to use an excess of the latter. This was not a limiting factor, as unchanged hydrocarbon was always recovered.

(23) A. G. Anderson, Jr., W. F. Harrison, and R. G. Anderson, *J. Amer. Chem. Soc.*, **85**, 3448 (1963).

(24) E. J. Cowles, Ph.D. Thesis, University of Washington, 1953.

(25) We thank Drs. J. D. Wilson and C. E. Scott for this measurement.

(26) H. J. Dauben, Jr., J. D. Wilson, and J. L. Laity, *J. Amer. Chem. Soc.*, **90**, 811 (1968).

(27) These experiments were performed by G. Scott Owen and Dr. Gershon Vincow. The McConnell relationship was used for the calculated hyperfine splitting values.

fine splittings $a_{H^1} = 0.64 \pm 0.01$ G, $a_{H^3} = -4.23 \pm 0.01$ G, and $a_{H^4} = 0.94 \pm 0.01$ G as compared with respective calculated values of 0.10, −4.71, and 1.25 G. The g value was 2.00258. These data are consistent with the structure of **25**.

The diamagnetic susceptibility for a planar, cyclic 14 π electron structure, *trans*-15,16-dimethyl-15,16-dihydropyrene,[28] has been measured as $\Lambda/\Lambda_{bz} = 5.5 \pm 1$.[29] Thus the value for **25** is somewhat less than might be anticipated on the basis of a completely node-separated peripheral π system,[30] and suggests some participation of the central unsaturation.

The melting point (250–258°) of **25** is appreciably higher than those of pyrene (150–151°), acepleiadylene (156–162°), cyclohepta[*bc*]acenaphthylene (142.5–143.5°), or naphtha[2,1,8-*cde*]azulene (197–200°), with which it is isomeric. In the hope of finding an explanation for this in the crystal structure or in the molecular dimensions, an X-ray structural determination was attempted.[31] The crystal, however, exhibited a degree of disorder prohibiting meaningful analysis.

Experimental Section

Melting points were taken on an Eimer and Amend block and are corrected unless otherwise noted. Boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 21 recording spectrophotometer using NaCl prisms and cells. Ultraviolet spectra were taken on a Cary Model 14 spectrophotometer. Pmr spectra were recorded on a Varian Model A-60, T-60, or DA 60-II spectrophotometer in CCl_4 with tetramethylsilane as internal reference standard unless noted otherwise. Volume ratios are given for mixed solvents for chromatography. Elemental analyses were performed by Dr. A. Bernhardt, Max-Plank-Institut für Kohlenforschung, Mülheim (Ruhr), West Germany, and Chemalytics, Inc., Tempe, Ariz.

Ethyl 6-Hydroxy-1,6,7,8,9,9a-hexahydro-2*H*-benzo[*cd*]azulenyl-6-acetate (2).—A mixture of 30 g of purified,[32] amalgamated, granular Zn and 250 ml of dry benzene was stirred under reflux (N_2 atmosphere) for 15 min. A portion (50 ml) of the benzene was withdrawn and added to a solution of 29.9 g (0.161 mol) of 1,6,7,8,9,9a-hexahydro-2*H*-benzo[*cd*]azulen-6-one (**1**) and 44 ml of ethyl bromoacetate and the whole was added to the original mixture. After the exothermic reaction had subsided, gentle refluxing was resumed, three portions of 6 g of zinc and 7 ml of ethyl bromoacetate were added at hourly intervals, and refluxing was continued for 30 min after the last addition. The cooled solution was then stirred with 150 ml of 6 *N* sulfuric acid for 15 min, the separated aqueous layer was washed with ether until clear, and the combined organic layers were washed with 6 *N* sulfuric acid, then with 10% aqueous ammonia until no appreciable color was extracted, and finally with saturated NaCl. Chromatography of the red-brown oil, obtained after removal of the solvent from the dried ($MgSO_4$) solution, on acidic alumina with 7:1 hexane–ethyl acetate gave **2** as a yellow oil which crystallized from hexane as colorless prisms (34.1 g, 77%): mp 72–72.5°; uv (cyclohexane) 263 nm (sh, log ϵ 2.77), 268 (2.95), and 276 (3.00); ir (CCl_4) 1723 cm^{-1}.

Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.37; H, 8.20.

Ethyl 1,2,3,4-Tetrahydro-5*H*-fluorenylidene-4-acetate (4).—In the manner described for the preparation of **2**, from the reaction of 3.02 g (16.4 mmol) of 1,2,3,4-tetrahydro-5*H*-fluoren-4-one (**3**), 6.5 ml (4.4 ml plus three 0.7-ml portions) of ethyl bromoacetate, and 6.8 g (5 g plus three 0.6-g portions) of Zn with 25 ml of benzene as solvent but with 7:1 petroleum ether (bp 30–60°)–ethyl acetate as the eluent was obtained 2.18 g (56% net) of **4** as colorless needles: mp 74.5–76°; uv (cyclohexane) 229 nm (log ϵ 3.94), 236 (3.96), 243 (4.05), 252 (3.96), and 330 (4.49).

Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.38; H, 7.02.

Dehydration of Ethyl 6-Hydroxy-1,6,7,8,9,9a-hexahydro-2*H*-benzo[*cd*]azulenyl-6-acetate (2). Method A.—Following the method of Chuang, *et al.*,[33] from 10 g (37 mmol) of **2**, 5.04 g (40 mmol) of thionyl chloride, and 7 g (90 mmol) of pyridine was obtained 9.4 g (84%) of a mixture of ethyl 1,8,9,9a-tetrahydro-2*H*-benzo[*cd*]azulenyl-6-acetate (**8**) and ethyl 1,6,7,8,9,9a-hexahydro-2*H*-benzo[*cd*]azulenylidene-6-acetate (**9**): bp 154–156° (0.5 mm); $n^{25.5}D$ 1.5641; uv (ethanol) 256 nm (log ϵ 3.97); ir (neat) 1717 and 1735 cm^{-1}.

Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.68; H, 7.86. Found: C, 79.43; H, 8.13.

Method B.—A solution of 4.28 g (15.6 mmol) of **2**, 100 mg of *p*-toluenesulfonic acid, and 50 ml of toluene was refluxed until no more H_2O was observed to collect in a Dean–Stark trap (2.5 hr). The cooled solution was washed with H_2O until the wash was no longer acidic to litmus and the solvent was then removed. Removal of the solvent from a dried ($MgSO_4$) ethereal solution of the residual oil left 3.72 g (93%) of product identical (ir and nmr) with that obtained in A.

Method C.—Following the method of Gilmore and Horton,[34] from 10 g (37 mmol) of **2** and 70 ml of 98–100% formic acid was obtained 9.2 g (97.5%) of product identical (ir and nmr) with that in A.

1,6,7,8,9,9a-Hexahydro-2*H*-benzo[*cd*]azulenylidene-6-acetic Acid (11).[35]—A solution of 6.5 g (25.3 mmol) of a mixture of **8** and (mostly) **9**, 130 ml of ethanol, 6.5 g (0.116 mol) of KOH, and 150 ml of H_2O was refluxed for 3 hr under a N_2 atmosphere and the solvent was then removed by distillation. The solution was extracted with ether, treated with Norit, and acidified with 6 *N* hydrochloric acid to give an impure solid. Recrystallization from *n*-hexane gave 5.25 g (91%) of **11** as colorless needles: mp 104–107.5°; uv (ethanol) 269 nm (log ϵ 4.04).

Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.07. Found: C, 78.86; H, 6.79.

***trans*-1,6,7,8,9,9a-Hexahydro-2*H*-benzo[*cd*]azulenyl-5-acetic Acid (13). Method A.**—A solution of 6 g (27.3 mmol) of the unsaturated acid **11** in 150 ml of absolute ethanol took up the theoretical amount of H_2 at 2 atm in the presence of 0.1 g of prereduced platinum oxide in 2 hr. Filtration, removal of the solvent, and recrystallization of the crude product from *n*-hexane or acetonitrile gave 6 g (98%) of **13** as colorless plates, mp 139.5–140.5°.

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.07; H, 7.67.

Method B.—A solution of 3.72 g (14.5 mmol) of the unsaturated esters **8** and **9** in absolute ethanol was treated with H_2 at *ca.* 4 atm over *ca.* 0.1 g of prereduced platinum oxide for 14 hr. Removal of the solvent and catalyst left 3.68 g (98%) of saturated ester **12** containing a small amount of **9** (nmr spectrum). A solution of 3.03 g (11.8 mmol) of this product, 3 g of KOH, 65 ml of ethanol, and 75 ml of H_2O was refluxed for 3 hr. The ethanol was removed by distillation and the aqueous solution was washed with ether and then acidified with 6 *N* hydrochloric acid. The oil which separated was extracted with ether. Distillation of the solvent from the ethereal layer and crystallization of the residual oil from acetonitrile gave 0.95 g of **13**, mp 137–140° (uncorrected), and a second crop of 0.121 g (40% total yield), mp 132–138° (uncorrected).

***trans*-1,5,6,6a,7,8,9,9a-Octahydro-2*H*-indeno[5,4,3-*cde*]azulen-5-one (15). Method A.**—A mixture of 5 g (21.8 mmol) of the trans saturated acid **13** and 6 g (50 mmol) of thionyl chloride was allowed to stand at room temperature for 1 hr and then refluxed for 15 min. Distillation gave 4 g (16 mmol) (75%) of the acid chloride, bp 139–143° (0.4 mm). A solution of this product in 20 ml of dry benzene was added dropwise (90 min) to a stirred suspension of 2.66 g (20 mmol) of $AlCl_3$ in 35 ml of dry benzene at 5–10°. The mixture was allowed to come to room temperature slowly (12 hr). Ether (10 ml) was added followed by 50 ml of 6 *N* hydrochloric acid. The separated aqueous layer was extracted with ether. Removal of the solvent from the combined, washed

(28) V. Boekelheide and J. B. Phillips, *J. Amer. Chem. Soc.*, **89**, 1695 (1967).

(29) J. L. Laity, Ph.D. Thesis, University of Washington, 1968.

(30) See the discussion in ref 1.

(31) This experiment was performed by Dr. H. L. Ammon.

(32) J. von Braun and O. Kruber, *Ber.*, **45**, 384 (1912).

(33) C.-K. Chuang, Y.-L. Tien, and Y.-T-Huang, *Chem. Ber.*, **68**, 867 (1935).

(34) R. C. Gilmore and W. J. Horton, *J. Amer. Chem. Soc.*, **73**, 1411 (1951).

(35) The saponification of the mixture of **8** and **9** often obtained afforded a mixture of **10** and **11** having a broad melting range (*e.g.*, 83–140°), and catalytic (Pt) reduction of this material gave a corresponding mixture of **13** and **14**, mp 113–142° (42%).

(10% hydrochloric acid, 5% sodium bicarbonate, saturated NaCl), and dried ($MgSO_4$) extracts and recrystallization of the crude residual ketone from aqueous ethanol gave 2.5 g (55%) of **15** as colorless needles: mp 112–114° (uncorrected); uv (ethanol) 261 nm; ir (CCl_4) 1720 cm^{-1}.

Anal. Calcd for $C_{15}H_{16}O$: C, 84.83; H, 7.60. Found: C, 84.74; H, 7.57.

Method B.—A mixture of 1.71 g (7.44 mmol) of **13** and 38 g of commercial (84.3% P_2O_5) polyphosphoric acid in a flask loosely stoppered with glass wool was stirred and heated at 90° for 35 min, during which time the color became red-brown. Ice water (100 ml) was added, the light yellow solid which separated was extracted into ether, and the ethereal layer was washed with saturated sodium bicarbonate (acidification of the basic layer and recrystallization of the precipitate from acetonitrile gave 0.345 g of unchanged **13**) and saturated NaCl. Removal of the solvent and chromatography of the residue on acidic alumina with 10:1 hexane–ethyl acetate gave a small amount of yellow oil and then 0.797 g (63%) of **15**, mp 109.5–112° after recrystallization from *n*-hexane. Smaller runs (*ca.* 200 mg of **13**) heated for 25 min gave higher (up to 93%) yields.

1,5,6,8,9,9a-Hexahydro-2*H*-indeno[5,4,3-*cde*]azulen-5-one (16).—Finely powdered hydroxy ester **2** (12 g, 43.8 mmol) was mixed thoroughly with 250 g of commercial (84.3% P_2O_5) polyphosphoric acid. The mixture was heated with vigorous stirring in a water bath maintained at 92–95° for exactly 5 min (color change from orange to red-brown), then immediately poured onto 1 l. of crushed ice and stirred until the hydrolysis was complete. The collected (Büchner funnel with coarse filter paper) yellow-green precipitate was washed with water until the washings were neutral to litmus. A solution of the dried (air and then vacuum desiccator), grey-green solid in the minimal amount of benzene was chromatographed on acidic alumina. *n*-Hexane–ethyl acetate (10:1) removed an amber oil and 7:1 *n*-hexane–ethyl acetate eluted 7.72 g (84%) of **16**, obtained as a yellow solid, mp 132–145°, sufficiently pure for conversion to **17**. This material decomposed on standing but could be stored at −25° under N_2. Chromatography on silica gel using 10:1 *n*-hexane–ethyl acetate gave colorless plates: mp 140.5–142°; uv (cyclohexane) 242 nm (sh, log ϵ 4.37), 247 (4.51), 257 (sh, 4.36), 268 (4.29), 278 (4.15), 305 (3.11), 318 (3.32), 343 (sh, 2.39), and 336 (1.79); ir (CCl_4) 1710 cm^{-1}; nmr δ 2.92 (s, 1, α-CH_2) and 5.75 ppm (5, 1, vinylic H).

Anal. Calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.42; H, 6.61.

A 2,4-dinitrophenylhydrazone precipitated from ethanol and recrystallized from ethyl acetate as deep red microcrystals, mp 264–265° dec (uncorrected).

***cis*-1,5,6,6a,7,8,9,9a-Octahydro-2*H*-indeno[5,4,3-*cde*]azulen-5-one (17). Method A.**—A 32.4-mg (0.14 mmol) sample of tricyclic acid **14** was treated with polyphosphoric acid as described in method B for the preparation of the trans ketone **15**. Chromatography of the crude, yellow product on neutral alumina with dichloromethane gave 20 mg (60%) of **17** as colorless needles, mp 117–118° (uncorrected), ir (Nujol) 1705 cm^{-1}.

Anal. Calcd for $C_{15}H_{16}O$: C, 84.83; H, 7.60. Found: C, 84.68; H, 7.52.

Method B.—A mixture of 0.45 g (2.1 mmol) of **16**, 30 ml of acetic acid, and 57 mg of prereduced platinum oxide was treated with H_2 at 3 atm for 4 hr. A fresh portion of platinum oxide was added and the hydrogenation was continued overnight. The oil remaining after removal of the catalyst and solvent was chromatographed on neutral, activity II alumina. Elution with *n*-hexane and then 7:1 *n*-hexane–ethyl acetate removed a small oily fraction followed by two solids. Recrystallization of the second solid from *n*-hexane gave 0.15 g (33%) of **17**, mp 119.5–121.5°, identical (ir and nmr) with the product from A.

***cis*-1,5,6,6a,7,8,9,9a-Octahydro-2*H*-indeno[5,4,3-*cde*]azulene (19). Method A.**—To a cooled (ice bath), stirred mixture of 7.52 g (35.8 mmol) of crude ketone **16** and 100 ml of absolute ethanol was added 1.01 g (26.4 mmol) of sodium borohydride. The ice bath was then removed and the mixture was allowed to come to room temperature. After the ketone and borohydride had completely dissolved to give a clear amber solution, a thick suspension of white crystals of *cis*-5-hydroxy-1,5,6,8,9,9a-hexahydro-2*H*-indeno[5,4,3-*cde*]azulene (**18**) formed. [In one run the crystals were collected and washed with cold, absolute ethanol, mp 174–176° (uncorrected). *Anal.* Calcd for $C_{15}H_{16}O$: C, 84.87; H, 7.60. Found: C, 84.32; H, 7.34.] After 3 hr, 40 ml of ethanol (to dissolve the precipitate) and 2 g of Darco carbon were added followed by 2 ml of *ca.* 0.2 *M* chloroplatinic acid hexahydrate. Excess borohydride was destroyed and the solution was made acidic by the addition of 8 ml of concentrated hydrochloric acid and the mixture was treated with H_2 at 3 atm until the uptake of H_2 ceased (4.5 hr). After filtration and removal of the solvent from the filtrate, a solution of the residual amber oil (which slowly crystallized on standing) in the minimal amount of petroleum ether was chromatographed on a column (3.6-cm diameter) containing a bottom layer (9 cm) of neutral, activity I alumina separated from a top layer (8 cm) of basic alumina. Elution with petroleum ether afforded 4.7 g (66%) of **19** as colorless crystals: mp 75–76°; uv (cyclohexane) 262 nm (sh, log ϵ 2.66), 265 (2.75), 269 (2.96), 274 (2.85), and 278 (3.09); ir (CCl_4) 1870 and 1724 cm^{-1} (1,2,3,4-tetraalkylbenzene); nmr (CCl_4) 6.78 (s, 2, aromatic), 3.3–2.5 (m, 6, benzylic), and 2.5–0.8 ppm (m, 10, methylene).

Anal. Calcd for $C_{15}H_{18}$: C, 90.85; H, 9.15. Found: C, 91.03; H, 8.83.

Method B.—A solution of 0.148 g (0.698 mmol) of ketone **17**, 1 ml of 99–100% hydrazine hydrate, and 2 ml of ethanol was refluxed for 1.5 hr. The condenser was removed, 2.5 ml of diethylene glycol was added, and the mixture was heated to 180° over a 20-min period. One pellet (*ca.* 0.13 g) of KOH was added to the cooled solution and heating was then resumed until N_2 evolution ceased. The cooled solution was diluted with 40 ml of H_2O and extracted with ether. Removal of the solvent from the combined, washed (saturated NaCl), dried ($MgSO_4$) solution and chromatography of the residue on neutral, activity I alumina with *n*-hexane gave 13.5 mg (10%) of **19**, mp 71–74° alone and when mixed with the product from A.

***trans*-1,5,6,6a,7,8,9,9a-Octahydro-2*H*-indeno[5,4,3-*cde*]azulene (20).**—In the manner described in B for the conversion of **17** to **19**, from 0.5 g (23.6 mmol) of trans ketone **15** was obtained 0.38 g (80%) of **20** as colorless needles: mp 61–62.5°; uv (ethanol) 269 nm (log ϵ 3.21) and 278 (3.18).

Anal. Calcd for $C_{15}H_{18}$: C, 90.85; H, 9.15. Found: C, 90.81; H, 8.84.

5-Phenylpentanoic Acid (21).—A solution of 278 g (2.44 mol) of glutaric anhydride in 700 ml of anhydrous benzene was added over a period of 90 min to a cooled (5°), stirred suspension of 650 g (4.88 mol) of $AlCl_3$ in 550 ml of benzene. The mixture was allowed to come slowly (1 hr) to room temperature and was then refluxed for 1 hr before removing the solvent by distillation. Ice water (1 l.) was added cautiously to the residue and remaining traces of solvent were removed by steam distillation. After cooling and filtration, the residue was taken up in 10% sodium carbonate. Acidification of the alkaline solution with concentrated hydrochloric acid gave 405 g (86%) of 5-phenyl-5-oxopentanoic acid of sufficient purity for conversion to **21**. Recrystallization of a sample from *n*-hexane resulted in colorless plates, mp 130–132° (uncorrected) (lit.[36] mp 132°).

A mixture of 146 g (0.75 mol) of the oxopentanoic acid, 275 ml of H_2O, 625 ml of concentrated hydrochloric acid, 360 g of freshly prepared amalgamated zinc, and 300 ml of toluene was heated under reflux, four additional portions of 180 ml of concentrated hydrochloric acid were added at 6-hr intervals, and refluxing was continued for 12 hr after the last addition. Ether extracts of the separated aqueous layer were combined with the original organic layer and the whole was extracted with 10% KOH. After treatment with Norit, acidification of the alkaline solution with concentrated hydrochloric acid gave 124 g (93%) of **21**, mp 56–58° (uncorrected) (lit.[37] mp 57°).

Benzocycloheptene (22).—A mixture of 91 g (0.46 mol) of acid **21** and 91 g (0.77 mol) of thionyl chloride was refluxed for 2 hr and then distilled to give 72 g (73%) of 5-phenylpentanoyl chloride, bp 104° (0.6 mm) [lit.[36] bp 155° (22 mm)]. A solution of 70 g (0.45 mol) of the acid chloride in 550 ml of CS_2 was added dropwise (4 hr) to a refluxing mixture of 57.5 g (0.43 mol) of $AlCl_3$ in 175 ml of CS_2 and reflux was maintained for an additional 4 hr. After distillative removal of the CS_2, 400 g of ice water was added and the mixture was steam distilled. The distillate was saturated with NaCl and extracted with ether. Removal of the solvent from the dried ($CaSO_4$) extracts and distillation gave 49.6 g (92%) of 6,7,8,9-tetrahydro-5*H*-cycloheptabenzen-5-one,

(36) A. Ali, R. D. Desai, R. F. Hunter, and S. M. M. Muhammad, *J. Chem. Soc.*, 1013 (1937).

(37) W. Borsche and W. Eberlein, *Chem. Ber.*, **47**, 1465 (1962).

bp 82–84° (0.3 mm), n^{25}D 1.5636 [lit.[38,39] bp 138–139° (12 mm), n^{20}D 1.5636].

In the manner described above for the reduction of 5-phenyl-5-oxopentanoic acid to **21** except that the mixture was refluxed for 48 hr after the final addition of hydrochloric acid, from 49 g (0.33 mol) of the above ketone was obtained 44.3 g (91%) of **22**, bp 118–122° (33 mm), n^{25}D 1.5487 [lit.[39] bp 98–100° (13 mm), n^{20}D 1.5520].

Benzocycloheptene-1,5-diacetic Acid (24).—A mixture of 10 g (68 mmol) of benzocycloheptene (**22**), 26.2 g (0.154 mol) of recrystallized *N*-bromosuccinimide, 0.05 g of benzoyl peroxide, 0.02 g of azobisisobutyronitrile, and 75 ml of CCl_4 in a Pyrex flask was irradiated with uv light and refluxed for 1 hr and then cooled. The separated succinimide (14.5 g, 0.147 mol) was washed with 25 ml of cold CCl_4. Removal of the solvent from the combined organic solutions left a red oil (20.4 g). Chromatography over acidic alumina with 2:1 benzene–hexane gave a light yellow oil which darkened on standing. It was washed thoroughly with cold (10°) *n*-hexane to completely remove CCl_4. Analysis indicated the product to be **23** contaminated with *ca.* 20% of the corresponding monobromo compound.

A solution of 11.55 g of the yellow oil in 25 ml of anhydrous xylene was added dropwise (90 min) to a stirred suspension of sodiomalonic ester (from 1.75 g of Na and 39.5 g of ethyl malonate) in 50 ml of dry xylene and the mixture was then refluxed for 2 hr. Water (75 ml) was added to the cooled mixture, the separated aqueous layer was extracted with two 50-ml portions of ether, and the combined organic solutions were washed with H_2O and saturated NaCl. Drying ($MgSO_4$) and distillative removal of the solvent (25 mm) and excess ethyl malonate [bp 80–84° (10 mm)] left 13.7 g of crude ester product. This material was refluxed with 11 g of KOH, 40 ml of ethanol, and 20 ml of H_2O for 6 hr under N_2. The alcohol was removed (distillation), and the aqueous residue was diluted to 100 ml with H_2O before extraction with four 25-ml portions of ether. Acidification with 6 *N* hydrochloric acid gave a red, gummy precipitate which was separated and extracted with two 75-ml portions of H_2O. The combined aqueous solutions were continuously extracted with ether for 48 hr. Removal of the solvent from the dried ($MgSO_4$) ethereal solution left a red oil which was heated at 140° for 30 min and then at 180° for 10 min (CO_2 evolution). The cooled product was taken up in 10% KOH and the solution was extracted with ether. Treatment of the aqueous solution with Norite followed by acidification with 10% hydrochloric acid gave 2.75 g of brown oil. Crystallization from acetonitrile afforded 0.5 g (5%) of **24** as colorless plates, mp 254.5–255.5°.

Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.50; H, 6.91.

***cis*-1,6,7,8,9,9a-Hexahydro-2*H*-benzo[*cd*]azulenyl-6-acetic Acid (14).**—Diacid **24** (0.3 g) was treated with 4 g of polyphosphoric acid as described for the preparation of **15** from **13** except that the ethereal extracts of the diluted reaction mixture were washed with H_2O before extraction with 10% sodium bicarbonate, and acidification of the alkaline extracts gave 280 mg of light tan plates, mp 176–181°, presumed to be the crude tricyclic keto acid. This material was treated as described for the conversion of **17** to **19** except that 85% hydrazine hydrate was used, the mixture was heated to 165° after the addition of ethylene glycol, and the reflux period after the addition of KOH was 5 hr. Acidification of the ether-extracted alkaline solution gave 200 mg of impure acid, mp 112–135°. This product was treated with 1 g of amalgamated zinc, 3 ml of concentrated hydrochloric acid, 1 ml of H_2O, and 3 ml of toluene as described for the reduction of 5-phenyl-5-oxopentanoic acid to **21** except that five additions of concentrated hydrochloric acid (1 ml) were made at 12-hr intervals. The final mixture was extracted with ether and the extracts were extracted with 10% sodium bicarbonate. Acidification and recrystallization gave 120 mg (48%) of **14** as colorless plates, mp 117–119°.

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.11; H, 7.67.

Dicyclopenta[*ef*,*kl*]heptalene (Azupyrene) (25).—In a 50-ml, three-necked, pear-shaped flask equipped with a Hershberg dropping funnel, reflux condenser, and magnetic stirring bar was placed 2 g of **19** and the flask was heated (oil bath) to 140–150°.[40] To the stirred liquid was added 7 ml of ethyl diazoacetate over a period of 3 hr (N_2 evolution) and stirring and heating were continued at 150–160° for an additional 1.5 hr. The cooled, red-brown, viscous mixture was transferred onto a 5.5 × 15 cm column of acidic alumina with the aid of the minimal amount of dichloromethane. Unchanged **19** (1 g) was eluted with petroleum ether, and then dichloromethane–petroleum ether (1:3) removed pink and green product fractions. The pink solution (maroon when concentrated) became green on standing. Removal of the solvent from the combined product fractions gave 1.2 g of crude ester.

The combined ester products from four of the above reactions were treated with 4 g of KOH in 25 ml of methanol under reflux for 1.5 hr. The brown solution was added to 250 ml of H_2O and acidified with 2 *N* hydrochloric acid. The gelatinous precipitate was extracted into ether and removal of the solvent from the dried ($MgSO_4$) extracts gave 4.2 g of crude acid as a viscous brown oil.

A solution of the crude acid in 15 ml of methyl oleate was refluxed (*ca.* 350°) under an O_2-free N_2 atmosphere in the presence of 220 mg of 10% Pd/C catalyst[23] for 10 min, during which time the solution became dark green. The cooled mixture, diluted with a small quantity of petroleum ether, was chromatographed on a 5.5 × 20.5 cm column of neutral, activity II alumina. Petroleum ether eluted a blue band which was set aside and then a wide yellow-green band. The dark yellow-green oil residue from the latter fraction was chromatographed twice on Florisil (3.5 × 13 cm) with petroleum ether as the eluate to give 109 mg (2.5%) of **25** as a bronze solid, mp 249–254°. Subjecting the blue fraction to a second treatment with Pd/C afforded an additional 58 mg[41] for a total of 167 mg (3.8%). Recrystallization from methanol formed square, bronze platelets: mp 250–258° (sealed tube under N_2, uncorrected); uv and visible (cyclohexane) 252 nm (log ϵ 4.73), 267 (5.03), 285 (4.49), 299 (4.32), 308 (4.27), 334 (4.07), 343 (4.13), 356 (3.62), 409 (2.92), 442 (3.17), 452 (3.28), 459 (3.17), 470 (3.49), and 483 (4.11) plus poorly defined maxima at *ca.* 550 (1.64), 600 (1.64), 645 (1.60), 663 (1.60), 720 (1.31), 738 (1.26), and 770 (0.96); ir ($HCCl_3$) 1377, 1538, 1588, and 3000 cm^{-1}; nmr ($DCCl_3$) 7.34 (t, 2), 8.40 (s, 4), and 8.68 ppm (d, 4); mol wt (mass spectrometry) 202.076 (calcd, 202.078); $A/A_{bz} = 3.9 \pm 0.3$.

Anal. Calcd for $C_{16}H_{10}$: C, 95.02; H, 4.98. Found: C, 94.75; H, 4.99.

Registry No.—**1**, 14528-87-1; **2**, 38434-48-9; **3**, 7235-16-7; **4**, 38434-50-3; **8**, 38434-51-4; **9**, 38434-52-5; **11**, 38434-53-6; **13**, 38434-54-7; **14**, 38434-55-8; **15**, 38434-56-9; **16**, 38434-57-0; **16** DNP, 38434-58-1; **17**, 38434-59-2; **18**, 38434-60-5; **19**, 38434-61-6; **20**, 38434-62-7; **21**, 2270-20-4; **21** acid chloride, 20371-41-9; **22**, 1075-16-7; **23**, 38434-66-1; **24**, 38434-67-2; **25**, 193-85-1; ethyl bromoacetate, 105-36-2; 6,7,8,9-tetrahydro-5*H*-cycloheptabenzen-5-one, 826-73-3; sodiomalonic ester, ethyl, 28290-06-4.

Acknowledgment.—This work was supported in part by grants from the National Science Foundation.

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(39) Pl. A. Plattner, *Helv. Chim. Acta*, **27**, 804 (1944).

(40) Temperatures of less than 140° or greater than 160° gave much poorer results.

(41) In practice the blue fractions from several runs were combined and the 58 mg represents the average yield per fraction.

Cyclobutenone Derivatives from Ethoxyacetylene[1]

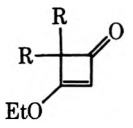
HARRY H. WASSERMAN,* J. U. PIPER, AND E. V. DEHMLOW

Department of Chemistry, Yale University, New Haven, Connecticut 06520

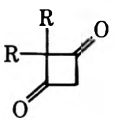
Received November 20, 1972

Cycloaddition reactions of ketenes to ethoxyacetylene have been investigated as routes to cyclobutenone derivatives. Ketenes are either used directly or formed *in situ* from the corresponding acid chlorides. 1,3-Cyclobutanedione prepared in this manner has been converted to a series of 3-substituted derivatives by reaction with a variety of nucleophiles, either directly or through the monoenol ether.

In earlier communications we have described the preparation of cyclobutenone ethers from ethoxyacetylene and ketenes, a reaction first observed by Arens and coworkers.[2] Our studies[3,4] have involved the preparation of ketenes *in situ* by the dehydrohalogenation of acid chlorides and have also included the preparation of the parent compounds in this series, 3-ethoxy-2-cyclobutenone (Ia) and 1,3-cyclobutanedione (IIa).



Ia, R = H
b, R = CH_3

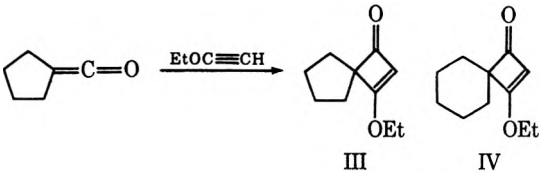


IIa, R = H
b, R = CH_3

We now report applications of this cycloaddition reaction to the preparation of derivatives in this series, as well as further transformations of I and II which may serve as useful methods for the formation of 3-substituted 2-cyclobutenones. Related work on dialkylketenes,[5,6] on the addition of ketenes to ynamines,[7-9] and on the preparation of the parent compound, 2-cyclobutenone,[10] has been reported in recent years.

When ketene is passed through a cold solution of ethoxyacetylene in methylene chloride, formation of Ia takes place slowly. The product, mp 26–27° (30%), exhibits strong absorption in the infrared at 1760 and 1580 cm^{-1}; its nmr spectrum includes singlets at τ 5.12 and 6.89 due to the vinyl and methylene ring protons, respectively, of the cyclobutenone system. Generation of dimethylketene *in situ* from isobutyryl chloride in the presence of ethoxyacetylene yields Ib (66%). The cyclobutenone structure is shown by absorptions at 1750 and 1575 cm^{-1} in the infrared, an ultraviolet spectrum almost identical with that of Ia, and a nmr spectrum exhibiting singlets at τ 5.27 and 8.81, areas 1:6, as well as absorption due to the ethyl protons.

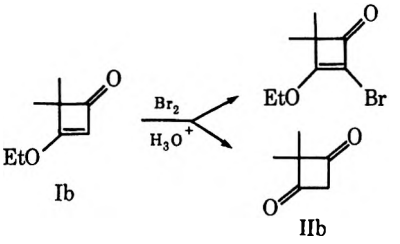
The cycloaddition of ketenes to ethoxyacetylene also provides a novel entry into the spiro[3.4]octane and spiro[3.5]nonane systems. Thus, tetramethyleneketene generated from cyclopentanecarboxylic acid chloride with trimethylamine gives III (27%), while in a similar fashion IV may be obtained from cyclohexanecarboxylic



III IV

acid chloride (65%). Both compounds are thermally unstable, and both give ultraviolet and infrared spectra typical of the cyclobutenone system.

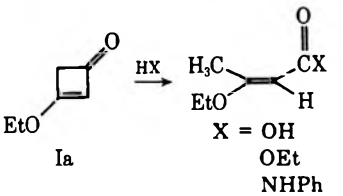
A solution of Ib in carbon tetrachloride instantly decolorizes bromine and then slowly evolves hydrogen



Ib IIb

bromide to give 2-bromo-3-ethoxy-4,4-dimethyl-2-cyclobutenone. The position of the bromine is confirmed by the nmr spectrum, which shows a quartet at τ 5.31, a triplet at 8.50, and a singlet at 8.77 with relative areas of 2:3:6. This assignment is also in keeping with the fact that 3-hydroxy-2,4-dimethylcyclobutenone undergoes a similar bromination.[11,12]

While compound Ia undergoes ring-opening reactions with water, ethanol, and aniline, Ib appears to be more resistant to ring cleavage. When stirred overnight with moist ether, Ia gives a poor yield of β-ethoxycrotonic acid as the only isolable product. Similarly, with hot ethanol, the ethyl ester of β-ethoxycrotonic acid is formed, and with aniline at room temperature a crystalline product is produced, the infrared and nmr spectra of which are consistent with those expected for the anilide of β-ethoxycrotonic acid.



Ia X = OH
OEt
NHPh

On the other hand, when Ib is treated with warm, dilute acid, hydrolysis to IIb occurs. More vigorous heating with aqueous acid[3] or base results in degrada-

(1) This investigation was supported in part by U. S. Public Health Service Research Grant GM-07874 from the National Institutes of Health.

(2) J. F. Arens, "Advances in Organic Chemistry, Methods and Results," Vol. 2, Interscience, New York, N. Y., 1960, p 117.

(3) H. H. Wasserman and E. Dehmlow, *Tetrahedron Lett.*, 1031 (1962).

(4) H. H. Wasserman and E. V. Dehmlow, *J. Amer. Chem. Soc.*, **84**, 3786 (1962).

(5) R. H. Hasek, P. G. Gott, and J. C. Martin, *J. Org. Chem.*, **29**, 2510 (1964).

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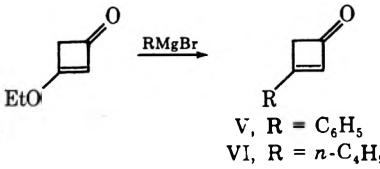
(11) D. G. Farnum, M. A. T. Heybey, and B. Webster, *ibid.*, **86**, 673 (1964).

(12) R. B. Woodward and G. Small, Jr., *ibid.*, **72**, 1297 (1950).

tion to methyl isopropyl ketone. In contrast to the reaction of Ia with aniline, Hasek, Gott, and Martin report[5] that the dimethyl derivative Ib reacts with ammonium hydroxide to give 3-amino-4,4-dimethyl-2-cyclobutenone and with piperidine to give the corresponding 3-piperidino derivative.[5] Thus it appears that Ib is less subject to ring-opening reactions than is Ia.

Considering the above results, it was surprising to observe that phenylmagnesium bromide and *n*-butylmagnesium bromide readily add to Ia in a conjugate manner with elimination of ethoxide ion to give 3-phenyl-2-cyclobutenone (V)[13] and 3-(1-butyl)-2-cyclobutenone (VI). The above results now make it possible



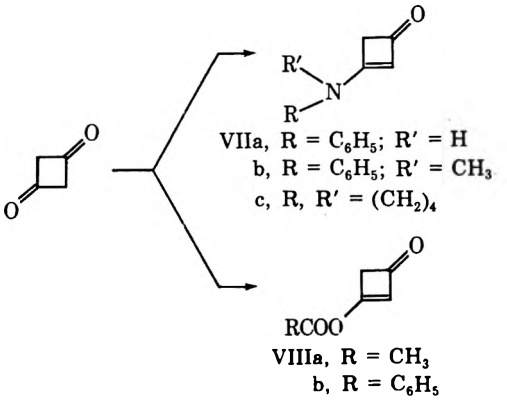
V, R = C_6H_5
VI, R = n-C_4H_9

in theory to vary alkyl substituents at each position of the cyclobutenone ring. Thus, substitution at the 2 position can be controlled by varying the acetylene used,[14] substituents at the 4 position may be changed by varying the ketene,[3-5] and substitution at the 3 position may be accomplished *via* the Grignard reaction. Using sodium methoxide in methanol, substitution at the 3 position proceeds further to give 3,3-dimethoxycyclobutanone.

The hydrolysis of Ia may be controlled to give the dione IIa (64%), by using cold ether previously shaken with concentrated hydrochloric acid. Under these conditions hydrolysis takes place almost immediately. Formation of IIa also takes place slowly when Ia is allowed to stand in a moist atmosphere at −10°. As reported for related compounds,[5,11] both IIa and IIb are highly acidic with pK_a's of 3.0 and 2.65, respectively. The ultraviolet spectra of IIa and IIb are similar to each other and to those of Ia and Ib, indicating that in dilute ethanol solutions IIa and IIb exist nearly completely in the enolic form. It was noted[5] that IIb exists mainly in the enol form in polar solvents, while in chloroform solutions the diketone form predominates. The same is true of IIa. The nmr spectrum of IIa in chloroform or acetonitrile solutions shows a singlet at τ 6.14, while in dimethyl sulfoxide three singlets at −0.25, 5.28, and 6.90 are observed. The infrared spectrum of IIa in chloroform shows only very weak bands attributable to the enolic form. Previous work suggests that the presence of a 2-methyl group stabilizes the enolic form, since both 2-methyl-[6] and 2,4-dimethylcyclobutane-1,3-dione[11] appear to exist in the enolic form in chloroform solutions (as shown by their infrared spectra). The mass spectrum of IIa is similar to those reported for other ketene dimers,[15] showing a parent peak (m/e 84) and peaks at $M/2$, M − 28, and M − 56 which are 6, 100, 1, and 7% of the base peak, respectively.

(13) S. L. Manatt, M. Vogel, D. Knutson, and J. D. Roberts, *J. Amer. Chem Soc.*, **86**, 2465 (1964).
(14) B. Rosebeek and J. F. Arens, *Rec. Trav. Chim. Pays-Bas*, **81**, 549 (1962).
(15) N. J. Turro, D. C. Neckers, P. A. Leermakers, D. Seldner, and P. D'Angelo, *J. Amer. Chem. Soc.*, **87**, 4097 (1965).

The formation of 3-amino-2-cyclobutenones (VII) takes place when equimolar amounts of amine and IIa are combined in methylene chloride solution at room temperature.



VIIa, R = C_6H_5; R' = H
b, R = C_6H_5; R' = CH_3
c, R, R' = $(CH_2)_4$

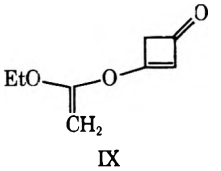
VIIIa, R = CH_3
b, R = C_6H_5

As noted for 3-piperidino-4,4-dimethyl-2-cyclobutenone,[5] compounds VIIa–c are amide-like, showing carbonyl frequencies in the infrared at 1730–1740 cm^{-1}. The nmr absorption peaks of the α protons on the pyrrolidine ring of VIIc are at τ 6.5 as compared to those in pyrrolidine itself at 7.26.

Reactions which reflect the enolic character of IIa include acylation and the addition of IIa to ethoxyacetylene. When ketene is bubbled through a solution of IIa in methylene chloride, the enol acetate VIIIa is formed. Assignment of structure is based on the nmr spectrum, which shows three singlets at τ 4.54, 6.68, and 7.65, areas 1:2:3. Upon exposure to moisture the product readily reverts to IIa. In the infrared there are anhydride-like carbonyl absorptions at 1795 and 1770 cm^{-1}. The analogous enol acetate of acetylacetone exhibits absorption at 1762 cm^{-1} for the vinyl ester carbonyl.[16] In the olefinic region of the infrared there is the expected absorption at 1565 cm^{-1} and a second (medium intensity) absorption at 1590 cm^{-1}.

The enol benzoate, VIIIb, can be prepared (39%) using equimolar quantities of 1-ethoxyvinyl benzoate[17] and IIa. It shows carbonyl absorption at 1760 cm^{-1} with a shoulder at 1770 cm^{-1}.

When cyclobutanedione (IIa) is treated with ethoxyacetylene in the presence of mercuric acetate in methylene chloride solution, IX is formed, although it is too



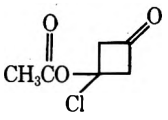
IX

unstable to permit isolation in pure form. The infrared spectrum exhibits carbonyl absorption at 1765 cm^{-1} and olefinic absorption at 1670 and 1580 cm^{-1} in methylene chloride solution. The nmr spectrum in chloroform shows singlets at τ 5.03 and 6.60 due to the vinyl and methylene ring protons, respectively, a triplet at 8.67 due to the methyl group, and a complex absorption (four protons) around 6.1 which is a combination of the methylene quartet centered at 6.06 (J = 7 Hz) and the doublet absorptions of the terminal

(16) R. Filler and S. M. Naqvi, *Tetrahedron*, **19**, 879 (1963).
(17) H. H. Wasserman and P. S. Wharton, *J. Amer. Chem. Soc.*, **82**, 661 (1960).

methylene protons at 6.12 and 6.32 (J = 4 Hz). Phenylmagnesium bromide undergoes reaction with IX to give V, but the reaction is not as clean as the preparation from Ia. Amines also react with IX to give VII. Here, the reaction of IX with pyrrolidine yields VIIc in much higher yield (89%) than in the comparable reaction with IIa (52%), although, in general, the combination of amines with IIa gives better results. Acids also react with IX to give VIII but, again, yields are poorer and products are less pure than in the methods described above.

In an attempt to prepare VIIIa by another method, IIa was dissolved in acetyl chloride and the solution was concentrated *in vacuo*. The liquid residue contained chlorine, and upon standing in the cold decomposed slowly to VIIIa. The process could be reversed by bubbling hydrogen chloride through a solution of VIIIa in benzene.



X

Structure X is proposed for the unstable product. Although the chlorine in X is reactive, *i.e.*, the compound reacts with sodium iodide in acetone and eliminates hydrogen chloride slowly upon standing, it is not as reactive as would be expected of a halogen β to a ketone carbonyl and α to an oxygen. For instance, X can be refluxed in ether or distilled *in vacuo* without significant decomposition. The infrared spectrum of X exhibits carbonyl absorption at 1805 and 1785 cm^{-1}. (Note high absorption at 1773 cm^{-1} for α-bromoethyl acetate.[18]) There is no absorption in the olefinic region. The nmr spectrum of X shows only two sharp singlets at τ 6.24 and 7.86, areas 4:3. The equivalence of the four ring protons is somewhat surprising and indicates a similar shielding effect by the chloro and acetate groups.

Experimental Section[19]

3-Ethoxy-2-cyclobutenone (Ia).—Ketene was bubbled through a stirred solution containing 40 g of ethoxyacetylene in 75 ml of methylene chloride cooled in an ice bath. The progress of the reaction could be followed by watching the disappearance of the carbon–carbon triple bond absorption at 2155 cm^{-1} in the infrared and the appearance of the carbon–oxygen and carbon–carbon double bond absorptions of the product. After 8–10 hr, some ethoxyacetylene still remained, but additional reaction time did not increase the yield and resulted in the formation of dark-colored side products. The volatile materials were removed under reduced pressure, leaving a dark liquid residue which solidified at −20°. This material was dissolved in 40 ml of 50:50 ether–petroleum ether (bp 30–60°), and the product was allowed to crystallize at −50° for 24 hr. Filtration in the cold gave 20 g (31%) of Ia, mp 22–25°. An analytical sample from ether–pentane melted at 26–27.5°: λ_{max} (anhydrous ethanol) 233 mμ (ϵ 12,450); ν (CCl_4) 1760, 1580 cm^{-1}; nmr (CCl_4) τ 5.12 (s), 5.74 (q), 6.89 (s), and 8.55 (t), areas 1:2:2:3.

Anal. Calcd for $C_6H_8O_2$: C, 64.27; H, 7.19; OC_2H_5, 40.19. Found: C, 64.03; H, 7.21; OC_2H_5, 38.11.

A solution of 250 mg of Ia in 10 ml of moist ether was stirred for 24 hr at room temperature. Concentration of the solution under reduced pressure left moist crystals which were recrystallized from acetonitrile to give 60 mg (21%) of β-ethoxycrotonic acid, mp 141.5–142° (lit.[20] mp 140°). A mixture melting point with an authentic sample was undepressed. In absolute alcohol Ia did not deteriorate appreciably in 24 hr at room temperature. After 4.5 hr of heating at 60°, however, ethyl β-ethoxycrotonate was formed almost quantitatively. The infrared spectrum was superimposable on that of an authentic sample.

β-Ethoxycrotonic Acid Anilide.—A solution of 224 mg (0.002 mol) of Ia and 186 mg (0.002 mol) of aniline in 10 ml of benzene was allowed to stand at room temperature in a nitrogen atmosphere for 4 days. Concentration of the solution under reduced pressure left a liquid residue, which solidified when stored in the refrigerator under nitrogen. Recrystallization from carbon tetrachloride gave 380 mg (93%) of white crystals: mp 108–110°; ν ($CHCl_3$) 3440, 3330 (broad), 1670, 1610, 1595 cm^{-1}; nmr ($CDCl_3$) τ 2.7 (m), 4.93 (s), 6.20 (q), 7.64 (s), 8.65 (t), areas 5:1:2:3:3.

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.83. Found: C, 70.06; H, 7.25; N, 7.00.

3-Ethoxy-4,4-dimethyl-2-cyclobutenone (Ib).—A solution of 6.7 g of triethylamine in 20 ml of anhydrous ether was added over a period of 45 min to a stirred solution of 6.7 g of isobutyryl chloride, 6.6 g of ethoxyacetylene, and a trace of mercuric acetate[21] in 150 ml of anhydrous ether cooled below 0°. Precipitation of the amine salt started immediately. After 1 week at room temperature, filtration gave 90–98% of the theoretical amount of triethylamine hydrochloride. The filtrate was concentrated under reduced pressure and the residual oil was distilled *in vacuo*, giving 5.1 g (66%) of Ib, bp 78–82° (9 mm). A center fraction was redistilled for analysis: bp 90–92° (26 mm); λ_{max} (95% ethanol) 233 mμ (ϵ 12,700); ν (CCl_4) 1750, 1575 cm^{-1}; nmr (CCl_4) τ 5.27 (s), 5.78 (q), 8.53 (t), and 8.81 (s), areas 1:2:3:6.

Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.35; H, 8.69.

2-Bromo-3-ethoxy-4,4-dimethyl-2-cyclobutenone.—A solution of 0.275 ml of bromine in 5 ml of carbon tetrachloride was added slowly to a cooled solution of 0.75 g of Ib in 15 ml of carbon tetrachloride. The bromine was decolorized instantaneously, and after 15 min a slow evolution of hydrogen bromide began. After warming on a water bath for 1 hr, the solvent was distilled, and most of the residual oil was soluble in a hexane–benzene mixture. This solution was chromatographed on activity II alumina using hexane as the eluent and the resulting material was distilled *in vacuo*. Direct distillation of the residual oil did not remove all of the impurities. The analytical material boiled at 96–98° (25 mm): λ_{max} (95% ethanol) 249 mμ (ϵ 9950); ν (CCl_4) 1780, 1600 cm^{-1}; nmr (CCl_4) τ 5.31 (q), 8.50 (t), 8.77 (s), areas 2:3:6.

Anal. Calcd for $C_8H_{11}BrO_2$: C, 43.86; H, 5.06; Br, 36.48. Found: C, 43.54; H, 4.94; Br, 36.41.

1-Keto-3-ethoxyspiro[3.4]oct-2-ene (III).—A solution of 6.3 g of cyclopentanecarboxylic acid chloride, 11 g of ethoxyacetylene, and 7.5 ml of triethylamine in absolute ether was stirred at 5° for 14 days, after which 5.85 g (89.7%) of triethylamine hydrochloride had precipitated. The filtered solution was concentrated *in vacuo*, and the residual brown oil was taken up in hexane. This solution was stirred for 20 min with alumina containing 8% of water to destroy any excess acid chloride. The solution was then shaken with dilute potassium hydroxide solution, stirred with fresh alumina (8% water), and concentrated *in vacuo*, leaving 2.17 g (27.5%) of almost pure Ic. An analytical sample was obtained by chromatography followed by molecular distillation. The material was chromatographed on activity II alumina. Elution with hexane and 2–5% ether gave a trace of impurities. Hexane containing 20% ether gave Ic, which was distilled in a molecular still: λ_{max} 234.5 mμ (ϵ 11,250); ν 1755, 1570 cm^{-1}. The compound is thermolabile and decomposes upon distillation at aspirator vacuum.

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.25; H, 8.64.

1-Keto-3-ethoxyspiro[3.5]non-2-ene (IV).—A solution of 15.6 g of cyclohexanecarboxylic acid chloride, 21 g of ethoxyacetylene, and 15 ml of triethylamine was stored at 5° for 3 weeks, after which 13.7 g (94%) of triethylamine hydrochloride precipitated. The filtered solution was concentrated *in vacuo*, leaving 12.5 g of almost pure IV as an oil: λ_{max} 236 mμ (ϵ 8850);

(18) E. Buckley and E. Whittle, *Can. J. Chem.*, **40**, 1611 (1962).

(19) Infrared spectra were recorded using a Perkin-Elmer 421 spectrophotometer, and nmr spectra using a Varian Associates A-60 nmr spectrometer with TMS as an internal standard.

(20) M. A. Dolliver, T. L. Gresham, G. B. Kistiakowsky, E. A. Smith, and W. E. Vaughan, *J. Amer. Chem. Soc.*, **60**, 440 (1938).

(21) The presence or absence of mercuric ions does not seem to influence the reaction.

ν 1755, 1575 cm^{-1}. The compound decomposes upon distillation at aspirator vacuum. A center cut from molecular distillation under high vacuum was analyzed.

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.36; H, 9.28.

Cyclobutane-1,3-dione (IIa).—3-Ethoxy-2-cyclobutenone (Ia) (4.6 g, 0.041 mol) was dissolved in 125 ml of cold ether which had previously been shaken with cold, concentrated hydrochloric acid. Concentration of the solution under reduced pressure left a semisolid residue, which was recrystallized from acetonitrile and washed with cold ether to give 1.0 g of crystals. The mother liquor yielded another 0.6 g. An additional 0.6 g was obtained by adding a drop of concentrated hydrochloric acid to the mother liquor and concentrating *in vacuo*. The total yield was 2.2 g (64%) of nearly white crystals. An additional crystallization from acetonitrile gave pure white crystals of IIa: mp 119–120° with exothermic decomposition; λ_{max} (absolute ethanol) 237 mμ (ϵ 11,800); ν ($CHCl_3$)[22] 1755, 1570 cm^{-1} (weak); nmr ($CDCl_3$) τ 6.14 (s); nmr (DMSO) τ −0.25 (s), 5.28 (s), 6.90 (s). The material decomposes upon standing at room temperature and more slowly when stored at −15°.

Anal. Calcd for $C_4H_4O_2$: C, 57.14; H, 4.80. Found: C, 57.01; H, 5.10.

2,2-Dimethylcyclobutane-1,3-dione (IIb).—A solution of 1.6 g of Ib in 6 ml of water, 4 ml of ethanol, and 2 ml of concentrated hydrochloric acid was heated at 80° for 1 hr. The cooled solution was extracted with methylene chloride, the extracts were dried over anhydrous sodium sulfate, and the solvent was removed *in vacuo*. The resulting semisolid mass on treatment with pentane gave 0.65 g (51%) of long crystal rods. The remaining oil consisted largely of unreacted starting material. After recrystallization from ether–petroleum ether, the material had mp 129–130°; λ_{max} (95% ethanol) 241 mμ (ϵ 14,100); ν ($CHCl_3$) 1750, 1575 cm^{-1} (weak).

Anal. Calcd for $C_6H_8O_2$: C, 64.27; H, 7.19. Found: C, 64.04; H, 7.24.

A vigorous reaction took place between IIb and diazomethane in ether. Removal of the volatile materials and molecular distillation of the residue gave 3-methoxy-4,4-dimethyl-2-cyclobutenone, ν 1745, 1575 cm^{-1}.

Anal. Calcd for $C_7H_{10}O_2$: C, 66.64; H, 7.99. Found: C, 66.25; H, 8.13.

A solution of 80 mg of IIb in 10% aqueous alcoholic sodium hydroxide was heated for 2 hr on a steam bath and acidified with hydrochloric acid. After warming for an additional 1 hr, 2,4-dinitrophenylhydrazine reagent was added and the 2,4-dinitrophenylhydrazone of methyl isopropyl ketone precipitated from the solution. After two recrystallizations from ethanol the melting point was 118–118.5° and the mixture melting point with an authentic sample was undepressed.

3-Phenyl-2-cyclobutenone (V).—To a cooled solution of 0.80 g (0.0072 mol) of Ia in 15 ml of ether was added 5.5 ml of an ether solution of phenylmagnesium bromide (0.0013 mol/ml). The resulting mixture was allowed to come to room temperature for 15 min and was then poured into 7% hydrochloric acid. The ether layer was removed and the aqueous layer was extracted twice with ether. The combined ether extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo* leaving a semisolid residue with a cinnamon-like odor. This was recrystallized twice from ether at −78° and the resulting material was sublimed at 40–44° (1 mm), giving 0.55 g (53%) of white crystals, mp 51–52°. Infrared and nmr spectral properties were identical with those reported by Roberts,[13] except that the small cross-ring coupling reported in the nmr was not observed on our instrument.

Anal. Calcd for $C_{10}H_8O$: C, 83.31; H, 5.59. Found: C, 83.48; H, 5.82.

3-(1-Butyl)-2-cyclobutenone (VI).—To a cooled solution of 2.24 g (0.02 mol) of Ia in 25 ml of ether was added 14 ml of a solution of *n*-butylmagnesium bromide (0.0014 mol/ml). The resulting mixture was allowed to come to room temperature for 15 min and was then poured into 7% hydrochloric acid. The ether layer was removed and the aqueous layer was extracted twice with ether. The combined ether extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo*, leaving an oil which was distilled *in vacuo*, giving 1.6 g (65%) of product: bp 35–60° (1 mm); ν (CCl_4) 1765, 1580 cm^{-1}; nmr (CCl_4) τ 4.13 (m), 6.92 (m), 7.42 (t, broad), 8.85, (m), 9.07 (m), areas 1:2:2:4:3.

Anal. Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 76.91; H, 9.83.

3,3-Dimethoxycyclobutanone.—A solution of 5.2 g (0.046 mol) of Ia in 10 ml of methanol was added to a solution of 1.0 g (0.044 g-atom) of sodium in 50 ml of methanol cooled in an ice bath. The resulting solution was allowed to come to room temperature over 15 min, and saturated salt solution was added followed by enough water to redissolve the precipitated salt. The solution was extracted with eight 30-ml portions of ether. The combined ether extracts were concentrated *in vacuo* to about 50 ml, dried over anhydrous sodium sulfate, and further concentrated to give 3.0 g (49%) of crude 3,3-dimethoxycyclobutanone as an oil. Chromatography of 1.5 g of this material on 25 g of methanol-deactivated silica gel eluted with ether–hexane (1:6) gave 1.0 g of pure material in the early fractions: ν (CCl_4) 1790 cm^{-1}; nmr (CCl_4) τ 6.78 (s), 6.97 (s), areas 3:2. Later fractions appeared to be contaminated with 3-methoxycyclobutenone.

Anal. Calcd for $C_6H_{10}O_3$: C, 55.37; H, 7.74. Found: C, 55.10; H, 7.56.

3-Anilino-2-cyclobutenone (VIIa).—A solution of 168 mg (0.002 mol) of IIa and 186 mg (0.002 mol) of aniline in 10 ml of methylene chloride was allowed to stand at room temperature for 8 days. Concentration of the solution under reduced pressure left a solid residue which was recrystallized from benzene to give 330 mg (98%) of VIIa: mp 136–137° dec; ν ($CHCl_3$) 1730, 1600, 1560 cm^{-1}; nmr ($CDCl_3$) τ 2.7 (m), 4.77 (s), 6.62 (s), areas 5:1:2.

Anal. Calcd for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.24; H, 5.51; N, 8.68.

3-(*N*-Methylanilino)-2-cyclobutenone (VIIb).—A solution of 168 mg (0.002 mol) of IIa and 214 mg (0.002 mol) of *N*-methylaniline in 10 ml of methylene chloride was allowed to stand at room temperature for 8 days. Concentration of the solution under reduced pressure left an oil which was taken up in ether. Upon cooling, 280 mg (78%) of crystalline VIIb was deposited: mp 87–88°; nmr ($CDCl_3$) τ 2.70 (s), 4.67 (s), 6.57 (s), 6.90 (s), areas 5:1:3:2; ν ($CHCl_3$) 1735, 1555 cm^{-1}.

Anal. Calcd for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.47; H, 6.62; N, 7.98.

3-Pyrrolidino-2-cyclobutenone (VIIc). **A. From Cyclobutane-1,3-dione (IIa).**—A solution of 168 mg (0.002 mol) of IIa and 142 mg (0.002 mol) of pyrrolidine in 15 ml of methylene chloride was allowed to stand at room temperature for 48 hr. Concentration of the solution under reduced pressure left a liquid residue which was triturated with two 10-ml portions of ether. Removal of the ether left 140 g (52%) of light yellow crystals, mp 40–41°. An analytical sample from ether–hexane melted at 41.5–42°: ν ($CHCl_3$) 1740, 1590 cm^{-1}; nmr ($CDCl_3$) τ 5.47 (s), 6.50 (m), 6.67 (s), 7.90 (m), areas 1:4:2:4.

Anal. Calcd for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.89; H, 8.25; N, 9.97.

B. From the 1-Ethoxyvinyl Enol Ether of Cyclobutane-1,3-dione (IX).—A solution of 168 mg (0.002 mol) of IIa, 160 mg (0.0023 mol) of ethoxyacetylene, and 5 mg of mercuric acetate in 10 ml of methylene chloride was allowed to stand at room temperature for 4 hr. A solution of 142 mg (0.002 mol) of pyrrolidine in 3 ml of methylene chloride was added to the resulting light yellow solution. The reaction was mildly exothermic. After standing at room temperature for 2 hr, the solvent was removed under reduced pressure, and the resulting oil was triturated with ether. Removal of the ether left 240 mg (89%) of light yellow crystals, mp 40–42°.

The Enol Acetate of IIa, VIIIa.—Ketene was bubbled for 2 hr through a solution of 0.60 g of IIa in 50 ml of methylene chloride cooled in an ice–salt bath. Concentration of the solution under reduced pressure left 0.85 g (95%) of almost pure VIIIa as a liquid which solidified in the refrigerator. Two recrystallizations from anhydrous ether at −78° gave 0.60 g (67%) of VIIIa: mp 29–31°; ν (CCl_4) 1795, 1770, 1590, 1565 cm^{-1}; nmr (CCl_4) τ 4.54 (s), 6.68 (s), 7.65 (s), areas 1:2:3. The compound is extremely sensitive to moisture, as is VIIIb, characterized below.

Anal. Calcd for $C_6H_6O_3$: C, 57.14; H, 4.80. Found: C, 57.28; H, 4.80.

The Enol Benzoate of IIa, VIIIb.—To a solution of 380 mg (0.002 mol) of 1-ethoxyvinyl benzoate[13] in 10 ml of methylene chloride was added 168 mg (0.002 mol) of IIa. The solution was allowed to stand in the refrigerator for 5 days and concentrated

(22) For assignments of bands in the infrared and Raman spectra see F. A. Miller, K. E. Kiviat, and I. Matsubara, *Spectrochim. Acta, Part A*, **24**, 1523 (1968).

under reduced pressure. The resulting semicrystalline residue was partially soluble in dry hexane. Cooling of the hexane gave 150 mg (39%) of white crystals: mp 65–68°; ν (CCl_4) 1770 (shoulder), 1760, 1590, 1565 cm^{-1}; nmr (CCl_4) τ 1.97 (m), 2.37 (m), 4.53 (s), 6.70 (s), areas 2:3:1:2.

Anal. Calcd for $C_{11}H_8O_3$: C, 70.21; H, 4.29. Found: C, 70.13; H, 4.34.

The 1-Ethoxyvinyl Enol Ether of IIa, IX.—A solution of 84 mg (0.001 mol) of IIa, 105 mg (0.0013 mol) of ethoxyacetylene, and 5 mg of mercuric acetate in 10 ml of methylene chloride was allowed to stand at room temperature for 5 hr. An infrared spectrum of the solution exhibited absorption at 1760, 1672, and 1578 cm^{-1}. In the nmr spectrum of the solution there is a vinyl ring proton peak at τ 5.03 (s) and ring methylene protons at 6.60 (s); the two terminal vinyl protons are superimposed on the methylene resonance of the ethoxy group at about τ 6.1. When the solvent was removed from the solution, the residue reacted violently with water to give IIa and ethyl acetate.

3-Acetoxy-3-chlorocyclobutanone (X).—A solution of 1.0 g of IIa in 25 ml of acetyl chloride was allowed to stand at room temperature for 2 hr. The excess acetyl chloride was removed under reduced pressure and the residue was distilled *in vacuo*, giving 1.36 g (73%) of X: bp 51–52° (17 mm); ν (CCl_4) 1805, 1785 cm^{-1}; nmr (CCl_4) τ 6.24 (s), 7.86 (s), areas 4:3.

A sample stored at −15° in a sealed tube decomposed to a 50:50 mixture of X and VIIIa after 2 weeks. A sample distilled at aspirator vacuum gave a distillate which was 87% VIIIa. Treatment of 2 drops of X with alcoholic silver nitrate gave an immediate precipitate of silver chloride. When X was treated with sodium iodide in acetone, sodium chloride precipitated upon warming.

When hydrogen chloride was bubbled through a solution of VIIIa in dry benzene, large quantities of X could be detected in the product by infrared and nmr spectroscopy.

Registry No.—Ia, 4683-54-9; Ib, 4313-48-8; IIa, 15506-53-3; IIb, 3183-44-6; III, 38425-45-5; IV, 10576-21-3; V, 38425-47-7; VI, 38425-48-8; VIIa, 38425-49-9; VIIb, 38425-50-2; VIIc, 38425-51-3; VIIIa, 38425-52-4; VIIIb, 38425-53-5; X, 38425-54-6; ketene, 463-51-4; ethoxyacetylene, 927-80-0; aniline, 62-53-3; β-ethoxycrotonic acid anilide, 38425-55-7; isobutyryl chloride, 79-30-1; 2-bromoethoxy-4,4-dimethyl-2-cyclobutenone, 38425-56-8; cyclopentanecarboxylic acid chloride, 4524-93-0; diazomethane, 334-88-3; 3-methoxy-4,4-dimethyl-2-cyclobutenone, 15517-68-7; phenyl bromide, 108-86-1; butyl bromide, 109-65-9; 3,3-dimethoxycyclobutanone, 38425-58-0; pyrrolidine, 123-75-1; 1-ethoxyvinyl benzoate, 38425-59-1.

Base-Induced Cyclizations of Alkyl-Substituted Propargyloxyethanols[1]

ALBERT T. BOTTINI* AND JOHN G. MAROSKI

Department of Chemistry, University of California, Davis, California 95616

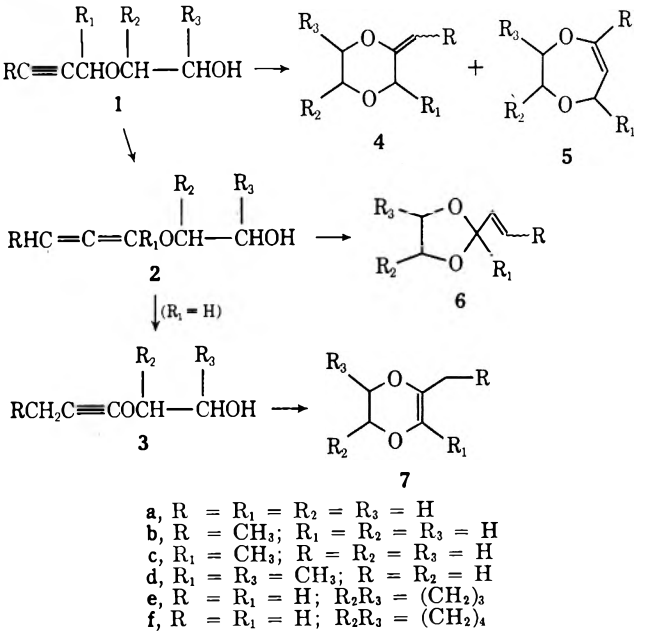
Received December 12, 1972

Cyclization reactions of alkyl-substituted propargyloxyethanols **1a–1f** induced by potassium hydroxide in water, dimethyl sulfoxide (DMSO), and *tert*-butyl alcohol were studied. Products obtained included the corresponding 2-methylene-1,4-dioxanes, 3,6-dioxacycloheptenes, 2-vinyl-1,3-dioxolanes, and 2-methyl-1,4-dioxenes. The mechanism proposed to account for base-induced cyclizations of propargyloxyethanol (ref 2) required modification to include two alternative pathways to the 2-methyl-1,4-dioxenes: cyclization of the allenyloxyethanol formed by prototropic rearrangement of the propargyloxyethanol, and, in DMSO only, base-induced rearrangement of the corresponding 2-methylene-1,4-dioxane.

The course of hydroxide-induced cyclization of propargyloxyethanol (**1a**) is strikingly dependent on reaction conditions.[2] In water, the main products are 2-methylene-1,4-dioxane (**4a**) and 3,6-dioxacycloheptene (**5a**); in the aprotic solvents decalin, dimethyl sulfoxide (DMSO), and triglyme, the main products are 2-vinyl-1,3-dioxolane (**6a**) and 2-methyl-1,4-dioxene (**7a**). A mechanism (Scheme I) that accounted for the dependence of product composition on solvent was proposed for the formation of **4a**–**7a**.[2] Formation of **4a** and **5a** was explained as occurring by intramolecular nucleophilic addition of alkoxide to the internal and terminal acetylenic carbons of **1a**, and the main pathways to **6a** and **7a**, respectively, were pictured as cyclizations of allenyloxyethanol (**2a**) and 1-propynyloxyethanol (**3a**), the products of successive prototropic rearrangements of **1a**.

Faure and Descotes,[3] who cyclized **1a** and six alkyl- and aryl-substituted propargyloxyethanols by treatment with potassium hydroxide in the diol corresponding to the substituted propargyloxyethanol, proposed other mechanisms for dioxene and dioxolane formation. They found that 1-(3-butyn-2-yloxy)-2-propanol (**1d**), the only propargyloxyethanol they examined that could not give a dioxene by the route shown in Scheme I, gave 2,3,5-trimethyl-1,4-dioxene (**7d**) as the major product; the only other product detected was 2-methylene-3,6-dimethyl-1,4-dioxane (**4d**). As **4d** and their other 2-methylene-1,4-dioxanes slowly isomerized to the

SCHEME I



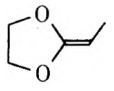
a, R = R_1 = R_2 = R_3 = H
b, R = CH_3; R_1 = R_2 = R_3 = H
c, R_1 = CH_3; R = R_2 = R_3 = H
d, R_1 = R_3 = CH_3; R = R_2 = H
e, R = R_1 = H; R_2R_3 = $(CH_2)_3$
f, R = R_1 = H; R_2R_3 = $(CH_2)_4$

(1) Taken from the Ph.D. Thesis of J. G. Maroski, University of California, Davis, 1971.

(2) A. T. Bottini, F. P. Corson, and E. F. Böttner, *J. Org. Chem.*, **30**, 2988 (1965).

(3) R. Faure and G. Descotes, *Bull. Soc. Chim. Fr.*, 1569 (1966).

corresponding 1,4-dioxenes under their reaction conditions, Faure and Descotes concluded that 1,4-dioxene formation took place by this route rather than cyclization of a 1-propynyloxyethanol (**3**). Significantly, it has been shown that thermal or hydroxide-induced isomerization of 2-methylene-1,4-dioxane (**4a**) could account for no more than a small fraction of the 2-methyl-1,4-dioxene (**7a**) obtained by treatment of propargyloxyethanol (**1a**) with sodium hydroxide in DMSO at 120°.[2] Negative evidence (they did not detect a 2-vinyl-1,3-dioxolane as a product from **1d** of **1f**) led the French workers to propose that 1,3-dioxolane formation occurred by cyclization of a 1-propynyloxyethanol to the corresponding ketene acetal (*e.g.*, **8**), followed by rearrangement of the double



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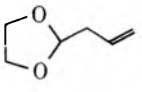
bond away from oxygen. It should also be noted here that Faure and Descotes did not detect a 3,6-dioxacycloheptene as a product from any of their reactions.

In order to determine the effect of alkyl substitution on the course of cyclization of propargyloxyethanols and, hopefully, clarify the mechanisms of 1,4-dioxene and 1,3-dioxolane formation, we examined base-induced cyclizations of the propargyloxyethanols **1a**–**1f**. Compounds **1d** and **1f** were also studied by Faure and Descotes. We treated **1b**–**1f** with KOH in water, DMSO, and *tert*-butyl alcohol (*t*-BuOH). In addition, **1c** was treated with KOH in triglyme, and **1c**, **1d**, and **1f** were treated with potassium *tert*-butoxide (KO-*t*-Bu) in *t*-BuOH. Under this range of conditions, **1c**, **1d**, and **1f** gave the four cyclic products corresponding to those obtained from **1a**. Compound **1b** also gave four cyclic ethers, which proved to be 2-allyl-1,3-dioxolane (**9**) and



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2-methyl-2-vinyl-1,3-dioxolane (**6c**) as well as the expected 1,3-dioxolane **6b** and 3,6-dioxacycloheptene **5b**. *trans*-2-Propargyloxycyclopentanol (**1e**) gave only the corresponding 3,6-dioxacycloheptane **5e** and 1,4-dioxene **7e**. The 3,6-dioxacycloheptenes, 1,3-dioxolanes, and 1,4-dioxenes were stable under the reaction and work-up conditions, but the 2-methylene-1,4-dioxanes were rearranged slowly to the corresponding dioxenes by base in DMSO, and **4f** rearranged rapidly to **7f** when heated above 120°.

Because of their possible involvement as intermediates in cyclizations of **1b** or **1c**, we also studied several reactions of the butadienyloxyethanols **2c**, **10**, and **11**.

$CH_2{=}C{=}CHCH_2OCH_2CH_2OH$ (**10**) $\quad CH_2{=}C(CH_2){-}COCH_2CH_2OH$ (**11**)

The propargyloxy alcohols **1b**–**1f** were prepared by treatment of the appropriate propargyl alcohol with either base and ethylene bromohydrin or substituted epoxide or acid and substituted epoxide. Analysis by vpc of the acetate of 1-(3-butyn-2-yloxy)-2-propanol (**1d**) indicated that it was a 1:1 mixture of diastereomers. 2-(2,3-Butadien-1-yloxy)ethanol (**10**) was prepared from allenylcarbinyl chloride and ethylene glycol, and the isomeric butadienyloxyethanols **2c** and **11** were obtained as by-products from reactions in *t*-BuOH of 2-(3-butyn-2-yloxy)ethanol (**1c**) with KOH and KO-*t*-Bu, respectively.

The cyclic products were characterized by means of their ir and nmr spectra, and the new compounds, with the exception of **5f**, gave satisfactory elemental analyses. In addition, the 2-methylene-1,4-dioxanes (**4**) were isomerized to the corresponding 2-methyl-1,4-dioxenes (**7**) with KOH in DMSO, **7c** and **7f** were oxidized with mercuric acetate according to the method described by Summerbell, *et al.*,[4] for oxidation of 1,4-dioxene and **7a**, and the 2-vinyl- and 2-(1-propenyl)-1,3-dioxolanes were synthesized by literature procedures[5] for this class of compounds.

Cyclization of 1-(3-butyn-2-yloxy)-2-propanol (**1d**) in water gave a 2.1:1 mixture of the diastereomeric 2-methylene-3,5-dimethyl-1,4-dioxanes (**4d** and **4d′**) and a 1.6:1 mixture of the diastereomeric 4,7-dimethyl-3,6-dioxacycloheptenes (**5d** and **5d′**). As it seems reasonable that the trans isomers would be more stable and would form *via* lower energy transition states, the predominant diastereomers (**4d** and **5d**) are assigned the trans configuration. Significantly, **4d** and **5d** had the lower refractive indexes,[6] and the minor 2-methylene-3,5-dimethyl-1,4-dioxane (**4d′**) rearranged more rapidly than **4d** to 2,3,5-trimethyl-1,4-dioxene (**7d**) on treatment with KOH in DMSO. The diastereomeric 2,4-dimethyl-2-vinyl-1,3-dioxolanes (**6d** and **6d′**) were formed in a ratio of 1:1.5 from **1d** and 1.5:1 from acid-catalyzed condensation of ethylene glycol and methyl vinyl ketone. As the latter reaction conditions should give the equilibrium mixture (the major product had the lower refractive index[6]), and as the work of Rommelaere and Anteunis[7] indicates that the more stable diastereomer should have the *RR,SS* configuration (cis methyl groups), this configuration is assigned to the minor dioxolane from **1d**, *i.e.*, **6d**.

Reactions in Water.—The yields and compositions of cyclic products obtained from treatment of propargyloxyethanol (**1a**) and its alkyl-substituted homologs **1c**–**1f** with aqueous KOH are summarized in Table I. Note that the results obtained with **1a** are very similar to those obtained earlier[2] using NaOH.

Comparison of the results obtained with **1a** and **1c** shows that substitution of a methyl group at propargyl carbon results in a significant increase in the methylenedioxane (**4**):dioxacycloheptene (**5**) ratio and reduces the yield of dioxolane (**6**) to barely a trace. Further comparison with the results obtained with **1d** shows that substitution of a methyl at carbinol carbon leads to a further increase in the **4**:**5** product ratio.

The decrease in the amount of seven-membered ring product on substitution of a methyl group at propargyl carbon can be attributed to electronic and steric factors. The transition state **4c**‡ leading to 2-methylene-

(4) R. K. Summerbell, G. Kalb, E. Graham, and A. Allred, *J. Org. Chem.*, **27**, 4461 (1962).

(5) (a) H. Hibbert and M. S. Whelen, *J. Amer. Chem. Soc.*, **51**, 3115 (1929); (b) R. F. Fischer and C. W. Smith, *J. Org. Chem.* **25**, 319 (1960); (c) D. L. Heywood and B. Phillips, *ibid.*, **25**, 1699 (1960).

(6) H. Van Bekkum, A. Van Veen, R. Verkade, and B. Wepster, *Recl. Trav. Chim. Pays-Bas*, **80**, 1310 (1961).

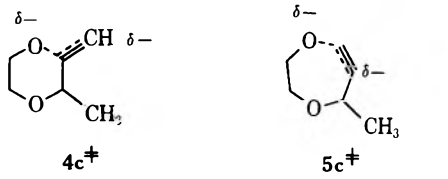
(7) Y. Rommelaere and M. Anteunis, *Bull. Soc. Chim. Belg.*, **79**, 11 (1970).

TABLE I
YIELDS AND PRODUCT COMPOSITIONS FROM REACTIONS OF PROPARGYLOXYETHANOLS WITH AQUEOUS POTASSIUM HYDROXIDE[a]

Compd	Yield, %	Composition, % 4	5	6	7
1a[b]	54	36	44	20	2
1a	72	39	36	24	<1
1c	68	62	37	<1	<1
1d	72	87[c]	12[d]	<1	<1
1e	52	<1	95	<1	5
1f	98	93	3	4	<1

[a] Reaction mixtures were 2 *M* in 1 and 2 *M* in base, and reactions were carried out for 12 hr at reflux. [b] The base was NaOH. [c] As a 2.1:1 mixture of diastereomers. [d] As a 1.8:1 mixture of diastereomers.

3-methyl-1,4-dioxane is similar electronically to the transition state leading to **4a**. However, the transition state **5c**‡ leading to 7-methyl-3,6-dioxacycloheptene is destabilized relative to the transition state leading to **5a** because of the closer proximity of the methyl group at propargyl carbon to the developing negative charge on unsaturated carbon.



4c‡ **5c**‡

Because of the greater internal angle strain in seven-membered rings of first-row elements, substitution of a methyl group leads to a greater increase in energy due to nonbonded interactions than is the case when a methyl group is substituted for hydrogen at the less hindered position on a six-membered ring, *i.e.*, equatorial rather than axial. It is likely that part of this difference in nonbonded interactions is also responsible for the lower energy of **4c**‡ compared to **5c**‡. The view that steric factors are partly responsible for the decrease in importance of the seven-membered ring product that results on methyl substitution is consistent with the results obtained with the dimethyl-substituted propargyloxyethanol **1d**, which gives an even greater **4**:**5** product ratio.

The importance of steric factors in cyclizations of propargyloxyethanols was demonstrated dramatically by the markedly different courses of cyclization of *trans*-2-propargyloxycyclopentanol (**1e**) and *trans*-2-propargyloxycyclohexanol (**1f**). Nearly all of the product from the cyclopentane was the corresponding dioxacycloheptene **5e**, whereas the cyclohexane gave over a 90% yield of the corresponding 2-methylene-1,4-dioxane **4f**. It seems reasonable that the energy associated with the trans fusion of six- and five-membered rings, which would be reflected in the transition state leading to **4e**, is responsible for preferred cyclization of **1e** to **5e**. In contrast, the relatively strain-free trans-fused **4f** is formed in preference to **5f**.

No cyclic products were formed when either 2-(2-butyn-1-yloxy)ethanol (**1b**) or 2-(2,3-butadien-2-yloxy)ethanol (**2c**) were treated with refluxing aqueous KOH for 12 hr. More than 70% of the **1b** and **2c** was recovered unchanged. This shows that methyl substitution significantly slows nucleophilic addition at acetylenic or allenic carbon, and that **2c** is not rearranged to **1c** under these reaction conditions. Note that both **1b** and **2c** undergo cyclization when treated with base in nonaqueous solvents, and these reactions are discussed below.

Reactions in DMSO and in Triglyme.—In Table II are given the yields and compositions of cyclic products from treatment of the propargyloxyethanols **1a–1f** and related compounds with KOH in DMSO. Also included in Table II are similar data for reactions of **1a**, **1b**, and 2-(2,3-butadien-2-yloxy)ethanol (**2c**) with KOH in triglyme.

TABLE II
YIELDS AND PRODUCT COMPOSITIONS FROM REACTIONS OF PROPARGYLOXYETHANOLS AND RELATED COMPOUNDS WITH POTASSIUM HYDROXIDE IN DMSO OR TRIGLYME[a]

Compd/Solvent	Reaction time, hr	Yield, %	Composition, % 4	5	6	7
1a/DMSO[b]	0.7	33	4	7	18	71
1a/TG[c]	0.5	58	<1	2	12	86
1b/DMSO	0.5	48[d]		12	70	
10/DMSO	0.5	35[e]		19	67	
1c/DMSO	0.5	65	14	14	11	61
1c/TG[c]	0.7	72	10	6	7	76
2c/DMSO	4.1	80	3	2	45	50
2c/TG	9.2	84			32	68
11/DMSO	12	5			100	
1d/DMSO	0.1	80	32[f]	7[g]	23[h]	38
1e/DMSO	12	78		35		65
1f/DMSO	0.5	80			6	94

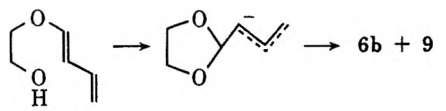
[a] Reaction mixtures were 2 *M* in compound and 2 *M* in KOH and reaction temperature was 100° unless noted otherwise. [b] Reference 2; base was NaOH. [c] Temperature 180–190°. [d] Includes 17% **9**. [e] Includes 14% **9**. [f] As a 2.4:1 mixture of diastereomers. [g] As a 1.3:1 mixture of diastereomers. [h] As a 1.5:1 mixture of diastereomers.

Before discussing the results in Table II, it should again be noted that the 2-methylene-1,4-dioxanes (**4**) undergo some rearrangement to the corresponding 2-methyl-1,4-dioxenes (**7**) in the presence of KOH in DMSO. For example, about half of the **4a** rearranges to **7a** in 0.7 hr when treated under the reaction conditions at 120°. In contrast and in confirmation of earlier results,[2] there is no significant rearrangement of **4a** to **7a** in 0.7 hr when the base is NaOH.[8]

The reactions of 2-(2-butyn-1-yloxy)ethanol (**1b**) and 2-(2,3-butadien-1-yloxy)ethanol (**10**) with KOH in DMSO gave similar mixtures of 2-methyl-3,6-dioxacycloheptene (**5b**), 2-(1-propenyl)-1,3-dioxolane (**6b**), and 2-allyl-1,3-dioxolane (**9**), and this indicates that these cyclizations occur by common pathways. As the per cent of the seven-membered ring product **5b** was significantly greater from the allene than from the acetylene, it seems likely that cyclization of the allene is the major pathway to **5b** from both **1b** and **10**, *i.e.*, **1b** → **10** → **5b**. This is consistent with results noted earlier which showed that methyl substitution on a carbon–carbon multiple bond slows nucleophilic addition. The isolation of nearly identical ratios of the dioxolanes **6b** and **9** from the acetylene **1b** and the allene **10** indicates that these products were formed from a

(8) This cation effect on base efficiency in DMSO has been observed by others. For example, D. J. Cram, C. A. Kingsbury, and B. Rickborn [*J. Amer. Chem. Soc.*, **83**, 3688 (1961)] reported that rates of racemization and isotope exchange decreased by about two powers of ten when NaO-*t*-Bu was used in place of KO-*t*-Bu in DMSO.

common intermediate, and the most likely intermediate is 2-(1,3-butadien-1-yloxy)ethanol (12) formed



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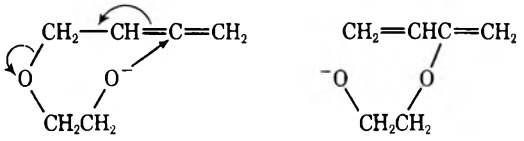
by prototropic rearrangement of **10**. In addition to the rearrangement of **1c** to 2-(1,3-butadien-2-yloxy)-ethanol (**11**) *via*, presumably, the allene isomer **2c** observed in this research, other examples of base-induced rearrangements of acetylenes or allenes to conjugated dienes are recorded in the literature.[9] Further, base-induced cyclizations analogous to that suggested for **12** have been observed for 1,3-cyclohexa-[10a] and 1,3-cycloheptadienyloxyethanol.[10b]

Interestingly, examination by vpc of the ether extracts of the reaction mixtures from **1b** and **10**, but not the distilled cyclic products, showed the presence of 2-methyl-2-vinyl-1,3-dioxolane (**6c**) in amounts which represented yields of 3–4% based on **1b** or **10**. The **6c** could not have arisen from 2-(2,3-butadien-2-yloxy)-ethanol (**2c**) because this compound yields **6c** and 2,3-dimethyl-1,4-dioxene (**7c**) in a 2.1:1 ratio in triglyme and a 1.1:1 ratio in DMSO under the reaction conditions, and no **7c** was obtained. It was found that 2-(1,3-butadien-2-yloxy)ethanol (**11**) cyclizes to only **6c** during vapor phase chromatography, and **11** is the likely source of the **6c** observed from the acetylene **1b** and allene **10**. A reasonable route to **11** is an S_N2' displacement of alkoxide by alkoxide on **10**.



Comparison of the results obtained with **1a** and **1c** in both DMSO and triglyme reveals that the most obvious result of substitution of a methyl group at propargyl carbon is a significant increase in the yields of the 2-methylene-1,4-dioxane and 3,6-dioxacycloheptene. This indicates that the inductive effect of the methyl group slows the rate of prototropic rearrangement of **1c** to 2-(2,3-butadien-2-yloxy)ethanol (**2c**) by destabilizing the intermediate carbanion. Thus, the importance of ring closure to **4c** and **5c** is enhanced.

Isolation of a significant amount of 2-methyl-2-vinyl-1,3-dioxolane (**6c**) from reactions of 2-(3-butyn-2-yloxy)ethanol (**1c**) in DMSO and in triglyme provides a decisive argument against the mechanism proposed by Faure and Descotes[3] for 2-vinyl-1,3-dioxolane formation because the required 2-(1-propynyloxy)ethanol (**3**) cannot be formed from **1c**.

Of even more significance was the large yield of 2,3-dimethyl-1,4-dioxene (**7c**) obtained from reactions of **1c** in DMSO and triglyme. Some of the **7c** formed in DMSO certainly arose by base-induced rearrangement of 2-methylene-3-methyl-1,4-dioxane (**4c**). However, only half of the **4c** rearranged to **7c** when a mixture of the four cyclic products from **1c** was treated with KOH under the reaction conditions for an extended period, *i.e.*, for 12 hr, rather than the 0.5-hr reaction time used for **1c**. Further, **4c** is stable in triglyme under the reaction conditions. Therefore, at least one intermediate other than the dioxane **4c** must be involved in the formation of **7c** from **1c**.

Insight into the mechanism of 2-methyl-1,4-dioxene (**7**) formation was gained by studying the behavior of 2-(2,3-butadien-2-yloxy)ethanol (**2c**) when treated with KOH in DMSO and triglyme. Reactions at 100° monitored by nmr spectroscopy revealed that 2-methyl-2-vinyl-1,3-dioxolane (**6c**) and 2,3-dimethyl-1,4-dioxene (**7c**) were formed as **2c** was destroyed. In addition to **6c** and **7c**, reaction of **2c** with KOH in DMSO gave small amounts of 2-methylene-3-methyl-1,4-dioxane (**4c**) and 7-methyl-3,6-dioxacycloheptene (**5c**) (3 and 2%, respectively), which indicates that slow isomerization of the allene **2c** to the acetylene **1c** occurs in this solvent. This shows as well that **4c** is not an important source of the dioxene **7c** from this reaction of **2c** because only a small amount of the stable seven-membered ring product **5c** was observed, and **4c** and **5c** are formed in a ratio of about 1:1 on cyclization of **1c**. The possibility that **2c** cyclizes directly to **4c** and/or **5c** seems unlikely because no evidence was obtained that indicated the presence of these cyclic products in the reaction mixture of **2c** in triglyme. It may be concluded therefore that **2c** cyclizes directly to **6c** and **7c** in triglyme, and that rearrangement of **2c** to **1c** does not occur to a significant extent in that solvent.

The results with **2c** clearly implicate this compound as the important intermediate in the formation of 2,3-dimethyl-1,4-dioxene (**7c**) from 2-(3-butyn-2-yloxy)-ethanol (**1c**) in triglyme. The different **7c**:**6c** ratios obtained from **1c** and **2c**, 11:1 and 2.1:1, can be explained on the basis of the more than 80° temperature difference at which the reactions were carried out. The small quantity of **2c** available required that the reaction be followed by means of nmr spectroscopy, and it was not practicable for us to attempt the reaction at 180–190°, the temperature range used for preparative scale runs with the propargyloxyethanols **1a** and **1c**. Comparison of the **7c**:**6c** product ratios obtained from **1c** and **2c** in DMSO, 5.5:1 and 1.1:1, indicates that the allene **2c** and, to a lesser extent, the methylenedioxane **4c** are both important as intermediates for **7c** from **1c** in that solvent.

It should be noted here that treatment of 2-(1,3-butadien-2-yloxy)ethanol (**11**) with KOH in DMSO at 100° did not give a detectable amount of either of the six-membered or seven-membered ring products. Presence of a small amount of 2-methyl-2-vinyl-1,3-dioxolane (**6c**) was indicated by vpc. However, it was shown subsequently that about 10% of the **11** cyclized to **6c** under the vapor phase chromatographic conditions. As the observed amount of **6c** was about 10% of the recovered **11**, it seems that the dioxolane **6c** was not formed in a significant amount by treatment with KOH in DMSO. Although **11** is not an intermediate in the base-induced cyclizations, its formation is important because it removes the allene intermediate **2c**

(9) For examples, see E. D. Bergmann, "The Chemistry of Acetylene and Related Compounds," Interscience, New York, N. Y., 1948, p 23; W. Smadja, *Ann. Chim.* (*Paris*), **10**, 105 (1965), and references cited therein; H. A. Selling, J. A. Rompes, J. H. Van Boom, S. Hoff, L. Bradsma, and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, **88**, 119 (1969); J. A. Rompes, S. Hoff, P. P. Montijn, L. Bradsma, and J. F. Arens, *ibid.*, **88**, 1145 (1969).

(10) (a) A. T. Bottini, F. P. Corson, K. A. Frost, II, and W. Schear, *Tetrahedron*, **28**, 4701 (1972); (b) K. A. Frost, II, unpublished work.

from the reaction coordinate leading to **6c** and **7c**, thereby decreasing the yield of these products.

The importance of **2c** as an intermediate in formation of 2,3-dimethyl-1,4-dioxene (**7c**) indicates that allenyloxyethanol (**2a**) may be an important intermediate in formation of 2-methyl-1,4-dioxene (**7a**) as well as 2-vinyl-1,3-dioxolane (**6a**) from **1a** in nonaqueous solvents. Substitution of a methyl group for hydrogen at C_1 of allenyloxyethanol should favor formation of the dioxene by reducing its rate of formation less than the rate of formation of the dioxolane. This is consistent with the larger 7:6 product ratio seen for **1c**. On the other hand, if **2a** is the single important intermediate for formation of **7a**, the relative free energies of the transition states leading to **6a** and **7a** from **2a** are particularly sensitive to changes in solvent because the **6a**:**7a** product ratio changes from 20:1 in water to 1:4 in DMSO to 1:7 in triglyme.[2] This corresponds to a relative change in free energies of over 3.6 kcal. Although such a change is not out of reason, it seems difficult to rationalize. Therefore, in the absence of additional evidence, 2-(1-propynyloxy)ethanol (**3a**) should continue to be considered as a probable intermediate for formation of **7a** from propargyloxyethanol (**1a**). Significantly, the thioether analog of **3a**, 2-(1-propynylthio)ethanol, undergoes base-induced cyclization to 2,3-dihydro-5-methyl-1,4-oxathiin, and the thioether analog of allenyloxyethanol is not a significant intermediate in the reaction.[11]

Comparison of the behavior of the 1:1 mixture of diastereomeric 1-(3-butyn-2-yloxy)-2-propanols (**1d**) with that of **1c** on treatment with KOH in DMSO shows that substitution of carbinol carbon by a methyl group increases the yields of the dioxanes and dioxolanes and decreases the yields of the corresponding 3,6-dioxacycloheptenes and 1,4-dioxene. Increase in yield of the 1,4-dioxanes can be attributed to the greater nucleophilicity of the secondary alkoxide generated from **1d**, and the decrease in yield of the dioxacycloheptenes can be rationalized on the basis of increased steric hindrance in the seven-membered ring owing to the presence of the second methyl group. The increased yield of 1,3-dioxolanes and decreased yield of 1,4-dioxene can also be attributed to the increased nucleophilicity of the alkoxide. There should be less new carbon–oxygen bond formation in the transition states leading to **6d** and **7d** (**6d**‡ and **7d**‡) than in those leading to **6c** and **7c** (**6c**‡ and **7c**‡), and consequently there is likely to be less stabilizing allylic resonance developed in **7d**‡ than in **7c**‡. It should also be noted that part of the lower yield of the dioxene may be accounted for by the lesser tendency of the 2-methylene-1,4-dioxanes to rearrange.

On treatment with KOH in DMSO, the cyclopentane derivative **1e** gave a 35:65 mixture of the corresponding 3,6-dioxacycloheptene **5e** and dioxene **7e**, and the cyclohexane derivative **1f** gave a 6:94 mixture of the corresponding 2-vinyl-1,3-dioxolane **6f** and dioxene **7f**. Although the 3,6-dioxacycloheptene **5e** and the 1,3-dioxolane **6f** were undoubtedly formed by cyclization, respectively, of the starting propargyloxycyclopentanol **1e** and the allenyloxycyclohexanol **2f**, the origin of the two dioxenes is unclear. They could have been formed by cyclization of either or both of the corresponding allenyloxy alcohols (**2e** and **2f**) or 1-propynyloxy alcohols (**3e** and **3f**). In addition, part of the **7f** could have arisen by rearrangement of the dioxane **4f**, which is converted rapidly to **7f** under the reaction conditions. As the cyclopentane **1e** gave virtually none of the 1,4-dioxane **4e** on treatment with aqueous KOH, it is unlikely that **4e** is a significant intermediate in the formation of **7e**.

Reactions in *t*-BuOH.—Study of the effect of solvent on the course of base-induced cyclizations of the propargyloxyethanols was extended to include *t*-BuOH. Also, KO-*t*-Bu was used in addition to or in place of KOH with several of the propargyloxyethanols. Based on the results of Price and Synder[12] and Cram and coworkers,[13] it was anticipated that the rates of prototropic rearrangement and the nucleophilicity of oxygen would be greater in *t*-BuOH than in water but less than in DMSO. Substitution of KO-*t*-Bu for KOH was expected to result in faster rates of prototropic rearrangement and, because of the greater effective alkoxide concentration, faster rates of nucleophilic addition. The results are summarized in Table III. Note that all of the cyclic products were stable under the reaction conditions.

TABLE III
YIELDS AND PRODUCT COMPOSITIONS FROM REACTIONS OF PROPARGYLOXYETHANOLS WITH BASE IN *t*-BuOH[a]

Compd	Base	Yield, %	Composition, % 4	5	6	7
1a	KOH	61	5	8	65	22
1b	KOH	15[b]		57	37	
1c	KOH	38	42	39	6	12
1c	KO-*t*-Bu	36	37	28	10	26
1d	KO-*t*-Bu	58	35[c]	7[d]	25[e]	33
1e	KOH	61		48		52
1f	KOH	80	31	4	13	52
1f	KO-*t*-Bu	82	12	2	21	65

[a] Reaction mixtures were 2 *M* in compound and 2 *M* in base, and reactions were carried out at reflux temperature for 12 hr. [b] Includes 5% 9. [c] As a 1.8:1 mixture of diastereomers. [d] As a 1.9:1 mixture of diastereomers. [e] As a 1.4:1 mixture of diastereomers.

The compositions of the cyclic ethers obtained from **1a** and **1c**–**1f** with KOH in *t*-BuOH are clearly intermediate between those obtained in water and in DMSO. Substitution of KO-*t*-Bu for KOH gave compositions of cyclic ethers that were somewhat more similar to those formed in DMSO.

Interestingly, propargyloxyethanol (**1a**) gave 2-vinyl-1,3-dioxolane (**6a**) as the major product. This could be due to a slowing of the prototropic rearrangement of allenyloxyethanol (**2a**) to 1-propynyloxyethanol (**3a**) relative to its ring closure to **6a**. Alternatively, both **6a** and 2-methyl-1,4-dioxene (**7a**) could arise by cyclization of **2a**. The latter would require that the **6a**:**7a** product ratio from **3a** is a highly sensitive function of solvent, with the dioxolane **6a** being favored in hydroxylic solvents. The results seen with **1c** and **1d**, specifically the solvent dependence of the corresponding dioxolane:dioxene (6:7) ratio, require this latter explanation.

(11) A. T. Bottini and E. F. Böttner, *J. Org. Chem.*, **31**, 385 (1966).

(12) C. C. Price and W. H. Snyder, *ibid.*, **27**, 4639 (1962).

(13) D. J. Cram, B. Rickborn, and G. R. Knox, *J. Amer. Chem. Soc.*, **82**, 6412 (1960).

Significantly different ratios of dioxolane **6f** and dioxene **7f** were obtained from *trans*-2-propargyloxycyclohexanol (**1f**) with KOH and KO-*t*-Bu. This as well as the slightly different **4c**:**5c** ratios obtained from 2-(3-butyn-2-yloxy)ethanol (**1c**) on treatment with the two bases can be attributed to the fact that the reaction mixtures containing KOH also contain a small amount of water.

The results with 2-(2-butyn-1-yloxy)ethanol (**1b**) require only brief comment. 2-Methyl-3,6-dioxacycloheptene (**5b**) accounts for a much higher per cent of the products in *t*-BuOH than in DMSO, and the 2-(1-propenyl)-2-allyl-1,3-dioxolane (**6b**:**9**) product ratio is raised from 4.1:1 to *ca* 7:1.

During the course of the work with 2-(3-butyn-2-yloxy)ethanol (**1c**), it was observed that the per cent of 2-methyl-2-vinyl-1,3-dioxolane (**6c**) present in the distilled product fraction was substantially less than that indicated by vpc analysis of the ether extract of the reaction mixture. Careful fractionation of the reaction mixture led to isolation of 2-(2,3-butadien-2-yloxy)ethanol (**2c**) and fractions enriched in 2-(1,3-butadien-2-yloxy)ethanol (**11**). When subjected to the conditions used for chromatographic analysis, both **2c** and **11** gave **6c**. Similar observations were noted with the diastereomeric 1-(3-butyn-2-yloxy)-2-propanols (**1d**). Subsequent examination of the reaction mixtures indicated the presence of 1-(1,3-butadien-2-yloxy)-2-propanol, which cyclized on gas chromatography to a 1:1 mixture of the diastereomeric 2,4-dimethyl-2-vinyl-1,3-dioxolanes (**6d** and **6d'**).

Experimental Section

Temperatures are uncorrected. Ir spectra were obtained with a Beckman IR-8 spectrophotometer; spectra of samples available in only microliter quantities were obtained using micro-NaCl plates and a beam condenser. Unless stated otherwise, nmr spectra were obtained of CCl_4 solutions with a Varian Associates A-60A spectrometer; resonance frequencies in nmr spectra were determined relative to 1–2% internal tetramethylsilane. Vpc chromatograms were obtained with an Aerograph Model A-700 or A-90. Mass spectra were determined with a Consolidated Electrodynamics Corp. Type 21-104 mass spectrometer; an ionizing voltage of 70 eV was used. Microanalyses were performed at the Microanalytical Laboratory, University of California, Berkeley, and Galbraith Laboratories, Inc., Knoxville, Tenn. Potassium *tert*-butoxide (KO-*t*-Bu) was obtained from MSA Research Corp. The KOH used was Mallinckrodt 85% minimum assay.

2-(2-Butyn-1-yloxy)ethanol (1b).—To a rapidly stirred suspension prepared from 47 g (<0.71 mol) of coarsely powdered KOH and 100 g (1.43 mol) of 2-butyn-1-ol maintained at 10° under a Dry Ice reflux condenser was added dropwise 79 g (0.71 mol) of ethylene bromohydrin. During the addition KBr precipitated. When the addition was complete the cooling bath was removed, and the temperature of the mixture rose to 40° in 45 min. When the reaction was no longer exothermic, the mixture was heated at 70–80° for 1 hr. The KBr was removed by filtration and washed with ether (100 ml). The filtrate containing the ether wash consisted of two layers. The heavy layer, which was miscible with water, and the ether solution were distilled to give a forerun of 2-butyn-1-ol and 48.6 g (60%) of 2-(2-butyn-1-yloxy)ethanol (**1b**): bp 75° (4 mm); n^{24}D 1.4586; nmr δ 4.08 (q, J = 2.3 Hz, 2, $CH_2C{\equiv}C$), 3.57 (m, 4, OCH_2CH_2O), 3.32 (s, 1, OH), and 1.83 ppm (t, J = 2.3 Hz, 3, $C{\equiv}CCH_3$).

Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 63.05; H, 8.71.

2-(3-Butyn-2-yloxy)ethanol (1c) was prepared as described for 1b from 104 g (>1.58 mol) of KOH, 217 g (3.10 mol) of 3-butyn-2-ol, and 191 g (1.53 mol) of ethylene bromohydrin. The yield was 111 g (63%) of **1c**: bp 72–73° (12 mm); n^{22}D 1.4418; nmr δ 4.17 (q, d, J = 7 and 2 Hz, 1, CHO), 3.17–3.95 (m, 4, CH_2-CH_2), 3.13 (s, 1, OH), 2.42 (d, J = 2 Hz, 1, $HC{\equiv}C$), 1.41 ppm (d, J = 7 Hz, 3, CH_3).

Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 62.88; H, 8.85.

1-(3-Butyn-2-yloxy)-2-propanol (1d) was prepared in 33% yield as described by Faure and Descotes:[3] bp 72–74° (14 mm); n^{23}D 1.4362 (lit.[3] bp 168°; n^{25}D 1.4365); nmr δ 2.88–4.27 (m, 4, $CHOCH_2CH$), 2.48 (s, 1, OH), 2.33 (d, J = 2 Hz, 1, $HC{\equiv}$), 1.38 (d, J = 6 Hz, 3, CH_3), 1.08 ppm (d, J = 6 Hz, 3, CH_3).

The acetate was prepared in 93% yield from 10 g of **1d** using the procedure of Marmor:[14] bp 55–58° (3 mm); $n^{22.6}$D 1.4269; nmr δ 4.58–5.13 (m, 1, $OCHCH_2O$), 3.85–4.27 (m, 1, $OCHC{\equiv}$), 3.14–3.73 (m, 2, OCH_2), 2.32 (d, J = 2.5 Hz, 1, $C{\equiv}CH$), 1.93 (s, 3, CH_3CO), 1.36 (d, J = 6.6 Hz, 3, CH_3), 1.18 ppm (d, J = 6.6 Hz, 3, CH_3).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.50; H, 8.31. Found: C, 63.35; H, 8.22.

Analysis by vpc using a 24-ft TCEP column at 82° indicated the presence of the two diastereomeric acetates in a ratio of 49:51, assuming equal detector sensitivity for the two stereoisomers.

trans-**2-Propargyloxycyclopentanol (1e).**—Using a procedure patterned after that described[3] for preparation of **1f**, 150 g of cyclopentene oxide was converted in 54% yield to **1e**: bp 78–79° (1.5 mm); n^{22}D 1.4803; nmr δ 4.07 (d, J, = 2 Hz, 2, $CH_2C{\equiv}C$), 3.62–4.15 (m, 2, OCHCHO), 3.37 (s, 1, OH), 2.36 (t, J = 2 Hz, 1, $HC{\equiv}C$), 1.27–2.12 ppm [m, 6, $(CH_2)_3$].

Anal. Calcd for $C_8H_{12}O_2$: C, 68.59; H, 8.57. Found: C, 68.47; H, 8.68.

trans-**2-Propargyloxycyclohexanol (1f)** was prepared in 79% yield from 115 g of cyclohexene oxide by the method of Faure and Descotes:[3] bp 86–87° (3 mm); n^{22}D 1.4821 [lit.[3] bp 120° (20 mm); n^{22}D 1.4790]; nmr δ 4.23 (d, J = 2.5 Hz, 2, $CH_2C{\equiv}C$), 3.32 (m, 2, OCHCHO), 3.08 (s, 1, OH), 2.40 (t, J = 2.5 Hz, 1, $HC{\equiv}C$) 0.83–2.33 ppm [m, 8, $(CH_2)_4$].

2-(2,3-Butadien-1-yloxy)ethanol (10).—To a rapidly stirred mixture of 35.5 g (0.40 mol) of allenylcarbinyl chloride[15] and 22 g of dry ethylene glycol under nitrogen at 30–40° was added dropwise a solution prepared from 9.2 g (0.40 mol) of sodium and 248 g of dry ethylene glycol. When the addition was complete the stirred mixture was heated at 75° for 6 hr, cooled, and stirred at room temperature for 9 hr. The mixture was added to 250 ml of water and extracted with ether (4 × 100 ml). The organic phases were combined, dried (K_2CO_3), and distilled to give 6.4 g (95% pure, 13%) of **10**, bp 92–106° (25 mm). An analytical sample was obtained by preparative vpc on XF-1150: n^{24}D 1.4688; nmr δ 4.98–5.43 (m, 1, $CH_2CH{=}$), 4.62–4.82 (m, 2, $=C{=}CH_2$), 4.00 (d, t, J = 2.5 and 6.6 Hz, 2, $OCH_2CH{=}C$), and 3.37–3.74 ppm (m, 5, CH_2CH_2OH).

Anal. Calcd for $C_6H_{10}O_2$: C, 63.18; H, 8.77. Found: C, 62.95; H, 8.96.

Reactions of the Propargyloxyethanols (1a–1f) and 10 with Base.—*tert*-Butyl alcohol (*t*-BuOH) was distilled immediately before use, bp 82–83°. Freshly distilled dimethyl sulfoxide (DMSO), bp 84° (20 mm), was passed over Woelm neutral alumina, activity grade I, into a dry reaction vessel immediately before use; 15 g of alumina was used for each 40 ml of DMSO.

For all reactions carried out in water, *t*-BuOH, or DMSO, the reaction mixture was 2 *M* in **1** or **10** and 2 *M* in base. Reactions in water or *t*-BuOH were carried out at reflux temperature, those in DMSO at 100 ± 5°. The cooled *t*-BuOH and DMSO reaction mixtures were added to 1–3 volumes of water, and all aqueous solutions were extracted continuously with ether for 8–12 hr. The reaction of **1c** with KOH in triglyme was carried out as described for propargyloxyethanol (**1a**).[2] Ether solutions were dried (NaOH), analyzed by vpc, and distilled. The distilled product mixtures were again analyzed by vpc, and these analyses were checked by nmr and, in some cases, ir spectroscopy.

2-(2,3-Butadien-2-yloxy)ethanol (2c).—A mixture of 10.0 g (0.152 mol) of KOH, 75.0 ml of *t*-BuOH, and 17.5 g (0.153 mol) of **1c** was heated under reflux for 9.5 hr. In addition to the cyclic products, work-up gave a 0.3-g fraction with bp 73–78° (13 mm): ir 1945 cm^{-1} (s, $C{=}C{=}C$); nmr δ 5.24 (q, J = 3 Hz, $C{=}C{=}CH_2$), 3.60 (s, broad, CH_2CH_2), 2.92 (s, OH), and 1.87

(14) S. Marmor, "Laboratory Guide for Organic Chemistry," D. C. Heath, Boston, Mass., 1964, p 272.

(15) Prepared by Dr. J. E. Christensen according to the procedure of W. H. Carothers, G. J. Bercket, and A. M. Collins, *J. Amer. Chem. Soc.*, **54**, 4066 (1932).

ppm (t, J = 3 Hz, CH_3). Bands due to 2-(1,3-butadien-2-yloxy)ethanol (11) were also present in the ir and nmr spectra. Analysis by nmr, which was in accord with vpc analysis on XF-1150, indicated that the fraction was a 2:1 mixture of 2c and 11.

2-(1,3-Butadien-2-yloxy)ethanol (11).—A mixture of 17.1 g (0.155 mol) of KO-*t*-Bu, 75.0 ml of *t*-BuOH, and 17.2 g (0.151 mol) of 1c was heated under reflux for 8 hr. In addition to the cyclic products, work-up gave 1.4 g (8%) of 11: bp 66° (6 mm); mass spectrum m/e (rel intensity) 99 (20), 87 (38), 71 (74), 55 (60), 53 (45), 45 (29), 43 (100), 42 (28), 39 (24), 29 (24), 15 (30); uv λ_{max} 2320 Å (ϵ 10,000); nmr (20% in PhH) δ 5.54–6.42 (m, 2, CH=CH_2), 4.96–5.13 (m, 1, =CHC=), 4.08 (s, 2, C=CH_2), 3.62 (broad s, 4, CH_2CH_2), and 3.17 ppm (s, 1, OH).

Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 62.69; H, 8.88.

Reactions of 2-(2,3-Butadien-2-yloxy)ethanol (2c). A. With KOH in DMSO.—A heavy-walled nmr tube was charged under nitrogen with 92 μl of DMSO, 11.7 mg (0.177 mmol) of KOH, 7.7 mg of PhH (internal standard), and 19.9 mg of a 2:1 mixture of 2c and 11. The tube was sealed and, after the nmr spectrum of the mixture was taken, placed in an ethylene glycol bath maintained at 100° by the vapors of boiling water. From time to time the tube was removed from the bath and cooled, and the extent of the reaction was determined by nmr. The decrease in area of the triplet due to the methyl of 2c and the increase in the areas of the singlets due to the methyls of 2-methyl-2-vinyl-1,3-dioxolane (6c) and 2,3-dihydro-5,6-dimethyl-1,4-dioxene (7c) were monitored for 6 hr, at which time all of the 2c had reacted to give an 80% yield of a mixture that consisted of 3% 4c, 2% 5c, 45% 6c, and 50% 7c.

B. With KOH in Triglyme.—Following the procedure for the reaction in DMSO, a mixture of 96 μl of triglyme, 21.1 mg of a 2:1 mixture of 2c and 11, and 12.1 mg (0.184 mmol) of KOH was heated at 100°, and the extent of the reaction was determined from time to time by nmr. After 16.7 hr, the reaction mixture was analyzed by vpc using 1,4-dioxane as internal standard; 83% of the 2c had reacted, and the combined yield of 6c and 7c in a 1:1.1 ratio was 84%.

Reactions of 2-(1,3-Butadien-2-yloxy)ethanol (11). A. With KOH in DMSO.—A stirred mixture of 504 mg (4.4 mmol) of 11, 284 mg (4.30 mmol) of KOH, and 2.2 ml of DMSO was heated at 100° for 12 hr. The reaction mixture was cooled and added to 25 ml of water, and the aqueous mixture was extracted with PhH (5 × 8 ml). Vpc analysis and use of a calibration curve prepared from solutions of 9c in PhH indicated that up to 26 mg (5%) of 6c could have been present in the PhH extract. In order to estimate the amount of unreacted 11, a calibration curve was prepared using solutions of 2-(3-butyn-2-yloxy)ethanol (1c) in PhH. It was estimated that 243 mg (48%, uncorrected for sensitivity differences) of 11 was unchanged. That the material was 11 was confirmed by determination of its mass spectrum. Also present in the phH extract was a significant amount of high-boiling material, which was not identified.

B. With KO-*t*-Bu in *t*-BuOH.—A mixture of 496 mg (4.4 mmol) of 12, 506 mg (4.5 mmol) of KO-*t*-Bu, and 2.2 ml of *t*-BuOH was heated under reflux for 12 hr. Analysis of the PhH extract of the reaction mixture by vpc using the previously constructed calibration curves indicated that up to 30 mg (6%) of 6c could have been present in the extract in addition to 292 mg (59%, uncorrected for sensitivity differences) of 11. The identity of 11 was confirmed by determination of its mass spectrum.

Characterization of Cyclization Products.—Summarized below are pertinent data for individual compounds. The stationary phase of the vpc column used for purifying the compound is given in parentheses. Unless a compound was isolated in a relatively pure state (>97%) by distillation, its boiling point is not given.

2-Methylene-3-methyl-1,4-dioxane (4c) (XF-1150) had $n^{22}D$ 1.4476; ir 1650 cm^{-1} (m); nmr δ 4.35 (m, 1, C=CH), 4.16 (m, 1, C=CH), 3.50–4.14 (m, 5, OCH_2CH_2OCH), and 1.28 ppm (d, J = 6.5 Hz, 3, CH_3).

Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 63.12; H, 9.02.

***trans*-3-Methylene-2,5-dimethyl-1,4-dioxane** (4d) (XF-1150 and TCEP) had $n^{23}D$ 1.4415; ir 1645 cm^{-1} (s); nmr (TMS) δ 4.36 (narrow m, 1, C=CH), 4.14 (narrow m, 1, C=CH), 3.10–4.04 (m, 4, $OCHCH_2OCH$), 1.25 (d, J = 6 Hz, 3, $OCHCH_3C$=), and 1.07 ppm (d, J = 6 Hz, 3, $OCHCH_3CH_2O$).

Anal. Calcd for $C_7H_{12}O_2$: C, 65.65; H, 9.37. Found: C, 65.71; H, 9.62.

***cis*-3-Methylene-2,5-dimethyl-1,4-dioxane** (4d′) (XF-1150) had $n^{23}D$ 1.4426; ir 1645 cm^{-1} (s); nmr (TMS) δ 4.28 (s, 1, C=CH), 4.06 (s, 1, C=CH), 3.12–4.22 (m, 4, $OCHCH_2OCH$), 1.26 (d, J = 6.5 Hz, 3, $OCHCH_3C$=), and 1.16 ppm (d, J = 6.5 Hz, 3, $OCHCH_3CH_2O$).

Anal. Calcd for $C_7H_{12}O_2$: C, 65.65; H, 9.37. Found: C, 65.48; H, 9.52.

2,5-Dioxa-3-methylene-*trans*-bicyclo[4.4.0]decane (4f) had bp 68° (2 mm); ir 1645 cm^{-1} (s); nmr δ 4.33 (s, 1, C=CH), 4.10 (s, 3, OCH_2 and C=CH), 2.67–3.77 (m, 2, OCHCHO), and 0.5–2.34 ppm [m, 8, $(CH_2)_4$].

Anal. Calcd for $C_9H_{14}O_2$: C, 70.07; H, 9.16. Found: C, 70.10; H, 9.15.

The methylene-1,4-dioxanes 4c, 4d, 4d′, and 4f were also converted to the corresponding methyl-1,4-dioxenes by treatment with KOH in DMSO (see Stability Studies below).

2-Methyl-3,6-dioxacycloheptene (5b) (XF-1150) had $n^{25}D$ 1.4636; ir 1677 cm^{-1} (vs); nmr δ 4.62 (t, q, J = 5 and 1 Hz, 1, CH_2CH=CCH_3), 3.59–4.02 (m, 6, $OCH_2CH_2OCH_2$), 1.72 ppm (d, J = 1 Hz, 3, CH_3).

Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 62.94; H, 8.87.

7-Methyl-3,6-dioxacycloheptene (5c) (XF-1150) had $n^{22}D$ 1.4489; ir 1650 cm^{-1} (vs); nmr δ 6.12 (d, d, J = 8 and 2 Hz, 1, OCH=C), 4.45 (d, d, J = 8 and 2 Hz, 1, OCH=CH), 3.25–4.33 (m, 5, $CHOCH_2CH_2O$), and 1.22 ppm (d, J = 8 Hz, 3, CH_3).

Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 63.24; H, 8.94.

***trans*-4,7-Dimethyl-3,6-dioxacycloheptene** (5d) (XF-1150) had $n^{22.5}D$ 1.4469; ir 1640 cm^{-1} (s); nmr (TMS) δ 5.93 (d, m, J = 6 Hz, 1, OCH=C), 4.08–4.58 (m, 3, CH_2CHCH_3O, CH=CH-$CHCH_3$), 3.64–3.72 (m, 2, OCH_2CH), and 1.15 ppm (d, J = 6.0 Hz, 6, $OCHCH_3C$=, $OCHCH_3CH_2$).

Anal. Calcd for $C_7H_{12}O_2$: C, 65.65; H, 9.37. Found: C, 65.49; H, 9.61.

***cis*-4,7-Dimethyl-3,6-dioxacycloheptene** (5d′) (XF-1150) had ir 1645 cm^{-1} (s); nmr (TMS) δ 6.15 (d, d, J = 7.5 and 2.4 Hz, 1, OCH=C), 3.05–4.37 (m, 4, $OCHCH_2OCH$), 1.20 (d, J = 6.5 Hz, 3, $OCHCH_3C$=), and 1.13 ppm (d, J = 6.5 Hz, 3, $OCHCH_3CH_2O$).

Anal. Calcd for $C_7H_{12}O_2$: C, 65.65; H, 9.37. Found: C, 65.74; H, 9.39.

2,6-Dioxa-*trans*-bicyclo[5.3.0]dec-3-ene (5e) (XF-1150) had $n^{23}D$ 1.4842; ir 1655 cm^{-1} (s); nmr δ 6.15 (d, m, J = 7.5 Hz, 1, OCH=C), 4.33–4.57 (m, 1, OCH=$CHCH_2$), 3.35–4.09 (m, 4, OCH_2, OCHCHO), and 1.36–2.27 ppm [m, 6, $(CH_2)_3$].

Anal. Calcd for $C_8H_{12}O_2$: C, 68.59; H, 8.57. Found: C, 68.37; H, 8.64.

2,6-Dioxa-*trans*-bicyclo[5.4.0]undec-3-ene (5f) (Carbowax, isolated as a 1:1 mixture with 7f) had nmr δ 6.32 (d, t, J = 7 and ~0.5 Hz, 1, OCH=C), 4.84 (d, t, J = 7 and ~0.5 Hz, 1, OCH=CH), 3.92–4.30 (m, 2, OCH_2C=), 2.83–3.84 (m, OCHCHO, both isomers), 0.87–2.50 [m, $(CH_2)_4$, both isomers].

2-(1-Propenyl)-1,3-dioxolane (6b) was identical with the product obtained by the method of Heywood and Phillips:[5c] bp 141°; $n^{24}D$ 1.4407 (lit.[16] bp 147°; lit.[5c] $n^{30}D$ 1.4380); nmr δ 4.98–5.93 (m, 3, $CHCH$=$CHCH_3$), 3.56–4.04 (m, 4, OCH_2CH_2O), and 1.73 ppm (d, d, J = 5.8 and 0.6 Hz, 3, CH_3).

2-Methyl-2-vinyl-1,3-dioxolane (6c) was identical with the product obtained in 36% yield from methyl vinyl ketone and ethylene glycol using the method of Fischer and Smith:[5b] bp 110–112° [lit.[17] bp 111–112° (70 mm)]; $n^{23}D$ 1.4201; nmr δ 4.90–5.96 (m, 3, CH=CH_2), 3.68–3.92 (m, 4, OCH_2CH_2O), and 1.35 ppm (s, 3, CH_3).

Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 63.14; H, 8.75.

The diastereomeric **2,4-dimethyl-2-vinyl-1,3-dioxolanes** (6d and 6d′) (XF-1150) were identical with the products with bp 77–78° (128 mm) obtained in a combined yield of 32% from methyl vinyl ketone and propylene glycol by the method of Fischer and Smith.[5b] The *RR,SS* isomer (more stable form, 6d) had $n^{23}D$ 1.4133; nmr δ 4.92–6.08 (m, 3, CH=CH_2), 3.77–4.35 (m, 2, OCH_2CHO), 3.18–3.54 (m, 1, OCH_2CHO), 1.36 (s, 3, CCH_3CH=), and 1.20 ppm (d, J = 6 Hz, CH_2CHCH_3).

(16) J. P. Fourneau and S. Chantalou, *Bull. Soc. Chim. Fr.*, **12**, 845 (1945).

(17) J. Martinez Madrid and J. L. Mateo, *Markromol. Chem.*, **136**, 113 (1970).

TABLE IV

RESULTS OF STABILITY STUDIES OF CYCLIC PRODUCTS SUBJECTED TO BASE-INDUCED CYCLIZATION CONDITIONS[a]

Substituents	Solvent	Recovery, %	Initial composition % 4	5	6	7	Final composition % 4	5	6	7
a[b-d]	DMSO		38	36	22	4	21	34	20	25
a[b,d,e]	DMSO		38	36	22	4	3	33	23	41
a[b-d,f]	DMSO		38	36	22	4	40	36	20	4
a[b,d,f,g]	DMSO		38	36	22	4	29	36	20	16
c[c,h]	TG[i]	80	61	36	<1	3	63	32	<1	4
c[c,h]	DMSO	71	61	36	<1	3	31	31	<1	38
d	H_2O	70	65	9	26	<1	65	10	24	<1
d[j]	*t*-BuOH	68	24	11	44	20	27	12	37	24
d	DMSO	76	65	9	26	<1	2	4	25	69
e	H_2O	75	0	38	0	62	0	41	0	59
e	*t*-BuOH	94	0	38	0	62	0	38	0	62
e	DMSO	96	0	38	0	62	0	38	0	62
e[i]	DMSO	89	0	38	0	62	0	28	0	71
f	*t*-BuOH	78	>99	0	0	0	>99	0	0	0
f	DMSO	74	>99	0	0	0	<2	0	0	98

[a] Unless noted otherwise base was KOH, temperature was 100° in DMSO, 190° in triglyme, and reflux temperature in water and *t*-BuOH, reaction time was 12 hr, and a 1:1 mole ratio of base:cyclic product mixture was used. [b] Temperature 120°. [c] Reaction time 0.7 hr. [d] A 1:2 mole ratio of base:**4a** was used. [e] Reaction time 4.8 hr. [f] Base was NaOH. [g] Reaction time 4.4 hr. [h] Temperature 190°; sealed tube. [i] 90 mol % triglyme–10 mol % *t*-BuOH. [j] Base was KO-*t*-Bu.

Anal. Calcd for $C_7H_{12}O_2$: C, 65.64; H, 9.37. Found: C, 65.58; H, 9.94.

The *RS*,*SR* isomer (less stable form, **6d'**) had $n^{23}D$ 1.4154; nmr δ 4.91–6.11 (m, 3, $CH{=}CH_2$), 3.86–4.42 (m, 2, OCH_2CHO), 3.14–3.46 (m, 1, OCH_2CHO), 1.32 (s, 3, $CCH_3CH{=}$), and 1.18 ppm (d, J = 6 Hz, 3, CH_2CHCH_3).

Anal. Calcd for $C_7H_{12}O_2$: C, 65.64; H, 9.37. Found: C, 65.83; H, 9.62.

7,9-Dioxa-8-vinyl-*trans*-bicyclo[4.3.0]nonane (6f).—Treatment of 2.0 g (0.105 mol) of 7,9-dioxa-8-(2-chloroethyl)-*trans*-bicyclo[4.3.0]nonane, which was prepared in 52% yield from *trans*-1,2-cyclohexanediol, acrolein, and gaseous hydrogen chloride according to the method of Hibbert and Whelan,[5a] with 11.9 g of KO-*t*-Bu in 100 ml of DMSO at 77° for 3 hr gave a 14% yield of **6f**, which was identical with the product obtained from **1f**: bp 70–72° (6 mm); $n^{23}D$ 1.4671; nmr δ 4.80–6.20 (m, 4, $CHCH{=}CH_2$), 2.57–3.50 (m, 2, OCHCHO), and 0.42–2.50 [m, 8, $(CH_2)_4$].

Anal. Calcd for $C_9H_{14}O_2$: C, 70.09; H. 9.15. Found: C, 69.88; H, 9.19.

2-Allyl-1,3-dioxolane (9)[18] (XF-1150) had $n^{25}D$ 1.4366; nmr δ 5.45–6.12 (m, 1, $CH{=}CH_2$), 4.85–5.23 (m, 2, $CH{=}CH_2$), 4.77 (t, J = 4.8 Hz, $CHCH_2$), 3.69–3.94 (m, 4, OCH_2CH_2O), and 2.22–2.46 ppm (m, 2, $CH_2CH{=}$).

Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 63.03; H, 8.85.

2,3-Dimethyl-1,4-dioxene (7c) (XF-1150) had $n^{22}D$ 1.4474; ir 1700 cm^{-1} (s); nmr δ 3.92 (s, 4, OCH_2CH_2O) and 1.67 ppm (s, 6, $CH_3C{=}CCH_3$).

Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 63.37; H, 9.12.

Treatment of 2.31 g (0.0203 mol) of **7c** with 6.30 g (0.0197 mol) of mercuric acetate according to the method of Summerbell, *et al.*,[4] gave 3.42 g (87%) of mercury and 1.61 g (95%) of butane-2,3-dione. Ethylene glycol was also detected (vpc on Poropak Q) as a product, but its yield was not determined.

2,3,5-Trimethyl-1,4-dioxene (7d) (XF-1150) had $n^{23}D$ 1.4416 (lit.[3] bp 140°; $n^{25}D$ 1.4335); ir and nmr in excellent agreement with data reported by Faure and Descotes.[3]

2,5-Dioxa-3-methyl-*trans*-bicyclo[4.3.0]non-3-ene (7e) (XF-1150) had $n^{22}D$ 1.4710; ir 1673 cm^{-1} (s); nmr δ 5.62 (q, J = 1.3 Hz, 1, C=CH), 3.32–3.85 (m, 2, OCHCHO), 1.20–2.20 ppm [m with superimposed d at 1.63 ppm, J = 1.3 Hz, 9, $(CH_2)_3$ and CH_3].

(18) Synthesis of **9** has been claimed by U. Faass and H. Hilgert, *Chem. Ber.*, **87**, 1343 (1954).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.59; H, 8.57. Found: C, 68.81; H, 8.63.

2,5-Dioxa-3-methyl-*trans*-bicyclo[4.4.0]dec-3-ene (7f) had bp 50–51° (2.5 mm); $n^{23}D$ 1.4750 [lit.[3] bp 92° (18 mm); $n^{25}D$ 1.4772]; ir and nmr in excellent agreement with data reported by Faure and Descotes.[3] Treatment of 3.23 g (0.021 mol) of **7f** with 6.32 g (0.0198 mol) of mercuric acetate according to the method of Summerbell, *et al.*,[4] gave 3.75 g (94%) of mercury and 2.23 g (97%) of *trans*-1,2-cyclohexanediol, which was free of its cis isomer as determined by vpc on 4% Sorbitol–16% silicone 703.

Stability Studies.—Examination of the stability of the cyclic products was conducted under conditions that closely approximated the reaction conditions used for their preparation; generally, a mixture of the cyclic products was heated with base in water at reflux, in *t*-BuOH at reflux, in triglyme at 190°, or in DMSO at 100 or 120°. The work-up procedure was identical with that described for the cyclization reactions. Results are summarized in Table IV.

Registry No.—**1b**, 38644-91-6; **1c**, 18668-75-2; **1d**, 3973-21-5; **1d** acetate, 38653-27-9; **1e**, 38653-28-0; **1f**, 7229-32-5; **2c**, 38653-30-4; **4c**, 28125-74-8; **4d**, 38653-32-6; **4d'**, 38653-33-7; **4f**, 38653-34-8; **5b**, 38653-35-9; **5c**, 38653-36-0; **5d**, 38653-37-1; **5d'**, 38653-38-2; **5e**, 38653-39-3; **5f**, 38653-40-6; **6b**, 4528-26-1; **6c**, 26924-35-6; **6d**, 38653-43-9; **6d'**, 38653-44-0; **6f**, 38653-45-1; **7c**, 25465-18-3; **7e**, 38653-47-3; **7f**, 7196-96-5; **9**, 38653-49-5; **10**, 38653-50-8; **11**, 38653-51-9; 2-butyn-1-ol, 764-01-2; ethylene bromohydrin, 540-51-2; 3-butyn-2-ol, 2028-63-9; cyclopentene oxide, 285-67-6; allenylcarbinyl chloride, 25790-55-0; ethylene glycol, 107-21-1; methyl vinyl ketone, 78-94-4.

Acknowledgments.—This research was supported in part by Grant CA-10740 from the U. S. Public Health Service. Availability of the mass spectrometer was made possible by a grant from the National Science Foundation. We wish to thank Mr. J. Voth for determination of the mass spectra. We are grateful to Professor Rolf Huisgen for his helpful comments.

The Base-Induced Ring Enlargement of Halomethylenecyclobutanes. A Carbon Analog of the Beckmann Rearrangement

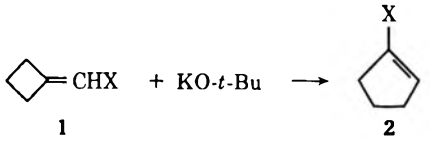
K. L. ERICKSON

Jeppson Laboratory, Clark University, Worcester, Massachusetts 01610

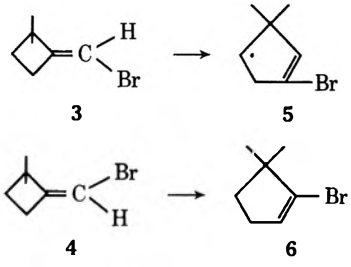
Received November 30, 1972

1-Chloromethyl-1-methylcyclobutane (**9**) and ethylthiomethylenecyclobutane (**15**) do not undergo ring enlargement with potassium *tert*-butoxide, although the latter compound does form the vinyl anion. Bromomethylenecyclobutane (**37**) rearranges in DMF in the presence of potassium *tert*-butoxide and potassium iodide to give *tert*-butoxymethylcyclobutene (**39**), 1-bromocyclopentene (**38**), and 1-iodocyclopentene (**40**). The formation of **40** is taken as evidence for the intermediacy of a carbene–bromide complex and a cyclopentyne–bromide complex in analogy to the Beckmann rearrangement of imine derivatives.

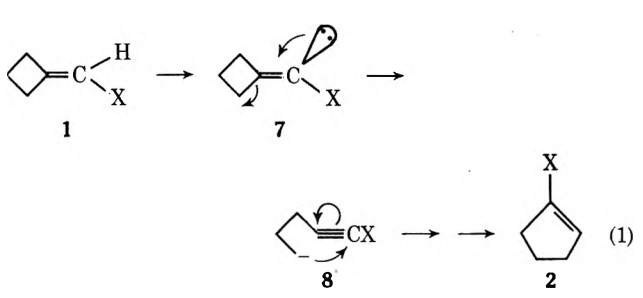
The base-induced rearrangement of 1-halomethylenecyclobutanes (**1**) to 1-halocyclopentenes (**2**) has been



under investigation in our laboratory for the past few years.[1] The stereospecificity of the rearrangement of the two unsymmetrical isomers **3** and **4** to **5** and **6**, re-



spectively, led us to postulate a cleavage–recombination mechanism for the ring enlargement process (eq 1).[1c]

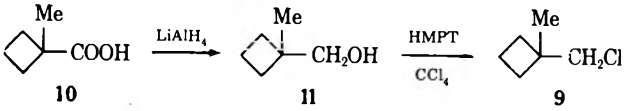


(1)

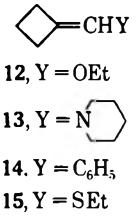
In attempts to provide further evidence in support of this mechanism, we have instead cast doubt upon its validity and have accumulated data more in agreement with an alternate mechanism. In addition, we have examined the sulfur analog of **1** and a nonvinyl analog to further delineate the generality of this reaction.

Results and Discussion

The only systems to date which have been found to undergo the ring-enlargement reaction are those with a vinyl halide substituent.[1b] To determine if the vinyl system is necessary, 1-chloromethyl-1-methylcyclobutane (**9**) was synthesized from 1-methylcyclobutanecarboxylic acid (**10**)[2] as shown below and subjected to

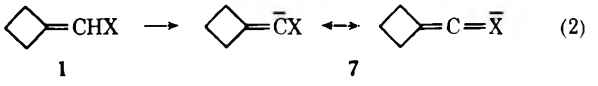


the rearrangement reaction conditions (potassium *tert*-butoxide at 100°). Compound **9** showed no tendency to react with potassium *tert*-butoxide even at 200°. After 6 days in refluxing *tert*-butyl alcohol-*O*-*d* in the presence of potassium *tert*-butoxide, no deuterium exchange had occurred. Chloride **9** thus fails to form a carbanion, without which no rearrangement is possible. The vinyl system is apparently necessary to sufficiently acidify the exocyclic hydrogens, but it alone is not adequate, as shown by the lack of rearrangement of compounds **12**, **13**, and **14**.[1b] In the case of 1-ethoxy-



methylenecyclobutane (**12**), this unreactivity has also been shown to be due to an inability to form the anion. Thus, after 6 days in refluxing *tert*-butyl alcohol-*O*-*d* and potassium *tert*-butoxide, no deuterium incorporation into **12** could be detected (nmr, mass spectrum).

While chloride, bromide, and iodide substituents would be expected to stablize vinyl anion **7** (see eq 2),



(2)

first-row elements (such as oxygen and nitrogen) cannot expand their octets and consequently cannot contribute any resonance stablization to the system. Presumably any methylenecyclobutane derivative with a vinyl substituent capable of stablizing the anion is a viable candidate for ring enlargement (providing other reactions do not compete). Since sulfur is known to be a good stabilizer of an adjacent negative charge, we undertook the synthesis of ethylthiomethylenecyclobutane (**15**) to determine if it would undergo the rearrangement.

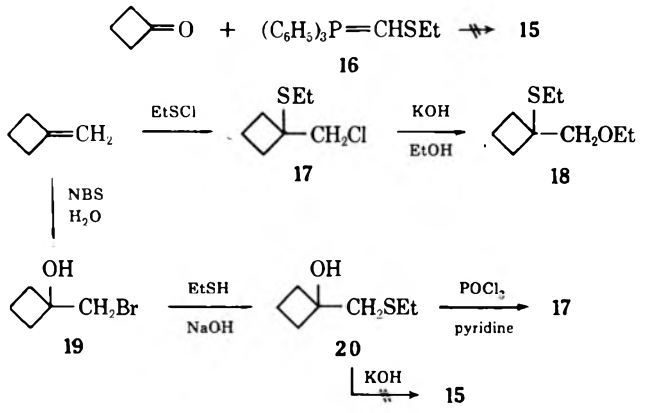
A variety of routes to **15** were simultaneously investigated (Schemes I and II). The most direct method, a Wittig reaction with cyclobutanone and ethylthiomethylenetriphenylphosphorane (**16**),[3] did not

(1) (a) K. L. Erickson, B. E. Vanderwaart, and J. Wolinsky, *Chem. Commun.*, 1031 (1968); (b) K. L. Erickson, J. Markstein, and K. Kim, *J. Org. Chem.*, **36**, 1024 (1971); (c) K. L. Erickson, *ibid.*, **36**, 1031 (1971).

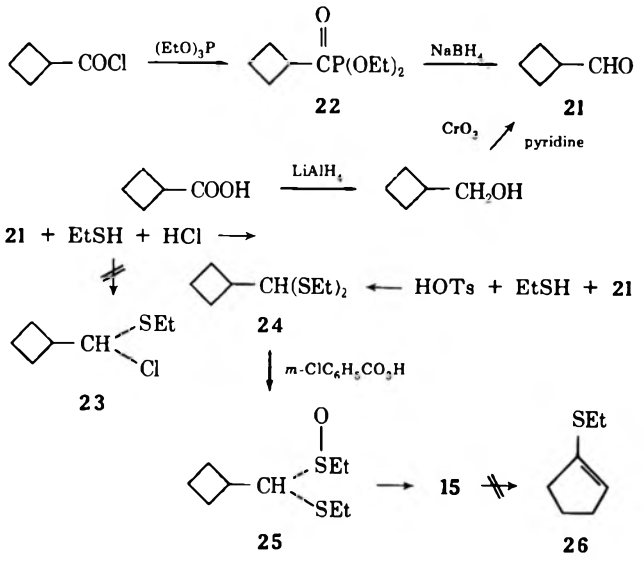
(2) D. G. Pratt and E. Rothstein, *J. Chem. Soc. C*, 2548 (1968).

(3) T. Mukaiyama, S. Fukuyama, and T. Kumamoto, *Tetrahedron Lett.*, 3787 (1968).

SCHEME I



SCHEME II



give any vinyl sulfide. Addition of ethanesulfenyl chloride to methylenecyclobutane proceeded in the wrong direction for our purposes, giving 1-chloromethyl-1-ethylthiocyclobutane (**17**), which readily afforded 1-ethoxymethyl-1-ethylthiocyclobutane (**18**) on treatment with alcoholic potassium hydroxide. Attempted phosphorus oxychloride dehydration of 1-(ethylthiomethyl)cyclobutanol (**20**), not unexpectedly, resulted in sulfur participation, affording **17** as the major product. Powdered potassium hydroxide[4] was likewise ineffective in eliminating water from **20**.

Other possible routes to **15** necessitated a more efficient synthesis of cyclobutanecarboxaldehyde (**21**) than we had previously used.[1b] Johnson and Rickborn[5] report such a synthesis, but we found their route lengthy compared to the two shown in Scheme II. Of these, the method of choice on a yield basis is the chromium trioxide–pyridine oxidation of cyclobutylmethanol.

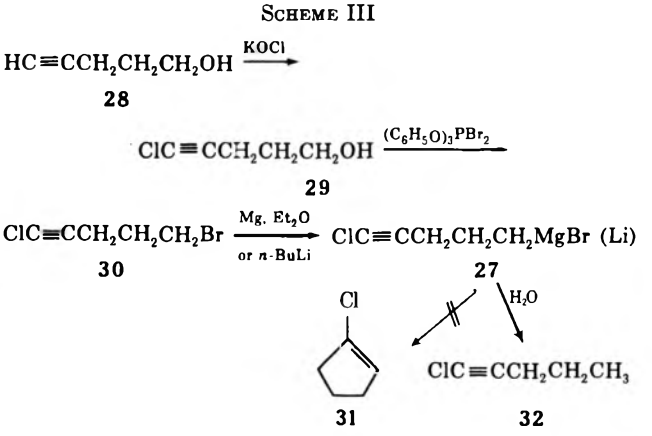
An attempt to prepare α-chloro thioether **23** from **21** gave instead thioacetal **24**. This material was prepared in better yield using *p*-toluenesulfonic acid in catalytic amounts. Direct elimination of ethanethiol from **24** by heating with catalytic phosphoric acid[6] resulted in extensive decomposition. Conversion to the monosulfoxide **25** followed by pyrolysis[7] was effective, however, in generating ethylthiomethylenecyclobutane (**15**). Surprisingly, this compound showed no tendency to react with potassium *tert*-butoxide either at 100° or at 200°. 1-Ethylthiocyclopentene (**26**), independently synthesized, was not produced, and the starting vinyl sulfide was recovered in good yields.

When **15** was treated with potassium *tert*-butoxide in refluxing *tert*-butyl alcohol-*O*-*d* (3 days), exchange of the vinyl (and allyl) hydrogen occurred, indicating that the vinyl anion can form in this system. Its failure to rearrange demonstrates that anion formation is not the only requirement which must be met before ring enlargement will occur. Thus, the halomethylenecyclobutanes remain unique in their ability to undergo this reaction.

Turning now to the mechanism of the ring enlargement, the major objections to the postulated cleavage–recombination mechanism are cyclobutyl ring opening to an unstabilized ion (**8**) and the lack of any acyclic product formation. This latter fact requires that ring closure of **8** be faster than any external attack on it (such as protonation).

Evidence for the intermediacy of acyclic ion **8** could be provided by generating it independently and demonstrating its facile ring closure to a cyclopentene system. The most direct method of achieving this is *via* the organometallic derivative, **27**, which was synthesized in three steps from 4-pentyn-1-ol (**28**) (Scheme III).

SCHEME III

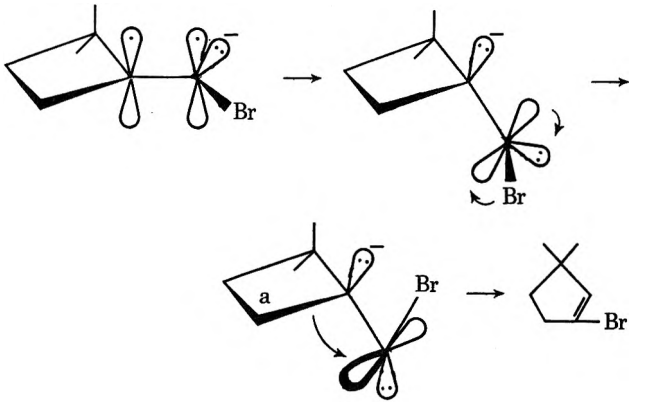


Ring closures of acyclic acetylenic Grignard and lithium derivatives have been reported to give five-membered rings quite readily in certain systems.[8] However, in our case, the cyclized product, 1-chlorocyclopentene (**31**), did not form. Both the Grignard and the lithium derivative gave large amounts of higher boiling material. The major volatile product was 1-chloro-1-pentyne (**32**), indicating that the proper organometallic derivative had indeed formed. If **27** is considered a reasonably good model for acyclic ion **8**, then its failure to close implies that the cleavage–recombination mechanism is incorrect.

There are at least two alternative mechanisms that can be considered which fit the available data and which avoid an acyclic intermediate. The first (Scheme IVa) involves a rehybridization of the vinyl system followed

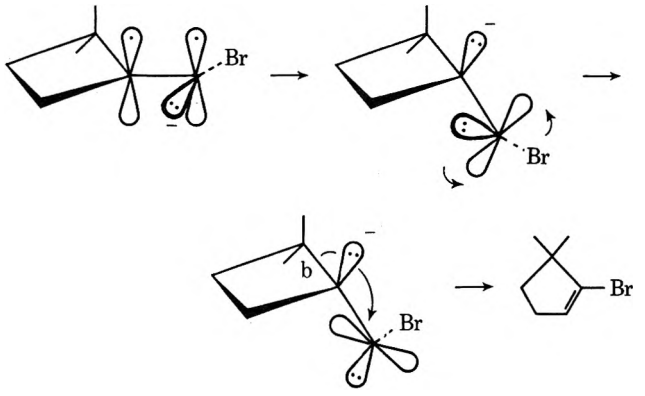
(4) C. C. Price and R. G. Gillis, *J. Amer. Chem. Soc.*, **75**, 4750 (1953).
(5) M. R. Johnson and B. Rickborn, *Org. Syn.*, **51**, 11 (1971).
(6) H. J. Boonstra, L. Brandsma, A. M. Wiegman, and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, **78**, 252 (1959).
(7) A. Deljac, Z. Stefanac, and K. Balenovic, *Tetrahedron, Suppl.*, **8**, 33 (1966).
(8) S. A. Kandil and R. E. Dessy, *J. Amer. Chem. Soc.*, **88**, 3027 (1966); H. G. Richey and A. M. Rothman, *Tetrahedron Lett.*, 1457 (1968).

SCHEME IVa

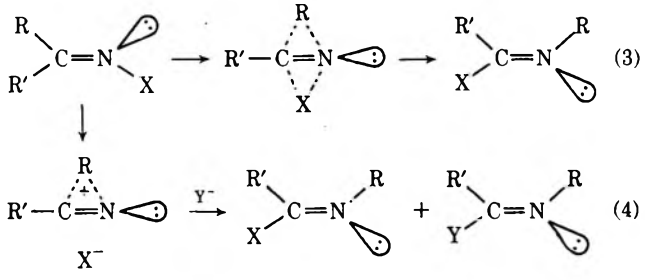


by rotation about the exocyclic bond in the direction indicated in order to avoid eclipsing of the two free-electron pairs and resulting in their maximum separation. At this point, the ring bond a is parallel to the empty lobe on the exocyclic carbon, and bond migration can occur. This migration involves transfer of an electron pair from an electron-rich site (carbanion) to an electron-poor site (carbene) and is analagous to a simple Wagner–Meerwein shift. Rehybridization and protonation give the final product. Using the same rationale, one obtains the proper product from the other isomer as well (Scheme IVb).

SCHEME IVb



A second possible mechanism is one analagous to the Beckmann rearrangement[9] (Scheme V). The Beckmann rearrangement proceeds with simultaneous trans migration of two groups (eq 3). Apparent cis migrations are



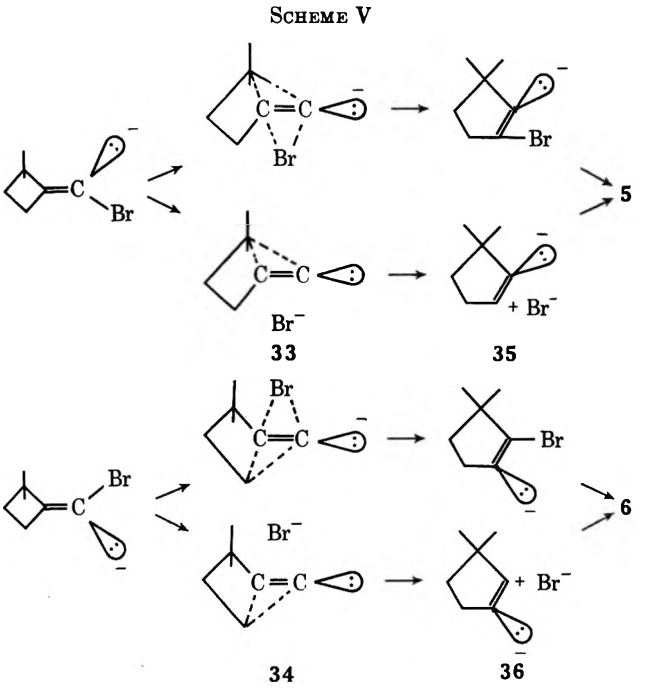
attributed to prior isomerization of starting materials.[10] In good solvents ion pairs are formed which may be trapped by extraneous counterions (eq 4).[11] If the

(9) L. G. Donaruma and W. F. Heldt, *Org. React.*, **11**, 1 (1960); P. A. Smith in "Molecular Rearrangements," Vol. 1, P. de Mayo, Ed., Interscience, New York, N. Y., 1963, p 483.

(10) P. T. Lansbury and N. R. Mancuso, *Tetrahedron Lett.*, 2445 (1965).

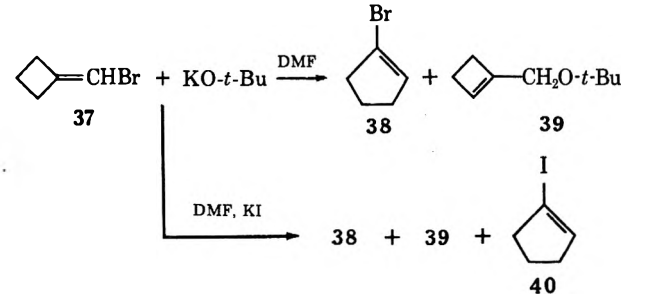
(11) C. A. Grob, H. P. Fischer, W. Raudenbusch, and J. Zergenyi, *Helv. Chim. Acta*, **47**, 1003 (1964).

SCHEME V



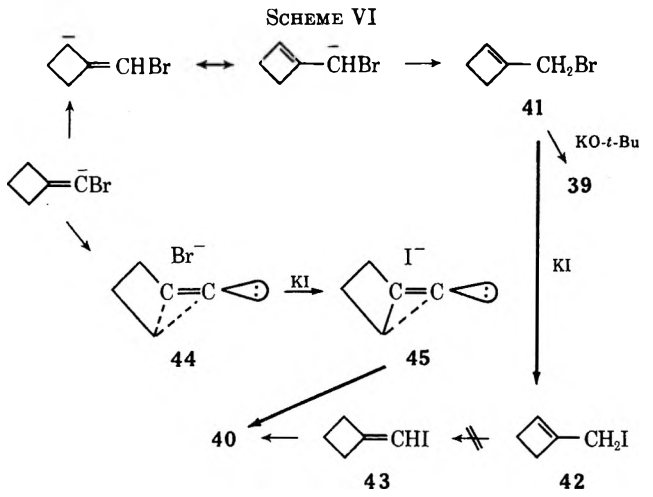
analogy holds for the vinyl bromide case, a carbene–bromide complex (**33**, **34**) would form in good solvents, leading directly to a cyclopentyne–bromide complex (**35**, **36**). In poor solvents or no solvent (as the reaction is normally run) the migration of the two groups may be synchronous with no apparent intermediates other than the initial and final carbanions. In this mechanism the ring carbon migrating for a given isomer is different from the one migrating in the rehybridization mechanism (Scheme IV), but the bromide also migrates here, and the end result is the same.

When bromomethylenecyclobutane (**37**) is allowed to react with potassium *tert*-butoxide in DMF (80°), the course of the reaction changes from that observed in the absence of solvent. With DMF the volatile products consist of a mixture of 20–25% 1-bromocyclopentene (**38**) and 75–80% 1-*tert*-butoxymethylcyclobutene (**39**). If the DMF reaction is run in the presence of added bromide ion (as KBr), the ratio of **38** to **39** rises to 35:65, and, when iodide ion is present (as KI), roughly equal quantities of **38** and **39** are produced, and the major product (35–55% of the volatile product mixture) is 1-iodocyclopentene (**40**).



1-*tert*-Butoxymethylcyclobutene (**39**) most likely arises from isomerization of the vinylic ion to the allylic ion followed by displacement of the bromide (Scheme VI). The presence of a good solvent permits isomerization to take place. In the absence of solvent, or in poor solvents, no isomerization occurs and **38** is the sole volatile product.

SCHEME VI

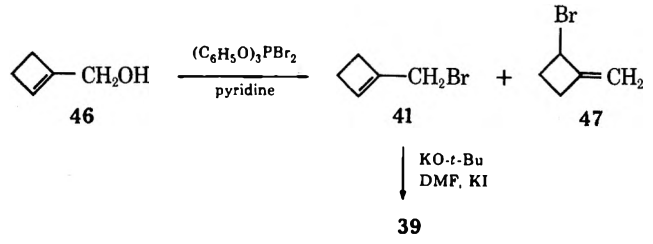


The critical question is whether 1-iodocyclopentene (**40**) arises simply from allyl bromide **41** giving allyl iodide **42** followed by isomerization back to the vinyl system **43** and then rearrangement, or whether **40** arises from trapping of an intermediate carbene–bromide complex (**44**) as postulated for the Beckmann mechanism (see Scheme VI).

Allylic halides **41** and **42** are not found in the product mixture; their conversion to **39** would be expected to be rapid. Once formed, **39** persists; it is stable to the reaction conditions. Other possible sources of 1-iodocyclopentene similiarly can be ruled out. Thus, 1-bromocyclopentene with potassium iodide and potassium *tert*-butoxide under the reaction conditions is recovered unchanged, and bromomethylenecyclobutane does not react with potassium iodide in DMF in the absence of potassium *tert*-butoxide. It remains, then, to determine whether allylic bromide **41** can revert to the vinyl system, and, with added iodide, whether **41** can give rise to **43** and thence **40**.

The synthesis of 1-bromomethylcyclobutene (**41**) was carried out as shown in Scheme VII. 1-Cyclobutene-

SCHEME VII



methanol (**46**) was prepared by the multistep method of Heyns and coworkers.[12] Various attempts were made to convert this alcohol to **41**, all of which resulted in mixtures of **41** and **47**. The method shown gave the best ratios of **41** to **47** (75:25).

These isomers did not resolve on the vpc (Carbowax), but nmr readily showed the presence of both. No serious attempt was made to achieve vpc separation, however, as it was expected that **41** would open to diene **48** on the instrument. This assumption is based upon the fact that cyclobutenes **39** and **46** both undergo partial ring opening to **49** and **50**, respectively, when collected from the vpc.

(12) K. Heyns, K. Molge, and W. Walter, *Ber.*, **94**, 1015 (1961).

48, X = Br
49, X = O-*t*-Bu
50, X = OH

Upon reaction with potassium *tert*-butoxide in DMF, with or without added iodide, **41** (25% **47**) gave good yields of 1-*tert*-butoxymethylcyclobutene (**39**). No bromomethylenecyclobutane (**37**) or 1-bromocyclopentene (**38**) were observed in the product mixture, nor were any organic iodides isolated when iodide ion was present. These results show that the allylic system does not revert to the vinylic system. Hence the formation of iodocyclopentene (**40**) from bromomethylenecyclobutane (**37**) and potassium iodide under the rearrangement reaction conditions is evidence for an intermediate whose halide can become detached. A carbene–bromide complex such as **44** postulated for the Beckmann mechanism is such an intermediate.

In the absence of solvent, bromomethylenecyclobutane (**37**) reacts with a mixture of potassium *tert*-butoxide and potassium iodide to give only the ring-enlarged bromide **38** in addition to recovered starting material. The presence of the additional solid (KI) hinders contact between **37** and the base with consequent slowing of the reaction. That no 1-iodocyclopentene is formed may be attributed to the heterogeneity of the reaction mixture and/or lack of formation of a carbene–ion complex. In the absence of a good stabilizing solvent, the rearrangement probably proceeds with simultaneous migration of both the ring carbon and the bromide as in the Beckmann rearrangement.

With molten potassium hydroxide serving as both the solvent and the base, bromomethylenecyclobutane (**37**) rearranges to **38** with about 50% conversion. With added iodide, product mixtures consist of 65% recovered **37**, 30% rearranged bromide (**38**), and 5% 1-iodocyclopentene (**40**). The allylic alcohol **46** was not found.

In summary, the uniqueness of halomethylenecyclobutanes to rearrange to 1-halocyclopentenes has been further demonstrated. This ring-enlargement reaction appears to proceed *via* the mechanism established for the Beckmann rearrangement rather than the cleavage–recombination mechanism originally postulated. Labelling experiments would provide definitive evidence for the double-migration mechanism.

Experimental Section

Melting and boiling points are uncorrected. Infrared spectra were recorded on Perkin-Elmer Models 137 and 337 spectrophotometers. The nmr spectra were recorded with a Jeolco Model C-60H spectrometer, using tetramethylsilane as an internal standard. Mass spectra were determined on a Hitachi Perkin-Elmer RMU-6D mass spectrometer. Vapor phase chromatographic analyses were performed on a Varian Aerograph Model 90-P3 chromatograph with the following columns: Carbowax 20M, QF-1, SE-30, SF-96, and FFAP (all columns were 20% stationary phase on a 60/80 Chromosorb W A/W DMCS support) and on a Varian Aerograph Model 600-D with the following columns: 5% QF-1 on 60/80 Chromosorb W and 3% SE-30 on 100/120 Chromosorb W. Elemental analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn., and Atlantic Microlab, Inc., Atlanta, Ga.

1-Methylcyclobutanemethanol (11).—In a 500-ml flask equipped with a dropping funnel, overhead stirrer, condenser, and drying tube were placed 200 ml of anhydrous ether and 6.46 g (0.170 mol) of lithium aluminum hydride. The resultant suspension was stirred while 15.60 g (0.136 mol) of 1-methylcyclobutanecarboxylic acid[2] in 60 ml of anhydrous ether was added at a rate to maintain gentle reflux. After all of the acid was added, the mixture was refluxed for 3 hr. While the reaction mixture was cooled in ice, a saturated solution of sodium sulfate was added dropwise until the magnesium salts coagulated. The mixture was then filtered, the solid was washed well with ether, and the filtrate was dried over $MgSO_4$. The ether was removed, and the residue was distilled to give 11.5 g (85%) of product: bp 70–71° (32 mm); ir (neat) 2.91, 3.35, 6.86, 7.27, 9.55, 9.77 μ; nmr ($CDCl_3$) δ 1.13 (s, 3 H), 1.80 (m, 6 H), 1.98 (s, 1 H), 3.47 (s, 2 H).

Anal. Calcd for $C_6H_{12}O$: C, 71.95; H, 12.08. Found: C, 72.13; H, 12.07.

1-Chloromethyl-1-methylcyclobutane (9).—The procedure of Downie and coworkers[13] was adapted for the preparation of this compound. A mixture of 8.0 g (0.08 mol) of 1-methylcyclobutanemethanol, 17 g (0.12 mol) of reagent grade carbon tetrachloride, and 20 ml of anhydrous ether was cooled in an ice bath with stirring while 13.0 g (0.08 mol) of hexamethylphosphorus triamide in 20 ml of anhydrous ether was added dropwise. An immediate reaction occurred with the formation of an orange-brown color. Toward the end of the addition, a brown oil separated. The mixture was warmed to room temperature and the ether was distilled, leaving a one-phase residue which was flash distilled. The distillate was then fractionated at atmospheric pressure to give a forerun of chloroform and carbon tetrachloride and 8.0 g (85%) of product: bp 122–123°; ir (neat) 3.36, 6.90, 7.01, 7.30, 7.82, 7.90, 13.0–14.4 μ; nmr (CCl_4) δ 1.21 (s, 3 H), 1.85 (m, 6 H), 3.52 (s, 2 H).

Anal. Calcd for $C_6H_{11}Cl$: C, 60.76; H, 9.35. Found: C, 60.73; H, 9.34.

On passage through the vpc, the chloride was partially converted to a hydrocarbon identified as 1-methylcyclopentene by comparison with authentic material.

Reaction of 1-Chloromethyl-1-methylcyclobutane (9) **with Potassium *tert*-Butoxide.**—In a flask equipped with a condenser, drying tube, and rubber serum cap was placed 0.62 g (0.0055 mol) of potassium *tert*-butoxide. This was heated to a bath temperature of 100–105°, and 0.59 g (0.0050 mol) of the chloride was injected by syringe through the serum cap. There was no obvious reaction. The mixture was kept at 100–105° for 30 min and then cooled, and water was added. Extraction with pentane gave an organic phase which was washed five times with water, and then dried, and the pentane was distilled. The residue consisted solely of starting alkyl chloride.

The reaction was repeated at a bath temperature of 200–205° for 30 min with the same results.

Deuterium Exchange Studies with 1-Chloromethyl-1-methylcyclobutane (9).—A mixture of 1.18 g (0.010 mol) of the chloride, 1.68 g (0.015 mol) of potassium *tert*-butoxide, and 5 ml of *tert*-butyl alcohol-*O*-*d* was refluxed for 3 days. Work-up as above gave recovered alkyl chloride with no detectable deuterium incorporation and 10% of a new compound which was not identified, but the ir (CCl_4) strongly suggests that it is 1-*tert*-butoxymethyl-1-methylcyclobutane (3.36, 6.84, 7.20, 7.33, 8.32, 9.19 μ).

Attempted Wittig Reaction of Ethylthiomethylenetriphenylphosphorane[3] with Cyclobutanone.—A THF suspension of 8.57 g (0.024 mol) of methyltriphenylphosphonium bromide was treated with 11.4 ml (0.024 mol) of 2.1 *M* phenyllithium solution. The mixture was stirred at 25° for 3 hr and then 0.012 mol of ethanesulfenyl chloride was added, and stirring was continued for 3 hr. To this mixture was added 0.84 g (0.012 mol) of cyclobutanone dropwise. The mixture was refluxed for 15 hr, poured onto ice, and extracted with ether. The ether was dried and removed to give a residue which was flash distilled. The distillate consisted of diethyl disulfide, cyclobutanone, and aromatic compounds. No ethylthiomethylenecyclobutane was detected.

Addition of Ethanesulfenyl Chloride to Methylenecyclobutane.—Ethanesulfenyl chloride was prepared by the method reported for the methyl isomer.[14] To 3.05 g (0.025 mol) of diethyl disulfide at −15 to −20° was added dropwise 3.38 g (0.025 mol) of sulfuryl chloride. The solution turned orange. It was warmed to 25° and distilled at 65 mm; the material boiling at 35–40° was collected [lit.[15] bp 39° (58 mm)].

Ethanesulfenyl chloride was added dropwise to 0.8 g (0.0117 mol) of methylenecyclobutane dissolved in methylene chloride cooled to −40° until a slight orange color persisted. The solvent was removed and the residue was distilled to give material boiling over a 10° range (49–59° at 10 mm). Vpc showed it to be one major product (~90%) contaminated with two other materials. The major compound **17** partially rearranged on the vpc (forming 1-ethylthio-1-cyclopentene), and spectral data were gathered directly on the distillates: ir (neat) 3.38, 6.89, 6.97, 7.23, 7.79, 7.89, 12.74, 13.60, 14.20 μ; nmr (CCl_4) δ 1.23 (t, 3 H), 1.6–2.8 (m, 8 H), 3.58 (s, 2 H). Because of the difficulty of purifying this material, an analysis was not obtained.

1-Ethoxymethyl-1-ethylthiocyclobutane (18).—Chlorosulfide **17** (0.82 g, 0.005 mol) was added to a solution of 0.4 g of KOH in 95% ethanol. The mixture was stirred at 25° for 2 hr and was then poured into ice and extracted with pentane. The pentane layer was washed with water and dried, and the pentane was removed. Distillation of the residue afforded 0.5 g (66%) of **18**: bp 52–54° (1.3 mm); ir (neat) 3.38, 3.50, 6.95, 7.29, 7.41, 7.92, 8.55, 9.02 μ; nmr (CCl_4) δ 1.22 (t, 6 H), 1.6–2.8 (m, 8 H), 3.35 (s, 2 H), 3.51 (q, 2 H).

Anal. Calcd for $C_9H_{18}OS$: C, 62.02; H, 10.41. Found: C, 62.21; H, 10.46.

1-(Ethylthiomethyl)cylcobutanol (20).—To 33 ml (0.0082 mol) of 10% NaOH was added 0.51 g (0.0082 mol) of ethanethiol. To this was then added dropwise 1.35 (0.0082 mol) of 1-(bromomethyl)cyclobutanol (19).[1b] The opaque mixture was stirred at 25° for 30 min, at the end of which time the oil had migrated from the bottom of the water layer to the top. The mixture was extracted with ether, the ether layer was dried, and the ether was removed. Distillation afforded 0.90 g (73%) of **20**: bp 51–53° (0.5 mm); ir (neat) 2.89, 3.36, 6.8–7.5, 7.7–8.2, 8.5–8.9, 9.20, 10.34, 10.88, 13.44 μ; nmr ($CDCl_3$) δ 1.22 (t, 3 H), 1.7–2.3, and 2.5–3.0 (m, 9 H).

Anal. Calcd for $C_7H_{14}OS$: C, 57.49; H, 9.65. Found: C, 57.51; H, 9.68.

Attempted Dehydration of 1-(Ethylthiomethyl)cyclobutanol (20).—To a mixture of 0.760 g (0.0050 mol) of phosphorus oxychloride in 8 ml of anhydrous pyridine at ice temperature was added 0.68 g (0.0046 mol) of the alcohol. A precipitate formed readily. The mixture was stirred at 25° overnight and was then poured onto ice and extracted with pentane. The pentane was washed with water, dried, and removed. The residue was distilled to give 0.5 g (65%) of 1-chloromethyl-1-ethylthiocyclobutane (17). A small amount (~15%) of another compound was present in the distillate, possibly the isomer, 1-(ethylthiomethyl)cyclobutyl chloride. No olefin was detected.

A second attempt at dehydration of **20** was made with powdered potassium hydroxide at 250°.[4] No vinyl sulfide was produced.

Cyclobutanecarboxaldehyde (21). **Method A.**[16,17]—To 11.85 g (0.100 mol) of cyclobutanecarbonyl chloride was added dropwise 16.60 g (0.100 mol) of triethyl phosphite at a rate to keep the internal temperature below 35°. The reaction was run in a nitrogen atmosphere. After the phosphite was completely added, the mixture was stirred at 25° for 30 min. Distillation at 1.7 mm afforded 18.2 g (83%) of **22** boiling at 103–104°: ir (neat) 5.88, 7.95, 8.55, 9.0–10.8, 12.55, 13.25, 13.86 μ; nmr ($CDCl_3$) δ 1.37 (t, 6 H), 1.7–2.7 (m, 6 H), 3.4–4.0 (m, 1 H), 4.25 (pentet, 4 H).

Anal. Calcd for $C_9H_{17}O_4P$: C, 49.90; H, 7.78. Found: C, 49.21; H, 7.86.

A suspension of 6.60 g (0.03 mol) of phosphonate **22** in 30 ml of water was cooled to 0°, and a solution of 0.76 g (0.02 mol) of sodium borohydride in 60 ml of water was added alternately with 6.26 g (0.046 mol) of potassium dihydrogen phosphate. The pH of the mixture was thus maintained between 6 and 7. The mixture was stirred for 20 min at 25°, and it was then made strongly basic with 10% NaOH and steam distilled. The aldehyde was extracted from the distillate with ether. Distillation at atmospheric pressure gave 1.2 g (46%) of aldehyde, bp 113–

(13) I. M. Downie, J. B. Lee, and M. F. S. Matough, *Chem. Commun.*, 1350 (1968).

(14) K. Pfannstiel, H. Koddebusch, and K. Kling, *Ber.*, **83**, 84 (1950).

(15) H. Brintzinger and M. Langheck, *ibid.*, **86**, 557 (1953).

(16) K. D. Berlin and H. A. Taylor, *J. Amer. Chem. Soc.*, **86**, 3862 (1964).

(17) L. Horner and H. Roder, *Ber.*, **103**, 2984 (1970).

115° (lit.[5] bp 56–59° (120 mm). The aldehyde was not stored but was used immediately.

The steam distillation residue, upon acidification and ether extraction, gave 0.77 g (26%) of cyclobutanecarboxylic acid.

Method B.[18]—Cyclobutylmethanol was prepared by lithium aluminum hydride reduction of cyclobutanecarboxylic acid.

To an ice-cooled, stirred solution of 56.94 g (0.727 mol) of pyridine (dried over 4A molecular sieves) in 900 ml of methylene chloride (washed with concentrated H_2SO_4 and water, dried, and distilled onto 4A molecular sieves) was added portionwise 36.0 g (0.36 mol) of chromium trioxide (dried over P_2O_5). The red-brown suspension was warmed to 25° and stirred at this temperature for 15 min. Cyclobutylmethanol (5.16 g, 0.06 mol) was added all at once, and the mixture was stirred at 25° for 30 min.

The solution was decanted into a separatory funnel, and the gummy precipitate was washed several times with ether; the washings were added to the methylene chloride solution. This was washed with 5% NaOH (2 × 100 ml), 5% HCl (3 × 100 ml), 5% $NaHCO_3$ (2 × 100 ml), and brine. It was dried ($MgSO_4$), and the methylene chloride was distilled off through a 200-cm Vigreux column. The residue was distilled at atmospheric pressure to give a total of 4.0 g (80%) of cyclobutanecarboxaldehyde. Earlier boiling fractions were freed of methylene chloride by vpc collection (Carbowax, 125°).

Reaction of Cyclobutanecarboxaldehyde with Ethanethiol and Hydrogen Chloride.—The method of Boonstra and coworkers[6] was used. To 0.34 g (0.005 mol) of aldehyde cooled to −40° was added dropwise 0.31 g of ethanethiol while a rapid stream of hydrogen chloride was bubbled through the mixture. A solid formed. The mixture was taken up in ether and dried, and the ether was removed. The residue was not the chloro sulfide but instead the diethyl thioacetal of cyclobutanecarboxaldehyde (**24**).

Attempted Elimination of Ethanethiol from Thioacetal 24.—The procedure of Boonstra and coworkers[6] was followed. The thioacetal was placed in a minidistillation apparatus with a drop of 85% phosphoric acid. The system was evacuated to 110 mm and heated to an oil-bath temperature of 145°, at which point violent decomposition occurred. Very little distillate was obtained and much residue remained. The only component in the distillate identified was starting material.

Diethyl Thioacetal of Cyclobutanecarboxaldehyde (24).—To a mixture of 3.30 g (0.039 mol) of the aldehyde and 60 mg of *p*-toluenesulfonic acid cooled in an ice bath was added dropwise 5.27 g (0.085 mol) of thioethanol. An immediate reaction generally occurred with separation of water. The mixture was heated at an oil-bath temperature of 70° for 10 hr; it was then poured into 10% NaOH and extracted with ether. The ether extract was dried, and the ether was removed. Distillation of the residue gave 6.3 g (85%) of thioacetal: bp 69–70° (0.6 mm); ir (neat) 3.35, 6.90, 7.25, 7.88, 7.97, 10.23, 12.46, 12.73, 13.48 μ; nmr (CCl_4) δ 1.25 (t, 6 H), 1.6–2.3 (m, 7 H), 2.64 (q, 4 H), 3.72 (d, 1 H).

Anal. Calcd for $C_9H_{18}S_2$: C, 56.78; H, 9.53. Found: C, 56.91; H, 9.62.

Ethylthiomethylenecyclobutane (15).—The general method of Deljac and coworkers[7] was used. To an ether solution of 4.9 g (0.0257 mol) of **21** cooled in ice was added dropwise an ether solution of 5.10 g (0.0257 mol) of 85% *m*-chloroperbenzoic acid. The ether was then stripped off, and methylene chloride was added to precipitate most of the *m*-chlorobenzoic acid, which was then filtered. The filtrate was washed with $NaHCO_3$ solution and dried, and the methylene chloride was removed to give 4.9 g (93%) of crude sulfoxide **25**: ir (neat) 3.36, 6.91, 7.39, 7.95, 9.52, 9.83, 10.31, 12.80, 13.60, 14.22 μ. It was not purified but was pyrolyzed directly.

The sulfoxide (1 g) was placed in a 5-ml round-bottom flask stuffed with glass wool and attached to a minidistillation setup. The pressure was reduced to 15 mm, and the flask was heated to a bath temperature of 150–160°. The distillate (0.45 g, 71%) generally contained ~10% impurities. The vinyl sulfide was purified by vpc (Carbowax, 125°): ir (neat) 3.38, 6.02, 6.88, 7.01, 7.25, 7.90, 12.18, 13.04, 13.76 μ; nmr (CCl_4) δ 1.24 (t, 3 H), 1.8–2.4 (m, 2 H), 2.4–3.0 (m, 6 H), 5.57 (m, 1 H).

Anal. Calcd for $C_7H_{12}S$: C, 65.56; H, 9.44. Found: C, 65.54; H, 9.49.

Reaction of Ethylthiomethylenecyclobutane (15) with Potassium *tert*-Butoxide.—The reaction was run as described for **9**. In no case was there any 1-ethylthiocyclopentene (**26**) produced. The starting material was recovered unchanged.

1-Ethylthio-1-cyclopentene (26).—This material was prepared by the method of Brandsma.[19] The vinyl sulfide was purified by vpc (Carbowax, 125°): ir (neat) 3.26 3.38, 6.22, 6.89, 7.24, 11.7–13.5 μ; nmr (CCl_4) δ 1.26 (t, 3 H), 1.8–2.2 (m, 2 H), 2.2–2.8 (m, 4 H), 2.75 (q, 2 H, overlapping allylic H's), 5.28 (m, 1 H).

Deuterium Exchange Studies with Ethoxymethylenecyclobutane (12).—The vinyl ether[1b] (150 mg) and 200 mg of potassium *tert*-butoxide were dissolved in 2 ml of *tert*-butyl alcohol-*O*-*d*, and the mixture was refluxed for 3 hr to 6 days. In no case was there any detectable vinyl (or allylic) hydrogen exchange (nmr, mass spectrum).

Deuterium Exchange Studies with Ethylthiomethylenecyclobutane (15).—The vinyl sulfide (150 mg) and 300 mg of potassium *tert*-butoxide were dissolved in 3 ml of *tert*-butyl alcohol-*O*-*d* and the mixture was refluxed for 3 days. Both nmr and mass spectrum indicated vinylic and allylic H exchange. The predominant isomers were d_4 and d_3, but some d_5 and d_6 were also formed.

5-Chloro-4-pentyn-1-ol (29).—A solution of potassium hypochlorite was prepared from 39.0 g of HTH[20] and was cooled in an ice bath. To this was added all at once 11.04 g (0.093 mol) of 4-pentyn-1-ol[21] and 60 ml of pyridine. The two-phase reaction mixture was stirred vigorously at 10–20° for 8 hr, and then it was extracted with ether. The ether extract was washed with water, 6 *N* HCl, water, and $NaHCO_3$ solution and was dried over $MgSO_4$, and the ether was removed *in vacuo*. On distillation, the residue afforded a forerun of starting material (1.1 g) and 7.6 g (50%) of 5-chloro-4-pentyn-1-ol (**29**): bp 86–87° (10 mm); ir (neat) 3.00, 3.38, 4.46, 9.46 μ; nmr ($CDCl_3$) δ 1.75 (pentet, 2 H), 2.23 (s, 1 H), 2.40 (m, 2 H), 3.77 (t, 2 H).

Anal. Calcd for C_5H_7ClO: C, 50.35; H, 5.95. Found: C, 50:51; H, 5.97.

1-Chloro-5-bromo-1-pentyne (30).—Triphenyl phosphite dibromide[22] was prepared as follows. To 22.32 g (0.072 mol) of triphenyl phosphite cooled in an ice bath was added dropwise 11.52 g (0.072 mol) of bromine. An instantaneous reaction occurred with the formation of a yellow-orange solid. After complete addition of the bromine, the mixture was stirred at ice temperature until the bromine color disappeared.

A mixture of 7.80 g (0.066 mol) of 5-chloro-4-pentyn-1-ol (**29**) and 5.70 g (0.073 mol) of pyridine was added dropwise to the ice-cooled triphenyl phosphite dibromide. The mixture was allowed to warm slowly (1 hr) to room temperature while the orange solid became a white paste. The mixture was poured into ice and extracted with ether. The ether extracts were washed with cold 6 *N* HCl and water, then dried over $MgSO_4$. After removal of the ether, the residue was distilled to give 5.9 g (50%) of 1-chloro-5-bromo-1-pentyne (**30**): bp 79–80° (12 mm); ir (neat) 3.40, 4.45, 6.97, 7.84, 8.01, 11.73, 12.5–13.3 μ; nmr (CCl_4) δ 1.8–2.6 (m, 4 H), 3.50 (t, 2 H).

Anal. Calcd for C_5H_6BrCl: C, 33.10; H, 3.33. Found: C, 33.34; H, 3.41.

1-Chloro-1-pentyne (32).—A solution of potassium hypochlorite was prepared from 9.7 g of HTH.[20] To this was added at ice temperature 2.21 g (0.032 mol) of 1-pentyne and 15 ml of pyridine. The mixture was then stirred vigorously at 25° for 4 days. It was worked up in the same manner as 5-chloro-4-pentyn-1-ol (**29**). Atmospheric distillation afforded a forerun of starting material and 0.9 g (28%) of 1-chloro-1-pentyne (**32**): bp 92° (lit.[23] bp 92°); ir (CCl_4) 3.34, 4.42, 6.83, 6.98, 7.23, 9.15, 9.24, 11.33, 14.28 μ.

Reaction of 1-Chloro-5-bromo-1-pentyne (30) with Magnesium and Lithium Reagents.—To 0.24 g (0.01 g-atom) of magnesium in anhydrous ether in a nitrogen atmosphere was added 1.8 g (0.01 mol) of 1-chloro-5-bromo-1-pentyne dropwise. Some difficulty was experienced in initiating the reaction and in keeping it going once it had started. When vpc indicated that most of the starting material had reacted, the mixture was poured into ice water and was extracted with ether. The ether extracts were dried, and the ether was removed by distillation. The volatile

(18) R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970).

(19) L. Brandsma, *Recl. Trav. Chim. Pays-Bas*, **89**, 593 (1970).

(20) M. S. Newman and H. L. Holmes, *Org. Syn.*, **17**, 65 (1937), note 1.

(21) E. R. H. Jones, G. Eglinton, and M. C Whiting, *ibid.*, **33**, 68 (1953).

(22) D. G. Coe, S. R. Landauer, and H. N. Rydon, *J. Chem. Soc.*, 2281 (1954).

(23) J. Normant, *Bull. Soc. Chim. Fr.*, 1876 (1963).

products were isolated by flash distillation and examined by vpc (Carbowax, 70°). The major product was identified as 1-chloro-1-pentyne, and no 1-chlorocyclopentene[24] could be detected. A substantial amount of higher molecular weight material was produced which was not investigated further. This reaction was repeated several times with the same results.

This halide showed no tendency to react with elemental lithium. It did, however, react with *n*-butyllithium, giving much the same results as the magnesium reaction.

1-Bromomethylcyclobutene (41).[12,25]—1-Cyclobutenemethanol (46) was prepared by the multistep method of Heyns and coworkers.[12] On vpc it underwent some ring opening to 2-hydroxymethyl-1,3-butadiene (50).[26]

Triphenyl phosphite dibromide[22] was prepared from 2.08 g (0.013 mol) of bromine and 4.03 g (0.013 mol) of triphenyl phosphite. To this was added dropwise with ice cooling a mixture of 1.0 g (0.012 mol) of 1-cyclobutenemethanol and 1.03 g (0.013 mol) of anhydrous pyridine. After the mixture had been stirred for 1 hr at 25°, it was flash distilled to give 0.6 g of distillate. Nmr (CCl_4) showed it to be a mixture of 75% 1-bromomethylcyclobutene (41) and 25% 2-methylenecyclobutyl bromide[25] (47): δ 2.5 (m), 3.8 (broad singlet), 4.8–5.3 (m, $=CH_2$), 6.0 (m, =CH). The ratio of vinyl H's was used to determine the composition of the mixture.

The ratio of endo to exo isomer varied from run to run and the composition of the mixture appeared to change on standing. Some runs afforded the inverse ratio of 75% 41 to 25% 47.

Reactions of Vinylic and Allylic Bromides with Potassium *tert*-Butoxide in DMF. General Procedure.—A slight excess of potassium *tert*-butoxide was dissolved in dry DMF and heated to a bath temperature of 80–90°. The bromide was injected beneath the surface of the hot solution and stirring was continued for 5–30 min.

The solution was cooled and water was added. The aqueous reaction mixture was extracted with pentane, and the pentane extracts were washed several times with water and finally with brine. The extracts were dried over $MgSO_4$, and the pentane was removed by distillation. The residue was generally flash distilled and the distillate was examined by vpc.

In reactions utilizing extraneous bromide or iodide ion, the DMF solution was saturated (80–90°) with powdered KBr or KI before injection of the vinyl or allyl bromide.

A. With Bromomethylenecyclobutane (37).—The vinyl bromide (40 μl) was injected into a solution of 60 mg of potassium *tert*-butoxide in 2 ml of dry DMF at a bath temperature of 80–90°. Work-up afforded a volatile product mixture consisting of 20–25% 1-bromocyclopentene[1b] and 75–80% 1-*tert*-butoxymethylcyclobutene (39). The latter compound displayed ir (neat) 3.28, 3.38, 6.05, 6.82, 7.20, 7.32, 8.33, 9.34, μ; nmr (CCl_4) δ 1.21 (s, 9 H), 1.40 (m, 4 H), 3.73 (m, 2 H), 5.73 (m, 1 H). On the vpc this compound underwent partial ring opening to 2-*tert*-butoxymethyl-1,3-butadiene (49): ir (neat) 3.22, 3.35, 5.51 (w), 6.28, 7.31, 7.37, 8.39, 9.06, 11.07 μ; nmr (CCl_4) δ 1.22 (s, 9 H), 3.98 (m, 2 H), 4.8–5.4 (m, 4 H), 6.31 (q, further split, 1 H).

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found (mixture of 39 and 49): C, 76.99; H, 11.55.

When the reaction was carried out in the presence of added KBr, the ratio of 39 to 38 was 65:35. With added KI, the ratio of 39 to 38 was ~50:50, and the total volatile product consisted of 35–55% 1-iodocyclopentene.[1b]

B. With 1-Bromomethylcyclobutene (41).—The allyl bromide (0.37 g), contaminated with 2-methylenecyclobutyl bromide, was injected into a solution of 0.42 g of potassium *tert*-butoxide and 2 ml of DMF at a bath temperature of 85°. Work-up afforded a volatile product mixture consisting of >90% 1-*tert*-butoxymethylcyclobutene (39). No 1-bromocyclopentene (38) or bromomethylenecyclobutane (37) were detected.

This reaction was carried out several times in the presence of KI. In no case was any 1-iodocyclopentene (40) observed as a product.

C. With 1-Bromocyclopentene (38).—The vinyl bromide (40 μl) was injected into a solution of 60 mg of potassium *tert*-butoxide and 1.2 g of KI in 3 ml of dry DMF at 85–90°. Work-up afforded only recovered starting material.

Reaction of Bromomethylenecyclobutane (37) with Potassium Iodide in DMF.—The vinyl bromide (20 μl) was injected into a DMF solution of 600 mg of KI at a bath temperature of 85–90°. The mixture was kept at this temperature for 10 min. Work-up as in the general procedure above afforded only recovered vinyl bromide.

Reaction of Bromomethylenecyclobutane (37) with Potassium *tert*-Butoxide and Potassium Iodide in the Absence of Solvent.—A mixture of 30 mg of potassium *tert*-butoxide and 300 mg of KI was ground together and heated to a bath temperature of 85°. The vinyl bromide (20 μl) was injected. Work-up afforded a mixture of 1-bromocyclopentene (38) and recovered starting material (37) in a ratio of 1:3. There was no 1-iodocyclopentene (40) detected.

Reaction of Bromomethylenecyclobutane (31) with Molten Potassium Hydroxide. A. In the Absence of Potassium Iodide.—The vinyl bromide (0.4 g) was injected into 1 g of molten KOH at a bath temperature of 180° and held at that temperature for 30 min. Work-up afforded about a 50:50 mixture of 1-bromocyclopentene (38) and recovered bromomethylenecyclobutane (37). No other volatile products were present.

B. In the Presence of Potassium Iodide.—This reaction was run several times in the same manner as for part A, but with added powdered KI (~500 mg). Work-up afforded product mixtures generally consisting of 30% 1-bromocyclopentene (38), 65% recovered bromomethylenecyclobutane (37), and 5% 1-iodocyclopentene (40).

Registry No.—**9,** 38401-40-0; **10,** 32936-76-8; **11,** 38401-41-1; **15,** 38401-42-2; **17,** 38401-43-3; **18,** 38401-44-4; **19,** 30800-70-5; **20,** 38401-46-6; **21,** 2987-17-9; **22,** 38401-48-8; **24,** 38401-49-9; **25,** 38401-50-2; **28,** 5390-04-5; **29,** 38401-51-3; **30,** 1192-04-7; **38,** 38401-52-4; **39,** 38401-53-5; **49,** 38401-54-6; cyclobutanecarbonyl chloride, 5006-22-4; *m*-chloroperbenzoic acid, 937-14-4.

Acknowledgments.—We thank Professor J. Wolinsky, Purdue University, for valuable suggestions during the course of this work, Sister M. R. Brennan, S. L., University of Hawaii, for determining the mass spectra, and Mr. R. Laurenitis for assistance in the synthesis of 1-chloromethyl-1-methylcyclobutane.

(24) L. K. Montgomery, F. Scardiglia, and J. D. Roberts, *J. Amer. Chem. Soc.*, **87**, 1917 (1965).

(25) E. R. Buchman and D. R. Howton. *J. Amer. Chem. Soc.*, **70**, 2517 (1948).

(26) W. J. Bailey, W. G. Carpenter, and M. E. Hermes, *J. Org. Chem.*, **27**, 1975 (1962); W. J. Bailey and M. E. Hermes, *ibid.*, **27**, 2732 (1962).

The Reactions of 1,1,2,2-Tetrachloro-3,4-bis(dichloromethylene)cyclobutane with Amines

DAVID KRISTOL*

Department of Chemical Engineering and Chemistry, Newark College of Engineering, Newark, New Jersey 07102

ROBERT SHAPIRO

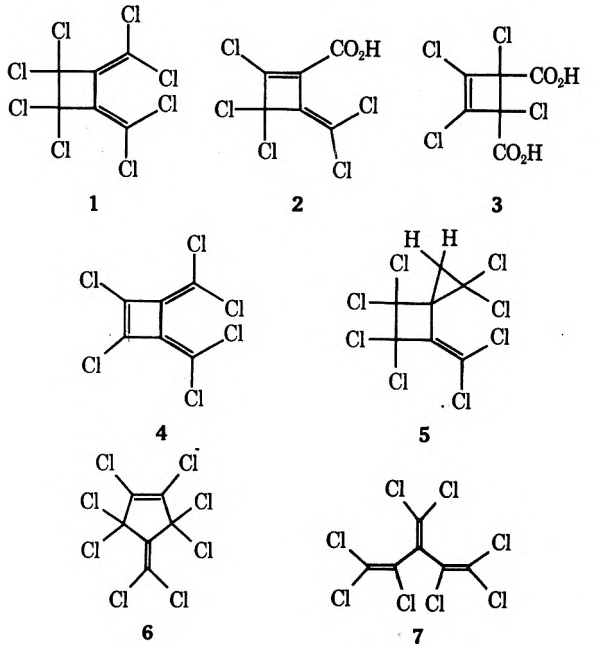
Department of Chemistry, New York University, New York, New York 10003

Received November 20, 1972

The title compound (1) reacts readily with ammonia to give 2-amino-3,3-dichloro-4-dichloromethylene-1-cyanocyclobutene. With primary or secondary aliphatic or aromatic amines, 1 affords N-substituted 2-alkyl (or aryl) amino-3,3-dichloro-4-dichloromethylenecyclobutenylcarboxamidinium chlorides. The reaction of 1 with phenylhydrazine proceeds with cyclization to give a cyclobutenopyrazole. The spectroscopic properties of these products, and of further transformation products derived from them, are described. A mechanism is proposed for the reaction.

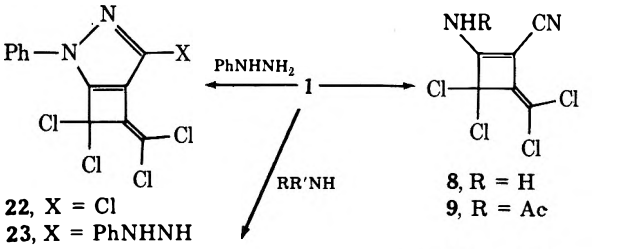
The reactions of small-ring chlorocarbons constitute a relatively unexplored area of organic chemistry. Nitriles,[1] ureas,[2] ketals,[3] oxazolidines,[3] ortho esters,[4] mercaptals,[5] and phenylhydrazones[6] have been prepared by the treatment of chlorocarbons with nucleophiles.

Compound 1,[7] 1,1,2,2-tetrachloro-3,4-bis(dichloromethylene)cyclobutane, which has been reported to yield 2 with sulfuric acid,[8] 3 with fuming nitric acid,[8]



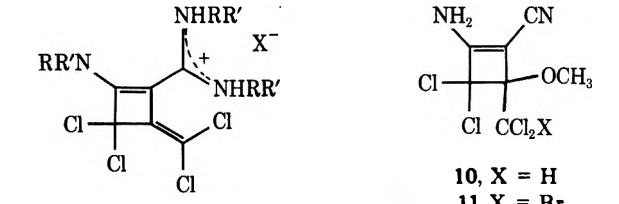
4 with a mixture of aluminum and aluminum chloride,[8] 5 with diazomethane,[9] 6 with aluminum chloride,[10] and 7 upon heating at 230°,[10] was selected as a possible source of novel reactions.

It was felt that the reactive sites of 1 might be susceptible to nucleophilic attack which would lead to dramatic functional changes. Indeed, reaction of 1 with various amines led to the formation of 8–23.



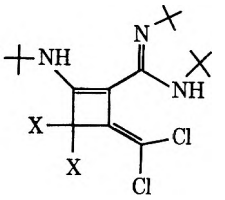
22, X = Cl
23, X = PhNHNH

8, R = H
9, R = Ac



12, R = H; R′ = *tert*-butyl; X = Cl
13, R = H; R′ = *tert*-butyl; X = NO_3
14, R = H; R′ = *tert*-butyl; X = HSO_4
15, R = H; R′ = isopropyl; X = Cl
16, R = CH_3; R′ = CH_3; X = Cl
17, R = H; R′ = Ph; X = Cl
18, R = H; R′ = *p*-CH_3Ph; X = Cl
19, R = H; R′ = *p*-CH_3OPh; X = Cl

10, X = H
11, X = Br



20, X = Cl
21, X = OCH_3

Results and Discussion

Reaction of 1 with ammonia in aqueous methanol at 4° yielded the aminonitrile 8, whose structure was established by means of spectral data and subsequent reactions. The uv spectrum indicated conjugated unsaturation; the ir spectrum displayed peaks attributable to NH_2 and conjugated nitrile (4.50 μ)[11] and two peaks assigned to C–C double bonds; the mass spectrum showed a molecular ion peak at *m/e* 242 with an isotopic cluster expected for four chlorine atoms.[12] The existence of an NH_2 was further established by the presence of broad, exchangeable protons in the nmr spectrum (which was notably lacking in CH absorp-

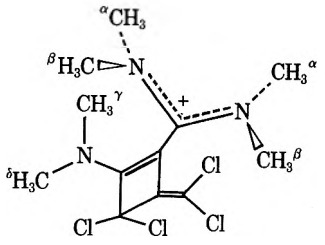
(1) (a) H. Khalaf, *Tetrahedron Lett.*, 4223 (1971); (b) S. W. Tobey and R. West, *ibid.*, 1179 (1963).
(2) T. G. Bonner and R. A. Hancock, *Chem. Ind. (London)*, 267 (1965).
(3) R. J. Knopf, *J. Chem. Eng. Data*, **16**, 486 (1971).
(4) H. Khalaf, *Tetrahedron Lett.*, 4239 (1971).
(5) E. P. Ordas, U. S. Patent 2,697,103 to Arvey Corp. (Dec 14, 1954).
(6) A. Roedig, G. Bonse, R. Helm, and R. Kolhaupt, *Chem. Ber.*, **104**, 3378 (1971).
(7) For the synthesis of 1 see W. M. Wagner and H. Kloosterziel, *Recl. Trav. Chim. Pays-Bas*, **81**, 925 (1962).
(8) (a) A. Roedig, B. Heinrich, F. Bischoff, and G. Markl, *Justus Liebigs Ann. Chem.*, **670**, 8 (1963); (b) J. Brandmuller and E. Ziegler, *Z. Anal. Chem.*, **200**, 299 (1964).
(9) A. Roedig and B. Heinrich, *Chem. Ber.*, **100**, 3716 (1967).
(10) G. Maahs, *Angew. Chem.*, **75**, 451 (1963).
(11) R. T. Conley, "Infrared Spectroscopy," Allyn and Bacon, Boston, Mass., 1966, p 116. Conjugated nitriles absorb in the 4.48–4.50-μ region, as compared to 4.42–4.46 μ for the unconjugated nitriles.
(12) F. W. McLafferty, "Interpretation of Mass Spectra," W. A. Benjamin, New York, N. Y., 1967, p 22.

tion, thus excluding hydrolytic ring opening) and the formation of the acetyl derivative, **9**. The uv spectrum of **9** differed from that of **8**, suggesting that the amino group was attached to the chromophore.

Reaction of **8** with HCl in aqueous methanol and with bromine in methanol gave the addition products **10** and **11**, respectively. The nmr spectra of both **10** and **11** displayed peaks assigned to methoxy and amine protons. In addition, **10** showed a singlet at τ 3.91, consistent with a hydrogen attached to a carbon bearing two chlorines.[13] The most prominent peak in the mass spectra of both **10** and **11** at m/e 203, corresponded to the loss of CCl_2H and CCl_2Br, respectively, which suggested that **10** and **11** are structurally similar. The uv spectral maxima at 267 and 268 mμ, of **10** and **11**, support this conclusion. It was next decided to investigate the reactions of **1** with amines.

When **1** was treated with *tert*-butyl-, isopropyl-, and dimethylamine, aniline, *p*-toluidine, and *p*-anisidine, a series of compounds with similar properties, was produced and was assigned the amidinium structures **12** and **15–19**. Elemental analysis indicated that each product contained 3 mol of amine. Each amidinium salt possessed a band in its ir spectrum in the 6.15–6.25-μ region which was assigned to the amidinium group.[14] The ionic nature of these salts was established by measuring the electrophoretic mobility of **12** and **16**, conversion of **12** to the nitrate salt **13** and to the bisulfate salt **14**, and reconversion of **14** to **12** by ion exchange. The amidine **20** was prepared from and reconverted to **12**.

The nmr spectra of the amidinium salts were quite revealing. Compound **16** displayed four distinct peaks in D_2O in a 1:2:2:1 ratio. This spectrum can be rationalized in the following manner. The planar amidinium group is prevented by the olefinic chlorine from becoming coplanar with the ring and, therefore,

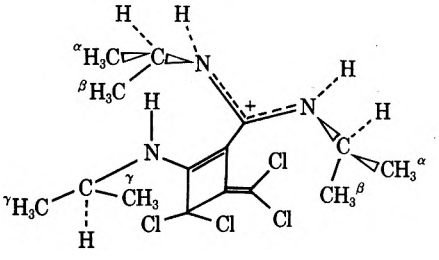


establishes a position orthogonal to the ring. Restricted rotation about the nitrogens of the amidinium group causes the attached methyls to be nonequivalent.[15] Thus the two internal α-methyls and the two external β-methyls form two sets of six identical protons. In addition, restricted rotation about the enamine nitrogen due to electron delocalization can cause the enamine methyls to be nonequivalent.[16] One would therefore expect the nmr spectrum of **16** to show four resonances in a 1:2:2:1 ratio.

The nmr spectrum of **12** in either $CDCl_3$ or C_6D_6–DMSO-d_6 displayed only two singlets, in a 1:2 ratio, for the *tert*-butyl groups. These spectra may be explained by assuming that the *tert*-butyl groups occupy the less crowded external amidinium positions, causing them to be magnetically equivalent. If the enamine *tert*-butyl preferentially occupies one position, or undergoes free rotation about the enamine nitrogen, a 1:2 ratio would be observed.

The isopropylamine product, **15**, displayed three doublets in its nmr spectrum, presumably because the isopropyl groups also occupy the external amidinium positions. Since the plane of symmetry of the molecule does not pass through the isopropyl methine carbons, the methyls of a given isopropyl group are magnetically nonequivalent.[17] However, the α- and β-methyls are equivalent. Since the enamine isopropyl methine carbon can lie in the plane of symmetry, the γ-methyls are equivalent. Each of these methyl absorptions would be split by the methine protons, thus generating the three observed doublets.

In an attempt to produce a cyclobutadiene derivative by a nucleophilic attack at the second dichloromethylene group, **12** was treated with KOH in methanol. However, instead of producing the desired product, the reaction yielded **21**. The equivalence of the methoxyls in it its nmr spectrum established that the product was formed by displacement of the ring chlorines rather than by displacement of the vinyl chlorines.



Because the reaction of **1** with amines had shown the presence of two reactive sites, it was anticipated that a bifunctional amine could produce a heterocyclic product. Phenylhydrazine was selected because attack by both nitrogens would lead to a stable five-membered ring. When **1** was treated with phenylhydrazine in a 1:4 molar ratio (3 mol was used to absorb the HCl which was produced), there was obtained **22**. When the reaction was run with a 1:6 molar ratio, **23** was produced. It was presumably formed by attack of phenylhydrazine on **22**. Strong peaks in the ir spectra of **22** and **23** at 6.58 and 6.64 μ, respectively, were attributed to the pyrazole rings.[18] The location of the phenyl ring in **22** and **23** has been inferred from mechanistic considerations (see the discussion below). However, the alternative structures **24** and **25** cannot be ruled out by the available physical and chemical evidence.

(13) The protons of 1,1,2,2-tetrachloroethane absorb at τ 4.06: F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy," Academic Press, New York, N. Y., 1969, p 252.

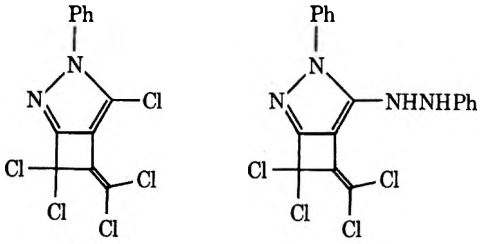
(14) The absorption of the C–N$^+$ bond of amidinium salts has been reported at 5.9–6.3 μ depending upon the specific molecule: (a) J. C. Grivas and A. Taurins, *Can. J. Chem.*, **37**, 1260 (1959); (b) P. Bassignana, C. Cogrossi, G. Polla-Mattiot, and S. Franco, *Ann. Chim. (Paris)*, **53**, 1212 (1963); (c) C. Jutz and H. Amschler, *Chem. Ber.*, **96**, 2100 (1963).

(15) (a) R. C. Neuman, G. S. Hammond, and T. J. Dougherty, *J. Amer. Chem. Soc.*, **84**, 1506 (1962); (b) R. C. Newman and L. B. Young, *J. Phys. Chem.*, **69**, 2570 (1965); (c) G. Scheibe, C. Jutz, W. Seiffert, and D. Grosse, *Angew. Chem., Int. Ed. Engl.*, **3**, 306 (1964).

(16) Several dimethylaminocyclobutenes display separate NCH_3 peaks: R. Breslow, D. Kivelevich, W. Fabian, and K. Wendel, *J. Amer. Chem. Soc.*, **87**, 5132 (1965).

(17) F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy," Academic Press, New York, N. Y., 1969, Chapter 6.

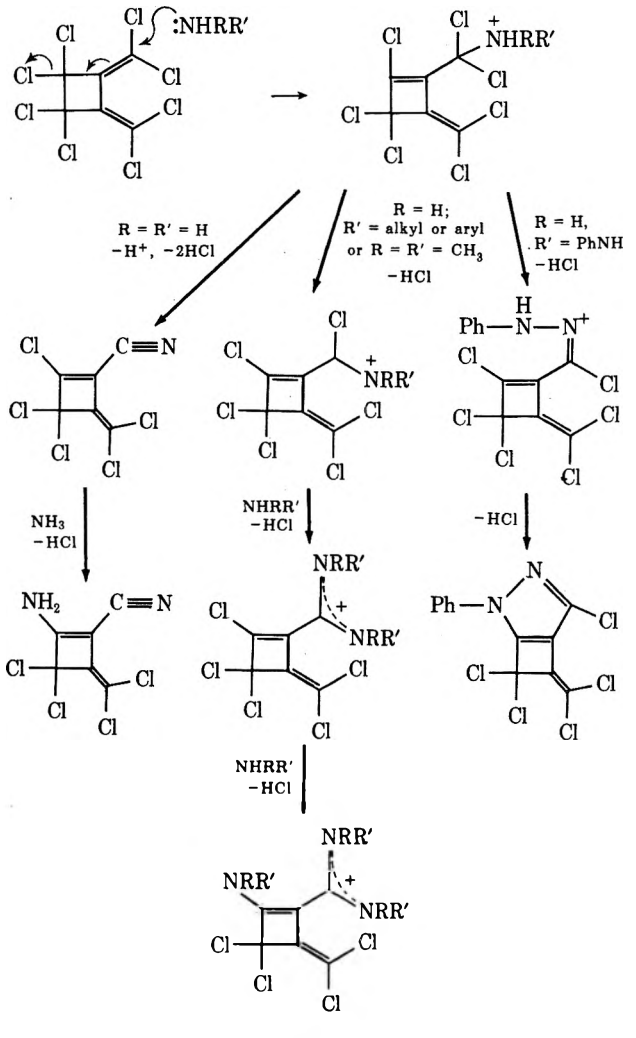
(18) (a) G. Zerbi and C. Alberti, *Spectrochim. Acta*, **18**, 407 (1962); (b) *ibid.*, **19**, 1261 (1963).



24 25

Mechanism of the Reactions.—The following steps are proposed to account for the formation of the products obtained from **1** (Scheme I).

SCHEME I



Initial attack by the amines *via* allylic rearrangement (SN2′), rather than by direct displacement (SN2), is suggested because α halogens accelerate SN2′ reactions[19] and retard SN2 reactions.[20] The formation of **2** from **1** by treatment with KOH presumably occurred *via* the SN2′ mechanism.

Nucleophilic displacement of the second ring chlorine to give either enamines or pyrazoles is reasonable in view of the presence of electron-withdrawing groups in the various intermediates.[21] Further atack by KOH on **2** did not occur, presumably because of the presence of the carboxylate ion.

Displacement of the second vinylic chlorine from the α-chloroimine to give amidinium salts has ample precedent.[22]

Conclusion.—The reactions of **1** with ammonia amines and phenylhydrazine produce nitriles, amidinium salts and pyrazoles, respectively.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Ultraviolet spectra were determined with a Perkin-Elmer Model 202 spectrophotometer, infrared spectra with a Perkin-Elmer Model 137, and nmr with a Varian A-60 using tetramethylsilane as internal reference. Analyses were performed by Mr. George Robertson, Florham Park, N. J., and Spang Micro-Elemental Laboratory, Ann Arbor, Mich., or by an F & M Elemental Analyzer, Model 185. Mass spectra were determined with a Varian M-66 employing a direct inlet system. Thin layer chromatography was performed on plates prepared with silica gel G or Adsorbosil-1 (Applied Science Laboratories, State College, Pa.) to which approximately 5% Radelin phosphor GS-115 had been added. Column chromatography was performed by using either Fisher reagent grade silica gel, 28–200 mesh, or Mallinckrodt CC7, 28–200 mesh. Ion-exchange chromatography was performed by use of Amberlite IRA-400 (Mallinckrodt Chemical Works).

2-Amino-3,3-dichloro-4-dichloromethylene-1-cyanocyclobutene (8).—Aqueous ammonia (15 ml, 240 mmol), cooled to 4°, was added to a solution of **1** (2.03 g, 5.7 mmol) in 200 ml of absolute ethanol at 4°. After 3 days at 4°, the solvent was removed under vacuum at ambient temperature. The solid residue thus obtained was treated with carbon tetrachloride. The mixture was filtered to remove ammonium chloride. The filtrate was evaporated and chromatographed on silica gel using methanol–chloroform (4:96) as solvent. The major band, R_f 0.38, was collected and yielded 847 mg (61%, colorless crystals, mp 139°) of **8**: λ_{max} 262 mμ (ϵ 8600), 314 (2900); ir (KBr) 2.90, 3.12 (NH_2), 4.50 (C≡N); mass spectrum (70 eV) *m/e* 242 with an isotopic cluster of peaks expected for four chlorines.

Anal. Calcd for $C_6H_2N_2Cl_4$: C, 29.54; H, 0.83; N, 11.49. Found: C, 29.45; H, 0.86; N, 11.11.

2-Acetamido-3,3-dichloro-4-dichloromethylene-1-cyanocyclobutene (9).—Aminonitrile **8** (2.00 g, 8.20 mmol), dissolved in 1 ml of acetic anhydride, was heated at 100° for 48 hr. Upon cooling, a solid slowly precipitated. The mixture was centrifuged. The centrifugate was decanted and treated with an equal volume of water, which caused more solid to deposit. The combined solids were washed with water and crystallized from carbon tetrachloride to afford 1.23 g (52%, colorless crystals, mp 232°) of **9**: λ_{max} 265, 341 mμ; ir (KBr) 3.16 (NH), 4.50 μ (C≡N); mass spectrum (70 eV) *m/e* 284, with an isotropic cluster of peaks which indicated four chlorines.

Anal. Calcd for $C_6H_4N_2OCl_4$: C, 33.60; H, 1.41; N, 9.80. Found: C, 33.71; H, 1.37; N, 10.09.

2-Amino-3,3-dichloro-4-dichloromethyl-1-cyano-4-methoxycyclobutene (10).—One milliliter of 5 *N* aqueous hydrochloric acid was added to aminonitrile **8** (100 mg, 0.41 mmol) in 1 ml of methanol. The solution was allowed to stand for 4 days at room temperature. The volume was reduced to approximately 1 ml by a stream of nitrogen. The solid which deposited was collected by filtration and crystallized from chloroform to yield 92 mg (36%, colorless crystals, mp 145–146°) of **10**: λ_{max} 267 mμ (ϵ 11,600); ir (KBr) 2.90, 3.10 (NH); 4.52 μ (C≡N); nmr ($CDCl_3$) τ 3.91 (s, 1 H), 4.20 (broad, 2 H), 6.27 (s, 3 H); mass spectrum (70 eV) *m/e* 274 with an isotopic cluster of peaks which indicated four chlorines.

Anal. Calcd for $C_7H_6N_2OCl_4$: C, 30.46; H, 2.19; N, 10.15. Found: C, 30.90; H, 2.13; N, 10.45.

(19) (a) P. De la Mare and C. Vernon, *J. Chem. Soc.* 3555 (1953); (b) J. D. Park, J. D. Lacher, and J. Dick, *J. Org. Chem.*, **31**, 1116 (1966).

(20) J. Hine, S. J. Ehrenson, and W. H. Brader, *J. Amer. Chem. Soc.*, **78**, 2282 (1956); **77**, 3386 (1955).

(21) S. Patai and Z. Rappaport, "The Chemistry of the Alkenes," Interscience, New York, N. Y., 1964, Chapter 8.

(22) (a) For the synthesis of amidinium salts from α-chloroimines, see H. Paul, A. Weise, and R. Dettmer, *Chem. Ber.*, **98**, 1450 (1965); (b) K. Fujimotom, T. Watanabe, J. Abe, and K. Okawa, *Chem. Ind. (London)*, 175 (1971); (c) for the mechanism, see Z. Rappaport and R. Ta-Shma, *Tetradron Lett.*, 3813 (1971); (d) for a review of the chemistry of α-chloroimines, see H. Ulrich, "The Chemistry of the Imidoyl Halides," Plenum Press, New York, N. Y., 1968.

2-Amino-4-bromodichloromethyl-3,3-dichloro-1-cyano-4-methoxycyclobutene (11).—A solution of one part liquid bromine in two parts methanol was added to aminonitrile **8** (500 mg, 2.05 mmol) in 2 ml of methanol. The mixture was allowed to stand overnight at room temperature and then evaporated to dryness under a stream of nitrogen. The crude solid thus obtained was crystallized from chloroform to yield 220 mg (24%, colorless crystals, mp 151–153°) of **11**: λ_{max} 268 mμ (ε 7500); ir (KBr) 3.05, 3.25 (NH_2), 4.60 μ (C≡N); nmr ($CDCl_3$) τ 3.83 (broad, 2 H), 5.77 (s, 3 H); mass spectrum (70 eV) *m/e* 352, with an isotopic cluster of peaks which indicated one bromine and four chlorine atoms.

Anal. Calcd for $C_7H_5N_2OBrCl_4$: C, 23.69; H, 1.42; N, 7.89. Found: C, 23.73; H, 1.41; N, 7.90.

***N,N'*-Di-*tert*-butyl-2-*tert*-butylamino-3,3-dichloro-4-dichloromethylenecyclobutenylcarboxamidinium Chloride (12).**—*tert*-Butylamine (183 g, 2.50 mol) was introduced dropwise, over a period of 1 hr, into a vigorously stirred solution of **1** (35.6 g, 0.10 mol) dissolved in 350 ml of diethyl ether. The solid (*tert*-butylammonium chloride) which deposited was separated by filtration. The filtrate yielded, upon evaporation, a solid residue which was crystallized from chloroform–hexane to give 30.3 g (65%, colorless crystals, mp 245°) of **12**: λ_{max} 273 mμ (ε 13,600); ir (KBr) 3.38 (NH, CH), 5.86 (exocyclic C=C), 6.20 μ (ring C=C and amidinium); nmr ($CDCl_3$) τ 0.12 (2 H, broad), 2.49 (1 H, broad), 8.55 (9 H, singlet), 8.65 (18 H, singlet); nmr (C_6D_6–DMSO-d_6) τ −0.48 (broad, 2 H), 1.85 (broad, 1 H) 9.03 (s, 9 H), 9.07 (s, 18 H); mass spectrum (70 eV) *m/e* 427.

Anal. Calcd for $C_{15}H_{30}N_3Cl_5$: C, 46.42; H, 6.49; N, 9.02. Found: C, 45.95; H, 6.56; N, 9.12.

Reaction of 12 with Silver Nitrate.—A 5% aqueous silver nitrate solution was added dropwise to a mechanically stirred solution of **12** (150 mg, 0.32 mmol) in 3 ml of methanol, until no further precipitation occurred. The solid was separated by filtration and then treated with chloroform. The mixture was filtered and the filtrate was evaporated to dryness. The solid thus obtained was crystallized from chloroform–hexane to yield the nitrate salt **13** (colorless crystals, mp 230°): λ_{max} 273 mμ (ε 18,500); ir (KBr) 3.08, 3.30 (NH), 3.38 (CH), 5.87 (exocyclic C=C), 6.20 (ring C=C, amidinium), and 7.25 (NO_3^-); nmr identical with that of **12**.

Anal. Calcd for $C_{18}H_{30}N_4O_3Cl_4 \cdot H_2O$: C, 42.37; H, 6.32; N, 10.98. Found: C, 42.42; H, 6.01; N, 10.80.

Reaction of 12 with Sulfuric Acid.—A solution of **12** (300 mg, 0.64 mmol) in 4 ml of 95% ethanol was warmed to 65°. Upon addition of four drops of 18 *M* sulfuric acid, an immediate formation of crystals was observed. The mixture was cooled to room temperature and then filtered. The crystals were recrystallized from chloroform to yield the bisulfate salt **14** (colorless crystals, mp 230° dec): λ_{max} 272 mμ (ε 20,700); ir 3.35 (CH, NH), 5.85 (exocyclic C=C), 6.20 (ring C=C, amidinium), 8.0–8.4 μ (HSO_4^-); nmr (DMSO-d_6) τ 2.17 (broad, 1 H), 7.80 (s, 18 H), 7.90 (s, 9 H); mass spectrum (70 eV) *m/e* 298.

Anal. Calcd for $C_{18}H_{31}N_3Cl_4SO_4$: C, 40.99; H, 5.93; N, 7.97; Cl, 26.40. Found: C, 40.45; H, 5.48; N, 7.78; Cl, 26.61.

Conversion of the Bisulfate Salt 14 to the Chloride Salt 12.—A solution of **14** (145 mg, 0.28 mmol) in 15 ml of 15% water–85% methanol was placed on a column containing 4.5 g of IR-400 anion exchange resin, equivalent to 15 mequiv of exchangeable chloride, in 15% water–85% methanol. The column was washed with 15% water–85% methanol; 30 ml of eluate was collected and then evaporated to dryness. The residue obtained was crystallized from chloroform–hexane to yield colorless crystals of **12**, mp 246–247°. The product was shown to be identical with authentic **12** by comparison of their ir spectra and a mixture melting point.

Reaction of 12 with Potassium Carbonate.—Solid potassium carbonate (470 mg, 3.4 mmol) was added to a vigorously stirred solution of **12** (1.6 g, 3.4 mmol) in a mixture of 240 ml of 95% ethanol and 240 ml of water. At the completion of addition the solution become opaque. Stirring was continued for several hours, during which time a solid deposited. The mixture was evaporated to half volume and filtered. The solid was washed with water, dried in a vacuum desiccator, and crystallized from chloroform–hexane to yield 177 mg (27%, colorless crystals, mp 238°) of *N,N'*-di-*tert*-butyl-2-*tert*-butylamino-3,3-dichloro-4-dichloromethylenecyclobutenylcarboxamidine (**20**): λ_{max} 272 mμ (ε 15,800); ir (KBr) 2.93 (NH), 3.36 (CH, NH), 5.84 (C=C), 6.08 (C=C), and 6.22 μ (amidine); nmr ($CDCl_3$) τ 0.08 (broad, 1 H), 8.42 (s, 9 H), 8.53 (s, 18 H); mass spectrum (70 eV) *m/e* 427.

Anal. Calcd for $C_{18}H_{29}N_3Cl_4 \cdot 2H_2O$: C, 46.46; H, 7.12; N, 9.03. Found: C, 46.44; H, 6.65; N, 9.02.

Conversion of Amidine 20 to Amidinium Salt 12.—A solution of 1 drop of 12 *M* HCl in 1 ml of methanol was added to **20** (43 mg, 0.1 mmol) in 1 ml of methanol. Upon removal of the solvent by a stream of nitrogen, a solid residue was obtained. The ir spectrum of the dry residue (abderhalden pistle, 80°) was identical with that of **12**. A mixture melting point determination of **12** and the product obtained from **20** showed no depression.

Reaction of 12 with Methanolic Potassium Hydroxide.—A 20-ml portion of a freshly prepared and filtered 1.5 *M* solution of potassium hydroxide in methanol was added to **12** (1.6 g, 3.4 mmol) in 24 ml of methanol. The reaction mixture was stirred at room temperature for 5 days, during which time a solid precipitated. The colorless solid was removed by filtration and washed with water to remove potassium chloride, then dried and crystallized from chloroform to yield 503 mg (37%, colorless colorless crystals, mp 222°) of *N,N'*-di-*tert*-butylamino-3,3-dimethoxy-4-dichloromethylenecyclobutenylcarboxamidine (**21**): λ_{max} 278 mμ (ε 14,700); ir (KBr) 3.02 (NH), 3.36 (NH, CH), 5.90 (C=C), 6.30 (amidine), 8.87 μ (ether); nmr ($CDCl_3$) τ −0.20 (broad, 1 H), 6.40 (s, 6 H), 8.53 (s, 18 H), 8.62 (s, 9 H); nmr (DMSO-d_6) τ 0.15 (broad, 1 H), 6.79 (s, 6 H), 8.74 (s, 18 H), 8.81 (s, 9 H); mass spectrum (70 eV) *m/e* 419.

Anal. Calcd for $C_{20}H_{35}N_3O_2Cl_2 \cdot 2H_2O$: C, 52.63; H, 8.61; N, 9.20. Found: C, 52.52; H, 8.00; N, 9.35.

Reaction of Amidine 21 with Dilute Hydrochloric Acid.—To a solution of 150 mg (0.36 mmol) of **21** in 5 ml of tetrahydrofuran was added 4 ml of 0.2 *N* aqueous hydrochloric acid. After several minutes at room temperature, the solution was evaporated to dryness. A solid residue was obtained which was crystallized from chloroform–hexane to yield colorless crystals, mp 232°, of *N,N'*-di-*tert*-butyl-2-*tert*-butylamino-3,3-dimethoxy-4-dichloromethylenecyclobutenylcarboxamidinium chloride (**21**) (HCl): λ_{max} 277 mμ (ε 17,300); ir (KBr) 3.40 (NH, CH), 5.92 (C=C), 6.25 μ (C=C, amidinium).

Anal. Calcd for $C_{20}H_{36}N_3O_2Cl_3$: C, 52.56; H, 7.94; N, 9.20. Found: C, 52.76; H, 8.10; N, 9.07.

Reaction of 1 with Isopropylamine.—A solution of 6.6 g (0.11 mol) of isopropylamine in 50 ml of tetrahydrofuran was added, dropwise, over a period of 3 hrs, to a well-stirred solution of 2.0 g (5.6 mmol) of **1** in 50 ml of tetrahydrofuran. During the addition a solid deposited. The solvent was evaporated to afford an oily mass of crystals, which was treated with chloroform. The undissolved isopropylamine hydrochloride was removed by filtration. Upon evaporation of the chloroform, a solid residue was obtained which was crystallized from chloroform–hexane to yield colorless crystals, mp 218–220° of *N,N'*-diisopropyl-2-isopropylamino-3,3-dichloro-4-dichloromethylenecyclobutenylcarboxamidinium chloride (**15**): λ_{max} 268 mμ (ε 19,100); ir (KBr) 3.40 (CH, NH), 5.82 (C=C), 6.15 μ (C=C, amidinium); nmr ($CDCl_3$) τ 0.49, 0.65 (broad, 3 H), 5.83 (broad) 6.30 (quartet) [The last two peaks integrated together as 3 H. Additional peaks were located at τ 8.55 (d, J = 6.5 cps), 8.64 (d, J = 6.5 cps), and 8.73 (d, J = 6.0 cps). The last three peaks integrated as 18 H.]; mass spectrum (70 eV) *m/e* 447.

Anal. Calcd for $C_{15}H_{24}N_3Cl_5$: C, 42.52; H, 5.71; N, 9.92. Found: C, 42.56; H, 5.60; N, 9.72.

Reaction of 1 with Aniline.—To a solution of 1.00 g (2.80 mmol) of **1** in 20 ml of tetrahydrofuran was added 2.00 g (21.5 mmol) of aniline. After several days at room temperature, the mixture was filtered to remove aniline hydrochloride. Evaporation of the filtrate and treatment with ethyl ether yielded a yellow solid which, upon crystallization from chloroform–carbon tetrachloride, afforded yellow crystals, mp 260°, of *N,N'*-diphenyl-2-anilino-3,3-dichloro-4-dichloromethylenecyclobutenylcarboxamidinium chloride (**17**): λ_{max} 290 mμ (ε 29,100); ir (KBr) 2.95 (NH), 3.50 (CH, NH), 5.87 (C=C), 6.17 (C=C, amidinium), 6.32 μ (aromatic).

Anal. Calcd for $C_{24}H_{15}N_3Cl_5 \cdot H_2O$: C, 53.00; H, 3.71; N, 7.73; Cl, 32.63. Found: C, 52.74; H, 3.39; N, 7.69; Cl, 32.42.

Reaction of **1** with *p*-anisidine and *p*-toluidine was carried out in an analogous manner.

Anal. Calcd for *p*-anisidine product (**19**): C, 52.67; H, 3.93; N, 6.82; Cl, 28.79. Found: C, 52.12; H, 4.12; N, 6.90; Cl, 30.78.

Anal. Calcd for *p*-toluidine product (**18**): C, 57.12; H, 4.26; N, 7.40; Cl, 31.22. Found: C, 56.53; H, 4.08; N, 7.33; Cl, 32.05.

Reaction of 1 with Dimethylamine.—A 250-ml portion of a saturated (10 *M*) solution of dimethylamine in isopropyl alcohol was slowly added to a well-stirred solution of 28.8 g (0.08 mol) of **1** in 250 ml of tetrahydrofuran. The reaction mixture was evaporated to dryness and treated with methylene chloride. The mixture was filtered and the filtrate was evaporated to afford a solid which was crystallized from chloroform–hexane to yield pale yellow crystals, mp 166–167°, of *N,N,N',N'*-tetramethyl-2-dimethylamino-3,3-dichloro-4-dichloromethylenecyclobutenylcarboxamidinium chloride (**16**): λ_{max} 273 mμ (ε 25,300), 372 (6100); ir (KBr) 3.42 (CH), 5.86 (C=C), 6.15 μ (C=C, amidinium); nmr ($CDCl_3$) τ 6.51 (s, 6 H), 6.61 (s, 3 H), 6.71 (s, 6 H), 6.74 (s, 3 H); nmr (D_2O) τ 6.60 (s, 3 H), 6.74 (s, 6 H), 6.84 (s, 6 H), 6.96 (s, 3 H); mass spectrum (70 eV) *m/e* 329.

Anal. Calcd for $C_{12}H_{15}N_3Cl_5 \cdot H_2O$: C, 36.07; H, 5.05; N, 10.52. Found: C, 35.93; H, 4.96; N, 10.58.

Reaction of 1 with Phenylhydrazine.—A solution of 6.05 g (56.0 mmol) of phenylhydrazine in 200 ml of tetrahydrofuran was added dropwise, under a stream of nitrogen, over a period of 2 hr, to a well-stirred solution of 5.0 g (14 mmol) of **1** in 200 ml of tetrahydrofuran. The precipitate which deposited (phenylhydrazine hydrochloride) was removed by filtration. The filtrate was concentrated and chromatographed on Silicar CC-7. Elution was performed with increasing concentrations of chloroform in carbon tetrachloride. Isolated from the column were orange crystals, mp 130°, of 2-phenyl-3,4-(3,3-dichloro-4-dichloromethylene)cyclobuteno-5-chloropyrazole (**22**): λ_{max} 240 mμ (ε 6200), 420 (5200); ir (KBr), 5.92 (C=C), 6.20 (C=C), 6.58 μ (pyrazole); mass spectrum (70 eV) *m/e* 352.

Anal. Calcd for $C_{12}H_5N_2Cl_5$: C, 40.56; H, 1.42; N, 7.90; Cl, 50.01. Found: C, 40.76; H, 1.26; N, 8.04; Cl, 50.02.

Reaction of 1 with Excess Phenylhydrazine.—A solution of 13.0 g (120 mmol) of phenylhydrazine in 200 ml of ethyl ether was added dropwise, under a stream of nitrogen, over a period of 2 hr, to a well-stirred solution of 7.12 g (20 mmol) of **1** in 200 ml of ethyl ether. The precipitate was filtered, washed with water to remove phenylhydrazine hydrochloride and crystallized from carbon tetrachloride–hexane to yield orange crystals, mp 158° of **23**, ir (KBr) 2.90, 3.00, 6.24, 6.64, 8.02, 8.48, 13.35, and 14.58 μ.

Anal. Calcd for $C_{18}H_{12}N_4Cl_4$: C, 50.73; H, 2.84; N, 13.15; Cl, 33.28. Found: C, 50.57; H, 3.07; N, 13.02; Cl, 32.93.

Registry No.—**1**, 1680-65-5; **8**, 38400-90-7; **9**, 38400-91-8; **10**, 38400-92-9; **11**, 38400-93-0; **12**, 38400-94-1; **13**, 38400-95-2; **14**, 38400-96-3; **15**, 38400-97-4; **16**, 38400-98-5; **17**, 38400-99-6; **20**, 38583-52-7; **21**, 38401-00-2; **21** (HCl), 38401-03-5; **22**, 38401-01-3; **23**, 38401-02-4; ammonia, 7664-41-7; isopropylamine, 75-31-0; aniline, 62-53-3; dimethylamine, 124-40-3; phenylhydrazine, 100-63-0.

Acknowledgment.—Robert Shapiro is the holder of a Public Health Service Career Development Award from the National Institute of General Medical Sciences.

Effect of Geometry and Substituents on the Electrochemical Reduction of Dibenzoylethylenes and Dibenzoylcyclopropanes

WILLIAM F. WINECOFF, III,[1] FRANK L. O'BRIEN,* AND DAVID W. BOYKIN, JR.*

Department of Chemistry, Georgia State University, Atlanta, Georgia 30303

Received August 24, 1972

The electrochemical reduction of the geometric isomers of dibenzoylethylene, dibenzoylstyrene, dibenzoylstilbene, dibenzoylcyclopropane, dibenzoylphenylcyclopropane, and dibenzoyldiphenylcyclopropane has been investigated by polarographic and cyclic voltammetric techniques. The polarographic waves were complicated by maxima; hence discussion and conclusions are based on the cyclic voltammetric results. The *cis*- and *trans*-dibenzoylethylenes show a remarkable 267-mV difference in ease of reduction. The dibenzoylethylenes become more difficult to reduce upon successive addition of phenyl groups. The difference between reduction of the geometric isomers of the dibenzoylethylenes reverses from the trans reducing at the more positive potential for dibenzoylethylene to the cis reducing at the more positive potential for dibenzoylstilbene. No discernible trends are observed for the dibenzoylcyclopropanes. The effects of structural changes on reduction potential are discussed.

Chemical reduction of dibenzoylethylenes has been extensively studied by Lutz and coworkers;[2,3] however, the analogous dibenzoylcyclopropanes have received considerably less attention.[4] The reduction of *cis*- and *trans*-dibenzoylethylene by a variety of reducing agents has not shown a demonstrable difference in ease of reduction of these isomers;[3] however, the marked liability of the cis isomer under the reaction conditions suggests that the relative ease of reduction of the cis isomer has not been assessed.[2b,3] On the other hand, preferential and facile reduction of *cis*- over *trans*-dibenzoylstilbene has been observed with $NaBH_4$, $LiAlH_4$, PCl_3, and aluminum isopropoxide.[2b,5] These results have been explained in terms of a "cis-group effect" which presumably arises in part as a result of dipole–dipole interactions of the proximate carbonyl groups and in part from reductions in π-orbital overlap in the cis isomer due to steric crowding. In contradistinction to the above reagents, Zn–HOAc, $SnCl_2$–HOAc–HCl, and sodium hydrosulfite reduce both isomers with apparently comparable ease.[2b,3a] Such differences do not appear to have been reported in the cyclopropane systems. Quantitative assessment of the relative ease of reduction by electrochemical methods should add to the understanding of the reduction of these unsaturated ketones.

There have been only a limited number of investigations comparing the effect of geometry on ease of electrochemical reduction for stereoisomers. *cis*- and *trans*-

(1) This work represents a partial fulfillment of the requirements for the B.S. degree by W. F. W.

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(4) (a) J. B. Conant and R. E. Lutz, *ibid.*, **49**, 1083 (1927); (b) E. P. Kohler and W. N. Jones, *ibid.*, **41**, 1249 (1919).

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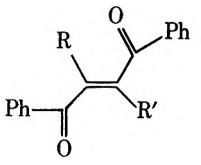
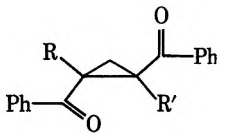
TABLE I

$E_{1/2}$ (−V) VALUES AT THE DROPPING MERCURY ELECTRODE (DME)



2



3

R, R′	trans[a]	cis[a]	Δ[b]	trans[a]	cis[a]	Δ[b]
H, H	0.87 (959-28-4)	1.11 (959-27-3)	0.24	1.43 (38400-84-9)	1.49 (3238-03-7)	0.06
H, Ph	1.20 (34880-76-7)	1.18 (13249-75-7)	−0.02	1.45 (30698-22-7)	1.48 (30698-21-6)	0.03
Ph, Ph	1.18 (10496-80-7)	1.19 (6313-26-4)	0.01	1.51 (38400-88-3)	1.44 (38400-89-4)	−0.08

[a] Registry numbers are given in parentheses. [b] $\Delta = E_{1/2}(\text{cis}) - E_{1/2}(\text{trans})$.

stilbene have been reduced electrochemically in DMF[6] and CH_3CN;[7] the $E_{1/2}$ values were −2.07 V cis and −2.08 V trans in DMF and −1.87 V cis and −1.73 V trans in CH_3CN. It appears that in this system there is little difference in the ease of reduction of the isomers. A study of fumaric and maleic acid and their esters in pyridine showed that the trans isomers were reduced at slightly more positive potentials.[8] On the other hand, fumaronitrile is reduced at a more negative value than maleonitrile, and *trans*-crotononitrile is reduced at a more negative value than *cis*-crotononitrile in aqueous media.[9] The easier reduction of these cis isomers was attributed to adsorption on the electrode.[9] The reduction of *cis*- and *trans*-dibenzoylethylenes in aqueous media shows that the trans isomer is more readily reduced than the cis isomer, $E_{1/2}$(trans) −0.46 V and $E_{1/2}$(cis) − 0.75 V.[10a,b]

As part of a continuing investigation[11] of the nonaqueous electrochemistry of α,β-unsaturated ketones, we have measured the polarographic half-wave potentials and the $E_{p/2}$ values from cyclic voltammetry for three sets of isomeric dibenzoylethylenes and dibenzoylcyclopropanes in an attempt to quantitatively assess the differences in ease of reduction in these systems. The geometric sets we have examined were also selected in order to assess the effect on reduction of systematic addition of phenyl groups to the double bond and the cyclopropane ring in these 1,4-diketone systems.

Results

Polarography.—The reduction of *trans*-dibenzoylethylene at the dropping mercury electrode in DMF exhibited two well-defined waves and exhibited no maxima. A plot of the log $[i/(id - i)]$ *vs.* E for the first wave yielded a straight line with a slope equaling 0.059, indicating that the reduction is a one-electron process. The presence of a stable free radical was confirmed by esr.[12] The polarograms for most of the other compounds studied were complicated by maxima. A typical example of the maxima problems encountered is shown in Figure 1. In an attempt to eliminate the polarographic maxima phenomena, limited studies altering various electrochemical parameters were undertaken. Changing the solvent to DMSO, altering the supporting electrolyte from TEAP to tetrabutylammonium iodide, and limited investigations employing the surfactants Triton-X and gelatin did not appreciably alter the appearance of the polarographic waves. Because of these problems the $E_{1/2}$ data presented in Table I are, doubtlessly, only rough estimates of the relative reduction half-wave potentials of these compounds; nevertheless, they may be used in a qualitative manner. Since it was the original objective of this investigation to accurately measure the $E_{1/2}$ values for the geometric isomers, an alternate method for assessing their reduction potentials was sought.

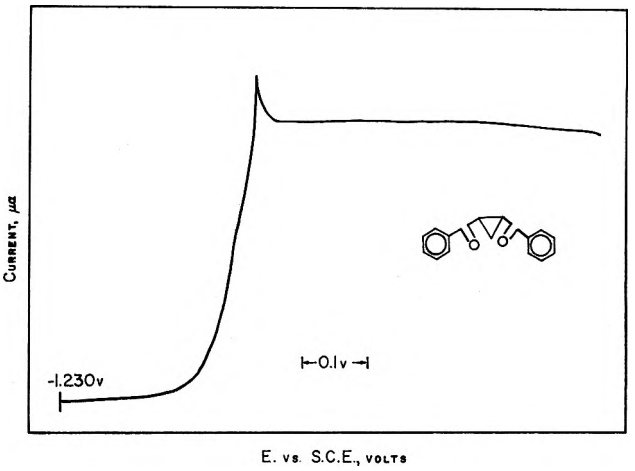


Figure 1.—Polarogram of *cis*-dibenzoylcyclopropane.

Cyclic Voltammetry. In spite of the fact that frequently the data obtained by linear sweep voltammetry at the hanging drop electrode (HDE) are less accurate than those obtained at the DME, the measurement is far less time consuming. The half-peak potential ($E_{p/2}$) while not directly relatable to the formal reduction potential, unless the exact electrode mechanism is known, is nevertheless experimentally a most useful measurement of the relative ease of oxidation or reduction. Also, additional information about reactive intermediates and chemical follow-up reactions is often obtained by reversing the voltage scan (cyclic voltammetry) and observing the oxidation of the reduction product(s) which has accumulated at the station-

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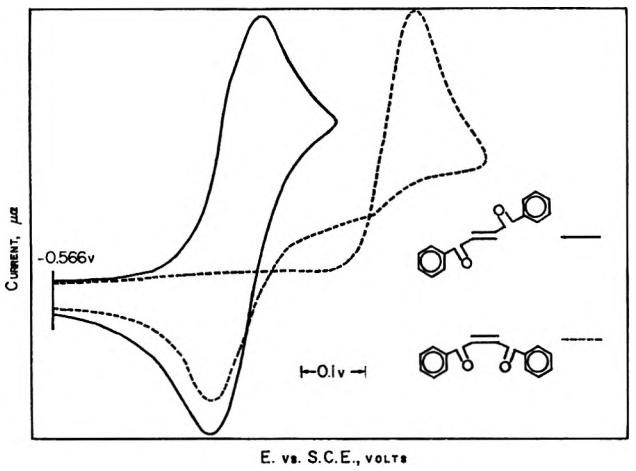


Figure 2.—Cyclic voltammograms of *cis*- and *trans*-dibenzoylethylene.

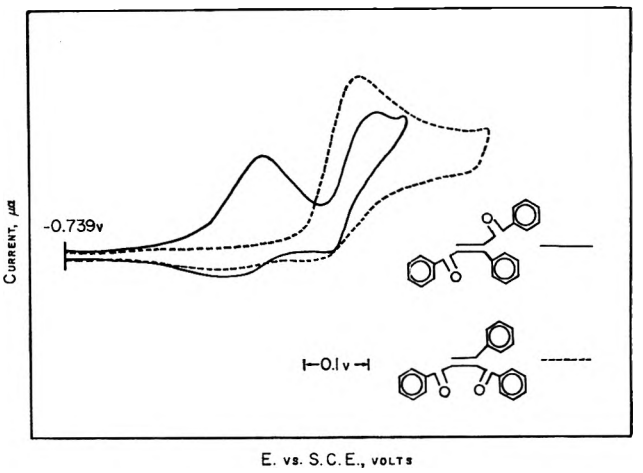


Figure 3.—Cyclic voltammograms of *cis*- and *trans*-dibenzoylstyrene.

ary electrode. The magnitude of the anodic response for reversible electron transfer, followed by an irreversible chemical reaction, is directly relatable to the half-life of the product of electron transfer (*e.g.*, the anion radical).[13a,b] It is expected by analogy with other α,β-unsaturated ketones[13c] that this type of process is important here.

Frequently, when polarographic maxima occur, adsorption peaks are observed at the HDE, which may be accompanied by a significant shift in the potential for the normal reduction wave. Only one compound, *trans*-dibenzoylstyrene, of the 12 studied exhibited a current–voltage curve with adsorption peaks. The values for $E_{p/2}$ for the six sets of geometric pairs are listed in Table II.

TABLE II

$E_{p/2}$ (−V) VALUES AT THE HDE

	2			3		
R, R′	trans	cis	Δ[a]	trans	cis	Δ[a]
H, H	0.89	1.15	0.27	1.43	1.50	0.07
H, Ph	1.19	1.19	0.00	1.46	1.48	0.02
Ph, Ph	1.22	1.19	−0.03	1.45	1.50	0.05

[a] $\Delta = E_{p/2}(\text{cis}) - E_{p/2}(\text{trans})$.

Discussion

There is a good qualitative parallel between the reduction potential values obtained by the two different electrochemical methods employed. The only serious discrepencies between the techniques are for the diphenyldibenzoylethylene and -cyclopropane pairs. In spite of this general agreement, this discussion will assume, owing to uncertainty in the DME values caused by maxima problems, that the data obtained by the HDE techniques are more reliable.

Dibenzoylethylenes.—Examination of the $E_{p/2}$ values for the dibenzoylethylene series reveals interesting trends. First, it is observed that for both cis and trans isomers, albeit not so pronounced in the cis series, the successive addition of a phenyl group to the ethylene carbon results in a successive shift in $E_{p/2}$ to a more negative value. However, the addition of the second phenyl group does not produce as large an effect as the first, and, therefore, a simple incremental effect of addition of a phenyl group is not observed. It is evident in this series that the inductive effect of the added phenyl group is not playing a predominate role in determining the $E_{p/2}$ values. The negative shift suggests that the important influence on the ease of reduction by the addition of a phenyl group to this system is to decrease stability of the presumed intermediate anion radical, which should be brought about by a decrease in coplanarity as a result of increased steric crowding.

The second interesting trend is seen by considering the effect on the Δ values [$\Delta = E_{p/2}(\text{cis}) - E_{p/2}(\text{trans})$] for the isomer with successive addition of a phenyl group to the parent system. The trans isomer of dibenzoylethylene is reduced in DMF at 267 mV less negatively than the cis isomer, which is of the same order of magnitude of the difference in aqueous media,[10a,b] an isomeric difference in ease of reduction which is without precedent! The addition of a single phenyl group to the parent system, forming the dibenzoylstyrene system, results in a leveling out of the differences between the isomers as shown by a Δ value of −5 mV. And finally, the addition of two phenyl groups to the system, to form the dibenzoylstilbene system, produced a reversal of the ease of the reduction. The cis isomer is reduced at a potential 32 mV less negative than the trans. In a series of geometric nitriles in which the cis isomers were reduced at more positive potentials than the trans isomers, the reversal was attributed to absorption phenomenon and intermoleculcar interactions.[9] No complicating maxima are seen in the current–voltage curves for *cis*- and *trans*-dibenzoylstilbene (see Figure 4). One plausible explanation for this reversal could be that in the dibenzoylstilbene case a special influence may be operative which stablizes the anion radical for *cis*-dibenzoylstilbene and therefore could account for the easier reduction of the cis than the trans isomer (*vide infra*).

Anodic sweep of the cyclic voltammograms of each isomer of the geometric sets provides additional information concerning the stability of the anion radicals produced on reduction. In Figure 2, for the dibenzoylethylene pair, it can be seen for the trans isomer

(13) (a) R. S. Nicholson and I. Shain, *Anal. Chem.*, **36**, 706 (1964); (b) E. R. Brown and R. F. Large in "Techniques of Chemistry, Physical Methods of Chemistry," Vol. I, Part IIA, A. Weissberger and B. W. Rossiter, Ed., Wiley-Interscience, New York, N. Y., 1971, Chapter 6; (c) J. P. Zimmer, J. A. Richards, J. C. Turner, and D. H. Evans, *Anal. Chem.*, **43**, 1000 (1971).

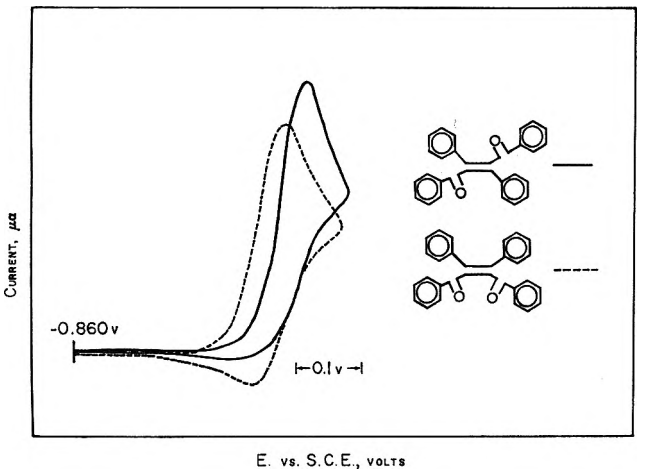


Figure 4.—Cyclic voltammograms of *cis*- and *trans*-dibenzoylstilbene.

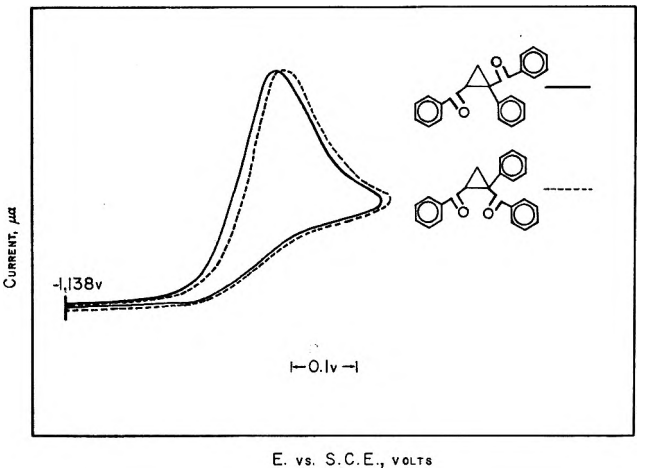
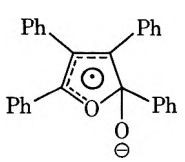


Figure 5.—Cyclic voltammograms of *cis*- and *trans*-phenyldibenzoylcyclopropane.

that reduction produces a relatively stable radical, whose esr signal has been observed[12] and which can be reoxidized at the expected potential. On the other hand, the absence of the reverse anodic wave suggests that the radical anion produced by reduction of the cis isomer is unstable and does not survive to be reoxidized. However, an oxidation wave is observed at the potential coinciding with that of the presumed trans anion radical, strongly suggesting that the *cis*-dibenzoylethylene anion radical is rapidly converted to the trans anion radical.

The cyclic voltammograms for the isomers of dibenzoylstyrene (Figure 3) are not as distinctive as the preceding ones. However, owing to the absence of significant anodic waves for both isomers, it can be deduced that the half-lives of the anion radicals are short with respect to *trans*-dibenzoylethylene. The large symmetrical peak at *ca.* 0.2 V anodic of the main reduction wave of the trans is due to adsorption.

The existence of a distinct anodic wave in the case of the cis isomer in the cyclic voltammograms of the dibenzoylstilbenes (Figure 4) indicates that the anion radical of the cis isomer is considerably longer lived than its trans isomer. $E_{p/2}$ values as well as increased lifetime of the intermediate (anion radical) produced on reduction of *cis*-dibenzoylstilbene exemplify the differences between the dibenzoylethylene and dibenzoylstilbene systems. These observations could be explained in terms of the appearance of a significant inductive effect arising from the phenyl or benzoyl groups due to diminution of coplanarity of the groups for the cis isomer relative to trans due to steric crowding. However, it was noted above that the shift of Δ upon addition of phenyl groups was in the wrong direction for the inductive effect to make a significant contribution. On the other hand, an attractive alternative interpretation is that, because of the proximity of the carbonyl groups in the cis isomer, a cyclic delocalized anion (such as **1**) is the stable intermediate. Similar intermediates have been proposed previously



1

by Lutz to account for "cis-group effects" on chemical reduction in these systems.[2] Obviously, **1** could not result from the trans isomer without rotation around the 2,3 carbon bond, although the energy barriers to such rotation in analogous systems are known to be low;[14] the distinct differences between the cyclic voltammograms for the isomers suggest this is not occurring to an appreciable extent. The intervention of an intermediate of the type **1** is particularly attractive since it has been shown that in the mild chemical reduction of 2,3-disubstituted *cis*-dibenzoylethylenes dihydrofuran intermediates can be isolated.[2a]

Dibenzoylcyclopropanes.—The results from the electrochemical reduction of the cyclopropane diketones were of particular interest in view of the continuing comparisons of the chemistry of cyclopropanes and ethylenes.[15] In this study, however, the double bond properties of cyclopropane were not as apparent as have been noted in other systems.

The $E_{p/2}$ data show that the trans isomers of the three cyclopropane pairs are reduced at lower potentials than their corresponding cis isomers. Such an observation is in accord with increased stabilization of intermediate radical anions [and/or the transition state(s) leading to same] due to greater delocalization in the trans isomer compared to the cis. Such delocalization no doubt involves the cyclopropane ring to some extent. It is clear from the cyclic voltammetry that compared to the ethylenes the cyclopropane anion radicals are relatively unstable. In contrast to the ethylene series, no oxidation wave was observed for any cyclopropane studied. Cyclic voltammograms typical of the cyclopropane series are shown in Figure 5. In further contrast to the ethylene series, no discernible trends in $E_{p/2}$ values (Table II) were observed upon successive addition of phenyl groups to the dibenzylcyclopropane system.

Experimental Section

Chemicals.—The preparation of the dibenzoylethylenes and the dibenzoylcyclopropanes has been reported.[2-5,16] Each com-

(14) H. H. Freedman, V. R. Sandel, and B. P. Thill, *J. Amer. Chem. Soc.*, **89**, 1762 (1967).

(15) (a) M. Charton in "The Chemistry of the Alkenes," Vol. 2, J. Zabicky, Ed., Interscience, New York, N. Y., 1970, p 511 ff; (b) A. B. Turner, R. E. Lutz, N. S. McFarlane, and D. W. Boykin, Jr., *J. Org. Chem.*, **36**, 1107 (1971).

(16) C. R. Taylor, Ph.D. Dissertation, University of Virginia, 1970.

pound was recrystallized from ethanol to a constant melting point and dried *in vacuo*. The purification of dimethylformamide and tetraethylammonium perchlorate has been previously described.[11]

Instrumentation and Procedures.—The three-electrode potentiostat of conventional design, the polarographic cell, the capillary constant, and the general electrochemical procedures have been reported previously.[11] The signal generator used for polarography and cyclic voltammetry consisted of an Analog Devices Model 119 operational amplifier connected in the typical voltage integrator circuit. The desired rates of voltage change were obtained by selection of appropriate values for the input resistor and feedback capacitor. Sweep reversal was affected manually by reversal of the integrator input voltage. The polarographic scan rate was 0.06 V/min, and for cyclic voltammetry the scan rate for potential measurement was 2.5 V/min. The hanging drop electrode was constructed in the usual manner by sealing a piece of platinum wire into soft glass tubing, polishing the end, and etching the exposed platinum with aqua regia. The recessed platinum contact was then plated with mercury at the beginning of each day. For each measurement two new drops of mercury from the DME were transfered to the HDE *via* a small glass spoon that was added to the polarographic cell.

The reported $E_{p/2}$ values are the average of at least three measurements per day on at least 2 different days. Most values agreed to within 5 mV or less with 13 mV the largest single deviation observed. Polarographic $E_{1/2}$ values were approximated graphically.

Acknowledgment.—We thank Professor R. E. Lutz and his coworkers for generous samples of the compounds used in this investigation.

Chemistry of Difluorocyclopropenes. Application to the Synthesis of Steroidal Allenes

PIERRE CRABBÉ,*[1] HUMBERTO CARPIO, ESPERANZA VELARDE, AND JOHN H. FRIED

Research Laboratories, Syntex, S. A., Apartado Postal 10-820, Mexico 10, D. F., Mexico

Received October 11, 1972

The synthesis of a number of trisubstituted allenyl steroids is reported. Reaction of *N*-(2-chloro-1,1,2-trifluoroethyl)diethylamine on difluorocyclopropenylcarbinols is shown to be a convenient route to trifluoromethylallenes. Chlorotrifluorotriethylamine reacts stereoselectively with cyclopropenonylcarbinols to provide allenic acid fluorides in high yield. Allenic acid fluorides are easily converted into β-keto esters. The structure and stereochemistry of the novel steroidal allenes are based on their chemical and spectroscopic properties.

Some time ago, we developed an interest in incorporating allene functionality into the steroid molecule. When this work was undertaken there had been no reports of allene-substituted steroids. However, several related publications have appeared in the more recent literature.[2,3] This report summarizes our findings related to the synthesis of novel 3- and 17-substituted allenyl steroids.[4]

Addition of difluorocarbene, generated by pyrolysis of the sodium salt of chlorodifluoroacetic acid[5] to the triple bond of the diacetate **1b**, readily obtained from **1a**,[4a] afforded the difluorocyclopropene derivative **2a**. Conversion of **2a** to its 17-monoacetate **2c** was achieved by sodium methoxide hydrolysis to **2b**, followed by partial acetylation. Reaction of the 3β-hydroxy compound **2c** with *N*-(2-chloro-1,1,2-trifluoroethyl)diethylamine (fluoramine) in dry methylene chloride[6] provided a mixture of three substances, which were separated by preparative thin layer chromatography (tlc). The major compound was the 3β-fluoro steroid **2d** (25%), the formation of which could be expected from previous experience with this reagent.[6d] A second substance obtained in 15% yield did not have any fluorine in the molecule, but showed ultraviolet (uv) absorption at 244 nm, a strong carbonyl band in the ir at 1820 cm^{-1}, and two olefinic protons in the nuclear magnetic resonance (nmr) spectrum, one of them substantially deshielded (see Experimental Section). These properties are consistent with structure **3a**, which presumably results from dehydration[6] of the 3β alcohol **2c**, followed by hydrolysis of the difluorocyclopropene to give the conjugated cyclopropenone **3a**, because of traces of water. The vinylic proton resonating at 8.11 ppm corresponds to the cyclopropenone proton,[7] while the doublet centered at 6.66 ppm is due to the vinylic hydrogen at C-2. The facile hydrolysis of a conjugated difluorocyclopropene to a conjugated cyclopropenone has been observed previously.[8] Additionally, a compound isomeric with **2d** was isolated in 3% yield. As in the case of **2d**, its mass spectrum exhibited a molecular ion at *m/e* 410, suggesting the presence of three fluorines in the molecule. The strong ir band at 1970

(1) Laboratoire de Chimie Organique, C. E. R. M. O., Université Scientifique et Médicale, Boite Postale 53, Grenoble 38.041, Cedex, France.

(2) (a) N. K. Chaudhuri and M. Gut, *J. Amer. Chem. Soc.*, **87**, 3737 (1965); (b) R. Gardi, R. Vitali, and P. P. Castelli, *Tetrahedron Lett.*, 3203 (1966); (c) R. Vitali and R. Gardi, *Gazz. Chim. Ital.*, **96**, 1125, 3203 (1966); (d) W. R. Benn, *J. Org. Chem.*, **33**, 3113 (1968); (e) L. A. Van Dijck, K. H. Schönemann, and F. J. Zeelen, *Recl. Trav. Chim. Pays-Bas*, **88**, 254 (1969); (f) L. A. Van Dijck, B. J. Lankwerden, J. G. Vermeer, and A. J. Weber, *ibid.*, **90**, 801 (1971); (g) P. P. Castelli, R. Vitali, and R. Gardi, *Gazz. Chim. Ital.*, **101**, 833 (1971); (h) R. Vitali and R. Gardi, *Tetrahedron Lett.*, 1651 (1972); (i) see also T. F. Rutledje, "Acetylenes and Allenes," Reinhold, New York, N. Y., 1969.

(3) (a) P. Rona and P. Crabbé, *J. Amer. Chem. Soc.*, **91**, 3289 (1969); (b) M. Biollaz, W. Haefliger, E. Velarde, P. Crabbé, and J. H. Fried, *Chem. Commun.*, 1322 (1971); (c) M. Biollaz, R. M. Landeros, L. Cuéllar, P. Crabbé, W. Rooks, J. A. Edwards, and J. H. Fried, *J. Med. Chem.*, **14**, 1190 (1971).

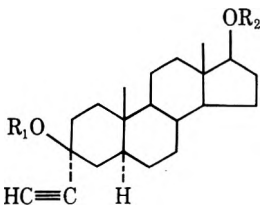
(4) Preliminary announcements of parts of this work have appeared: (a) P. Crabbé, R. Grezemkovsky, and L. H. Knox, *Bull. Soc. Chim. Fr.*, 789 (1968); (b) P. Crabbé, H. Carpio, and E. Velarde, *Chem. Commun.*, 1028 (1971); (c) P. Crabbé and E. Velarde, *ibid.*, 241 (1972).

(5) (a) W. M. Wagner, *Proc. Chem. Soc.*, 229 (1959); (b) J. M. Birchall, G. W. Cross, and R. N. Haszeldine, *ibid.*, 81 (1960).

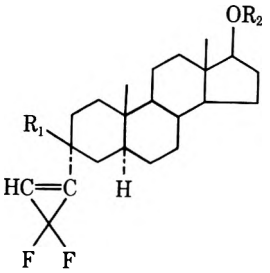
(6) (a) N. N. Yarovenko and M. A. Raksha, *Zh. Obshch. Khim.*, **29**, 2159 (1959); *Chem. Abstr.*, **54**, 9724*h* (1960); (b) D. E. Ayer, *Tetrahedron Lett.*, 1065 (1962); (c) L. H. Knox, E. Velarde, and A. D. Cross, *J. Amer. Chem. Soc.*, **85**, 2533 (1963); (d) L. H. Knox, E. Velarde, S. Berger, D. Cuadriello, and A. D. Cross, *J. Org. Chem.*, **29**, 2187 (1964); (e) L. H. Knox, E. Velarde, S. Berger, I. Delfin, R. Grezemkovsky, and A. D. Cross, *ibid.*, **30**, 4160 (1965), and references cited therein.

(7) See P. Anderson, P. Crabbé, A. D. Cross, J. H. Fried, L. H. Knox, J. Murphy, and E. Velarde, *J. Amer. Chem. Soc.*, **90**, 3888 (1968).

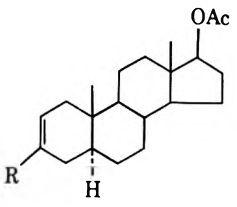
(8) (a) R. Breslow and G. Ryan, *J. Amer. Chem. Soc.*, **89**, 3073 (1967); (b) R. Breslow and L. Altman, *ibid.*, **88**, 504 (1966); (c) P. Crabbé, P. Anderson, and E. Velarde, *ibid.*, **90**, 2998 (1968).

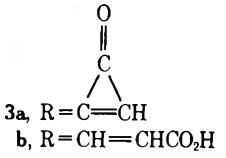


1a, $R_1 = R_2 = H$
b, $R_1 = R_2 = Ac$

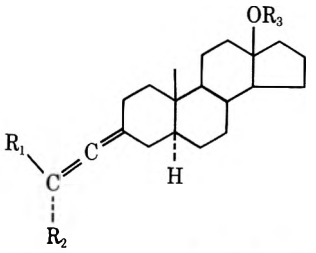


2a, $R_1 = OAc$; $R_2 = Ac$
b, $R_1 = OH$; $R_2 = H$
c, $R_1 = OH$; $R_2 = Ac$
d, $R_1 = F$; $R_2 = Ac$
e, $R_1 = OCH_2SCH_3$; $R_2 = Ac$

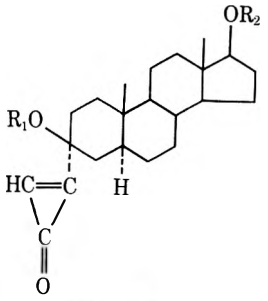




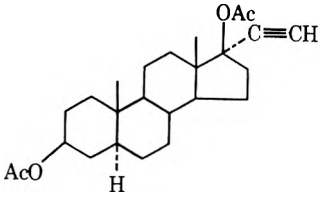
3a, R = C=CH
b, R = CH=CHCO$_2$H



4a, $R_1 = CF_3$; $R_2 = H$; $R_3 = Ac$
b, $R_1 = CO_2H$; $R_2 = H$; $R_3 = Ac$
c, $R_1 = COF$; $R_2 = H$; $R_3 = Ac$
d, $R_1 = CO_2Me$; $R_2 = H$; $R_3 = H$
e, $R_1 = CO_2H$; $R_2 = R_3 = H$



5a, $R_1 = R_2 = Ac$
b, $R_1 = R_2 = H$
c, $R_1 = H$; $R_2 = CHO$
d, $R_1 = H$; $R_2 = Ac$



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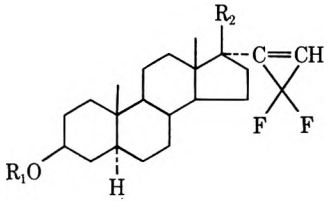
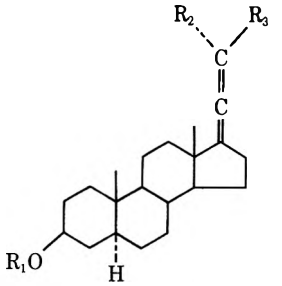


7a, $R_1 = Ac$; $R_2 = OAc$
b, $R_1 = H$; $R_2 = OH$
c, $R_1 = Ac$; $R_2 = OH$
d, $R_1 = Ac$; $R_2 = F$



8a, $R_1 = Ac$; $R_2 = CF_3$; $R_3 = H$
b, $R_1 = Ac$; $R_2 = H$; $R_3 = CF_3$
c, $R_1 = Ac$; $R_2 = H$; $R_3 = COF$
d, $R_1 = R_2 = H$; $R_3 = CO_2Me$
e, $R_1 = R_2 = H$; $R_3 = CO_2H$

cm^{-1} is consistent with the allenic structure **4a** assigned to this substance.

Attempts to dehydrate the 3β alcohol **2c** with acetic anhydride in anhydrous dimethyl sulfoxide[9] afforded the thiomethoxymethyl ether **2e**.

(9) See H. P. Albrecht and J. G. Moffatt, *Tetrahedron Lett.*, 1063 (1970).

Formic acid hydrolysis of the difluoromethylene grouping of **2a** under mild conditions gave the cyclopropenone **5a**. When submitted to stronger acidic conditions, **5a**, afforded the dienic acid **3b**, through the allenic acid intermediate **4b**, typified by its allene ir band at 1955 cm^{-1}. Formation of **4b** can be formulated as resulting from attack of water on the cyclopropenone carbonyl, with fragmentation and expulsion of the protonated acetate group. The allenic carboxylic acid **4b** is then readily isomerized to the diene **3b**.[4a]

The monohydroxy steroid **5d** was prepared from the diacetate **5a** by conventional technique. Treatment of **5d** with the fluoramine reagent in dry methylene chloride[6] gave the allenic acid fluoride **4c** in 72% yield. The structure of this compound was deduced from its physical properties (see Experimental Section). Moreover, when **4c** was exposed to methanol in the presence of hydrogen chloride, it was converted to the methyl ester **4d**. The stereochemistry of the allenes **4a–d** was deduced by correlation with that of the 17-allenyl steroids discussed in sequence.

Similarly, difluorocarbene addition to **6**[10] was followed by alkaline hydrolysis of the acetate groups of the difluoromethylene steroid **7a** to give the diol **7b**. Partial acetylation of the 3β hydroxyl **7b** gave the 3 monoacetate **7c**.

Reaction of the difluoromethylenecarbinol **7c** with the fluoramine reagent afforded a mixture of three isomeric substances, as evidenced by their molecular ion at *m/e* 410 (M^+). The first compound (6%) was the 17β-fluoro steroid **7d**. The nmr properties, in particular the 18-methyl proton resonance, of the fluoro derivative **7d**, reminiscent of those of its precursor **7c** (see Experimental Section), tend to support the β configuration for the newly introduced fluorine at C-17.[6d] The second fluoro steroid was the trifluoromethylallene **8a** (25%). The third substance was the isomeric allene **8b** (1%). Both isomers **8a** and **8b** showed a strong ir allene band at 1980 cm^{-1}. Additionally, compound **8b** was shown to be identical with the product obtained by treatment of 17α-trifluoropropynyl-5α-androstane-3β,17β-diol diacetate with zinc dust in diglyme.[11]

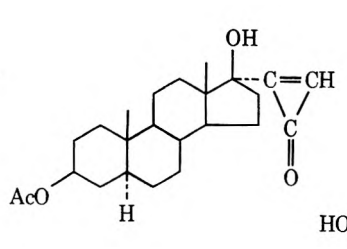
The configuration of the trifluoromethyl group at position 21 in the isomeric allenes **8a** and **8b** was deduced from their nmr properties. In compound **8a** the 18-methyl protons appeared as a sharp singlet at 0.861 ppm and the C-21 olefinic proton at 5.33 ppm. In contrast, in the 21β-trifluoromethyl derivative **8b**, the angular methyl was deshielded and now appeared at 0.925 ppm, whereas the multiplet corresponding to the 21-vinylic H was centered at 5.44 ppm.

Hydrolysis of the difluoromethylene grouping of **7c** with formic acid gave the cyclopropenonecarbinol **9**, with its characteristic ir absorption at 1820 cm^{-1} and cyclopropenonyl proton at 8.43 ppm in the nmr. Treatment of **9** with the fluoramine reagent provided the allenic acid fluoride **8c** in 81% yield. The structure of **8c** is based on its typical uv absorption at 226 nm and ir bands at 1960 (allene), 1810 (acid fluoride), and 1730 cm^{-1} (acetate). In particular, the 18-methyl protons appeared at 0.93 ppm, thus supporting the β

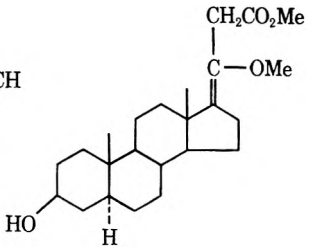
(10) (a) E. Velarde, P. Crabbé, A. Christensen, L. Tökés, J. W. Murphy, and J. H. Fried, *Chem. Commun.*, 725 (1970); (b) P. Crabbé, E. Velarde, L. Tökés, and M. L. Maddox, *J. Org. Chem.*, **37**, 4003 (1972).

(11) P. Crabbé and E. Velarde, paper in preparation.

stereochemistry of the acid fluoride moiety, and the 21 proton was a triplet (J = 4 Hz) at 5.51 ppm, owing to long-range coupling with fluorine.[4b]



9



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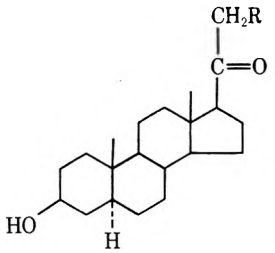
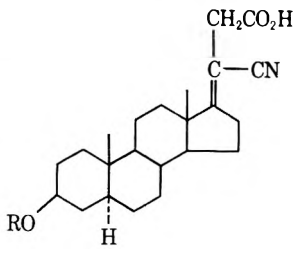


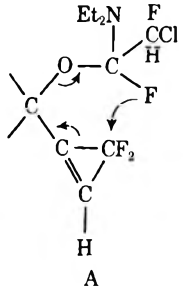
11a, R = CO_2Me
b, R = CO_2H
c, R = H



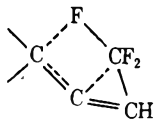
12a, R = Ac
b, R = H

It is of interest to note that the fluoramine reaction on **2c** and **7c** furnished the 3β-fluoro derivative **2d** and 17β-fluoro steroid **7d**, respectively, along with a modest yield of a mixture of isomeric trifluoromethylallenes. In the case of the 17-substituted steroid, the 21α isomer **8a** predominates. However, treatment of **5d** and **9** with the same reagent afforded in high yield only one acid fluoride, namely **4c** and **8c**, respectively. In the latter, the configuration of the substituent at C-21 is opposite to that in **8a**, as evidenced by the chemical shift of the 18-methyl protons (see above). These results seem to indicate that different reaction mechanisms are operative.

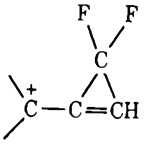
A tentative explanation of these results may imply that the allenes **4a** and **8b** are formed by a pathway involving an intermediate of type A. This compound



A



B



C

may then rearrange with introduction of the 3β fluorine through a four-centered system such as B. This would account for the very low yield of the β-oriented trifluoromethylallenes **4a** and **8b**. Should the intermediate A lead to the planar cationic intermediate C, loss of a C-2 proton followed by hydrolysis would give compound **3a**.

A rather different situation must prevail at position 17, probably because of the geometry of the five-membered ring. As above, the 21β-trifluoromethyl derivative **8b** would be formed from an intermediate A. This in turn may rearrange to the 17β-fluoro steroid **7d**, accounting for the low yield of the allene **8b**. The isomeric allenyl derivative **8a** may be formed from the carbonium ion species C, which has less of a tendency to eliminate a proton to form a cyclopentene, but rather reacts with fluoride ion to give the allene **8a**.

The greater electrophilicity of the cyclopropenone system and relative stability of the resultant allenic acid fluorides **4c** and **8c** must account for their formation in high yield.[12]

When the acid fluoride **8c** was allowed to react with sodium methoxide in methanol solution, it was converted into the corresponding methyl ester **8d**, with the signal of the 18-angular methyl appearing as a sharp singlet at 0.90 ppm. The free allenic acid **8e** was obtained by hydrolysis of **8d** with sodium hydroxide in acetone solution. Similarly, **4e** was formed by base treatment of **4c**.

Further treatment of **8d** with sodium methoxide afforded the enol ether **10**, devoid of uv absorption above 220 nm, resulting from Michael-type addition[13] of methoxide ion to the allenic ester group. Acid hydrolysis of the 17,20-enol ether **10** provided the β-keto ester **11a**, thus making this sequence a novel and efficient synthetic approach to β-keto esters. Whereas potassium carbonate hydrolysis of **11a** gave the free acid **11b**, treatment with 2% methanolic potassium hydroxide at reflux temperature cleaved the β-keto ester grouping, thus yielding quantitatively the known 3β-hydroxy-5α-pregnan-20-one **11c**.

Similarly, cyanide added as in the Michael reaction to the central carbon atom of the allenyl moiety of **8c**. Thus, treatment of **8c** with potassium cyanide in aqueous ethanol under reflux caused simultaneous alkylation at C-20 and hydrolysis of the acid fluoride, yielding the steroidal $\Delta^{17,(20)}$-20-cyano 22 acid as a mixture of the 3β acetate **12a** (55%) and the corresponding 3β alcohol **12b** (30%).

Experimental Section

Microanalyses were done by Dr. A. Bernhardt, Mülheim, West Germany. Melting points were determined with a Melt-Temp apparatus; they are corrected. Rotations were taken between 16 and 22° with a 1-dm tube at the sodium D line. Infrared spectra were taken with a Perkin-Elmer Model 21, NaCl prism. Ultraviolet absorption spectra were obtained with a Beckman spectrophotometer, Model DU. Unless otherwise stated, the nmr spectra were recorded at 60 MHz using 5–8% w/v solutions of substance in deuteriochloroform containing tetramethylsilane (TMS) as an internal reference. Resonance frequencies, ν, are quoted as parts per million downfield from the TMS reference (0.0 ppm). Coupling constants J are expressed in hertz (Hz) and are accurate to ±1 Hz; d = doublet, t = triplet, q = quartet, m = multiplet. The mass spectra were obtained with an Atlas CH-4 spectrometer. The ORD curves were obtained with a JASCO-UV-5-instrument. We are indebted to Dr. L. Throop, D. L. Tökés, and their associates, Syntex Research, Palo Alto, Calif., for several nmr and mass spectra.

3β,17β-Diacetoxy-3α-ethynyl-5α-androstane (1b).—3α-Ethynyl-3,17β-dihydroxy-5α-androstane (**1a**)[4] (27 g) in acetic acid (1350 ml) was treated with acetic anhydride (135 ml) and *p*-toluenesulfonic acid monohydrate (27 g) at room temperature for 2 hr. After usual work-up, 26.2 g of **1b** was obtained. Recrystallization from methanol afforded the analytical sample: mp 166–167°; $[\alpha]D$ +2°; ν_{max} 3210, 1740, and 1250 cm^{-1}; nmr 0.78 (18-H), 0.83 (19-H), 2.01 (3- and 17-OAc), 2.60 (acetylenic H), ~4.62 ppm (17α-H).

(12) The authors wish to thank a referee for useful suggestions related to these reaction mechanisms.

(13) (a) W. E. Truce and L. C. Markley, *J. Org. Chem.*, **35**, 3275 (1970); (b) M. Bertrand and J. Legras, *C. R. Acad. Sci.*, **260**, 6926 (1965).

Anal. Calcd for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 75.00; H, 9.16.

3β,17β-Diacetoxy-3α-(3,3′-difluoro-1′-cyclopropen-1′-yl)-5α-androstane (2a).—A solution of 16 g of **1b** in 50 ml of diglyme was refluxed in a nitrogen atmosphere, with gradual addition of 200 g of anhydrous sodium chlorodifluoroacetate in 375 ml of diglyme held at 60°. The mixture was cooled to room temperature, filtered over Celite, and evaporated to dryness under high vacuum. After treatment with activated carbon, the residue, dissolved in methylene chloride, was passed through a column of 250 g of Florisil, affording 11.2 g of crystalline **2a**. The pure sample of **2a** showed mp 118–120°; $[\alpha]D$ +17°; ν_{max} 1740 and 1240 cm^{-1}; nmr 0.78 (18-H), 0.88 (19-H), 2.03 (3- and 17-OAc), ~4.60 ppm (17α-H).

Anal. Calcd for $C_{26}H_{36}O_4F_2$: C, 69.31; H, 8.05; F, 8.43. Found: C, 69.45; H, 8.19; F, 8.20.

3β,17β-Dihydroxy-3α-(3,3′-difluoro-1′-cyclopropen-1′-yl)-5α-androstane (2b).—To 2.54 g of **2a** dissolved in 25 ml of anhydrous methylene chloride, a solution of 730 mg of sodium methoxide in anhydrous methanol was added. The mixture was left at room temperature for 3.5 hr, poured into water, extracted with methylene chloride, and crystallized from acetone–hexane, affording 1.5 g of **2b**. The analytical sample exhibited mp 101–103°; $[\alpha]D$ +23°; ν_{max} 3370 cm^{-1}; nmr 0.73 (18-H), 0.87 (19-H), 3.63 (17α-H), 7.32 ppm (difluorocyclopropene H).

Anal. Calcd for $C_{22}H_{32}O_2F_2$: C, 72.09; H, 8.80; F, 10.37. Found: C, 72.31; H, 8.89; F, 9.75.

17β-Acetoxy-3β-hydroxy-3α-(3,3′-difluoro-1′-cyclopropen-1′-yl)-5α-androstane (2c).—To 2.15 g of **2b**, 8 ml of pyridine was added, and the mixture was cooled in an ice bath. Subsequently, 1.8 ml of acetic anhydride was added, and the reaction mixture was left at 5° for 20 hr. After the usual isolation procedure, the residue was crystallized from acetone–hexane, affording 1.75 g of **2c**. A pure sample of **2c** showed mp 149–150°; $[\alpha]D$ +6°; ν_{max} 3420, 1720, and 1270 cm^{-1}.

Anal. Calcd for $C_{24}H_{34}O_3F_2$: C, 70.55; H, 8.39; F, 9.30. Found: C, 70.59; H, 8.46; F, 9.16.

Reaction of 17β-Acetoxy-3β-hydroxy-3α-(3,3′-difluoro-1′-cyclopropen-1′-yl)-5α-androstane (2c) with 2-Chloro-1,1,2-trifluorotriethylamine.—To a solution of 2 g of **2c** in 100 ml of anhydrous methylene chloride, 2 g of *N*-(2-chloro-1,1,2-trifluoroethyl)diethylamine was added. The reaction mixture was left at room temperature for 20 min, filtered through a column of 50 g of Florisil in methylene chloride, and evaporated to dryness. Elution with ethyl acetate afforded a material which crystallized from ethyl acetate, to give 270 mg of **3a**. The analytical sample was prepared by recrystallization from acetone, yielding 17β-acetoxy-3-(3′-oxo-1′-cyclopropen-1′-yl)-5a-androst-2-ene (**3a**): mp 192–193°; $[\alpha]D$ +53°; λ_{max} 244 nm (log ε 4.24); ν_{max} 1820, 1730, 1630, 1565, and 1240 cm^{-1}; nmr 0.76 (18-H, 19-H), 1.99 (17β-OAc), 4.35–4.82 (17α-H), 6.66 (d, $J \cong 14$ Hz, 2-H), 8.11 ppm (cyclopropenyl H).

Anal. Calcd for $C_{24}H_{32}O_3$: C, 78.22; H, 8.75; 0, 13.03. Found: C, 78.51; H, 8.67; O, 12.97.

The material eluted with methylene chloride was rechromatographed over 500 g of Florisil and eluted with a mixture of ether–hexane (3:97) to afford 115 mg of a crude product, which by successive recrystallizations from hexane yielded a pure sample of 17β-acetoxy-3-(2′β-trifluoromethylvinylidene)-5α-androstane (**4a**): mp 162–163°; $[\alpha]D$ +23°; ν_{max} 1970, 1735, and 1250 cm^{-1}; nmr (100 MHz) 0.78 (18-H), 0.87 (19-H), 2.01 (17β-OAc), 4.52, 4.60, 4.68 (t, 17α-H), 5.23 ppm (allenic H); ^{19}F nmr 60.19 ppm (d, J_{HF} = 5.8 Hz, $-CF_3$); mass spectrum *m/e* 410 (M^+), 335 ($M^+ - 75$), 309 ($M^+ - 101$).

Anal. Calcd for $C_{24}H_{33}O_2F_3$: C, 70.22; H, 8.10; F, 13.89. Found: C, 69.67; H, 7.88; F, 14.62.

Elution of the column with a mixture of ether–hexane (5:95) gave 500 mg of **2d** which, after three successive recrystallizations from methanol, afforded the analytical sample of 17β-acetoxy-3β-fluoro-3α-(3,3′-difluoro-1′-cyclopropen-1′-yl)-5α-androstane (**2d**): mp 175–177°; ν_{max} 3080, 1735, and 1260 cm^{-1}; nmr 0.79 (18-H), 0.85 (19-H), 2.01 (17β-OAc), 4.58 (17α-H), 7.37 ppm (difluorocyclopropene H); mass spectrum *m/e* 410 (M^+).

Anal. Calcd for $C_{24}H_{33}O_2F_3$: C, 70.22; H, 8.10; F, 13.88. Found: C, 70.43; H, 7.92; F, 14.07.

17β-Formyloxy-3α-(3′-oxo-1′-cyclopropen-1′-yl)-3β-hydroxy-5α-androstane (5c).—A mixture of 150 mg of **2b** and 1.5 ml of 90% formic acid was stirred for 15 min at room temperature and then poured into water. The crystals were collected by filtration and washed with water. Three successive recrystallizations from methylene chloride–hexane afforded the pure sample of **5c**: mp 178–179°; $[\alpha]D$ +6°; λ_{max} 264–268 nm (log ε 1.57) (MeOH); ν_{max} 3170, 1825, 1720, 1590, and 1170 cm^{-1}; nmr (100 MHz) 0.76 (18-H), 0.82 (19-H), 4.62 (m, 17α-H), 8.22 (formyloxy H), 9.97 ppm (cyclopropenyl H).

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66; O, 17.18. Found: C, 73.76; H, 8.51; O, 16.78.

3′-(17β-Acetoxy-5α-androst-2-en-3-yl)-*trans*-propenoic Acid (3b).—A mixture of 2 g of 3β,17β-diacetoxy-3α-(3′-oxo-1′-cyclopropen-1′-yl)-5α-androstane (**5a**) and 10 ml of 90% formic acid was refluxed for 15 min. It was then poured into water, and the crystals were collected by filtration and washed with water to neutrality. The dried crystalline material showed ν_{max} 1955 (allene), 1740 (17β-OAc), 1693 cm^{-1} (CO_2H), in agreement with structure **4b**. Recrystallization from methylene chloride–acetone afforded 860 mg of acid **3b**:[4] mp 275–276°; $[\alpha]D$ +63°; λ_{max} 262 nm (log ε 4.36); ν_{max} 2900, 1735, 1640, 1610, and 1240 cm^{-1}; nmr (100 MHz) 0.75, 0.81 (18-H, 19-H), 2.02 (17β-OAc), 4.59 (t, J = ~7 Hz, 17α-H), 5.75 (d, J = 15 Hz, =CHCO–), 7.33 ppm (d, J = ~15 Hz, =CH–).

Anal. Calcd for $C_{24}H_{34}O_4H_2O$: C, 71.25; H, 8.89. Found: C, 70.99; H, 8.47.

17β-Acetoxy-3α-(3,3′-difluoro-1′-cyclopropen-1′-yl)-3β-*O*-(thiomethoxymethyl)-5α-androstane (2e).—A solution of 0.8 ml of anhydrous dimethyl sulfoxide, 0.3 ml of acetic anhydride, and 100 mg of **2c** was left at room temperature for 36 hr. The reaction mixture was separated by tlc. The isolated product was crystallized from hexane to afford 70 mg of crystals. Recrystallization from ethanol provided the pure sample of **2e**: mp 111–112°; $[\alpha]D$ +77°; ν_{max} 3070, 1735, and 1245 cm^{-1}; nmr 0.78 (18-H), 0.86 (19-H), 2.02 (17β-OAc), 2.19 (SCH_3), 4.53 (m, 17α-H), 4.57 (SCH_2O), 7.51 ppm (t, $J \cong 2$ Hz, cyclopropene H).

Anal. Calcd for $C_{26}H_{38}O_3F_2S$: C, 66.64; H, 8.17; F, 8.11; S, 6.84. Found: C, 66.69; H, 7.93; F, 8.64; S, 7.18.

17β-Acetoxy-3α-(3′-oxo-1′-cyclopropen-1′-yl)-3β-hydroxy-5α-androstane (5d),—A mixture of 1.75 g of **2c** and 11 ml of formic acid was treated under the conditions described for the preparation of **5c**, affording 1.5 g of **5d**. Two successive recrystallizations from methylene chloride–wet acetone afforded the analytical sample of **5d**: mp 162–163°; $[\alpha]D$ +14°; ν_{max} 3180, 3020, 1835, and 1815 (shoulder), 1740, 1720 (shoulder), 1550, and 1245 cm^{-1}; nmr (100 MHz) 0.78 (18-H), 0.89 (19-H), 2.02 (17β-OAc), 4.58 (m, 17α-H), 8.43 ppm (s, cyclopropenyl H).

Anal. Calcd for $C_{24}H_{34}O_4 \cdot {}^3/_4H_2O$: C, 72.08; H, 8.95; O, 18.97. Found: C, 72.00; H, 9.08; O, 18.95.

3-(2′β-Carboxyfluorovinylidene)-5α-androstan-17β-ol Acetate (4c).—To a solution of 500 mg of **5d** in 35 ml of anhydrous methylene chloride was added 650 mg of *N*-(2-chloro-1,1,2-trifluoroethyl)diethylamine. The reaction mixture was left at room temperature for 1.25 hr. Then 0.4 ml of anhydrous methanol was added and the mixture was evaporated to dryness *in vacuo*. The residue was dissolved in hexane and treated with activated carbon. Crystallization from hexane afforded 360 mg of **4c**. Two successive recrystallizations from methylene chloride–hexane provided an analytical sample: mp 166–167° dec; $[\alpha]D$ +27°; λ_{max} 218 nm (log ε 4.26); ν_{max} 1950, 1825 (shoulder), 1800, 1740, and 1250 cm^{-1}; nmr 0.78 (18-H), 0.87 (19-H), 2.01 (17β-OAc), 4.59 (t, $J \cong 16$ Hz, 17α-H), 5.42 ppm (d, $J \cong 13$ Hz, allenic H); mass spectrum *m/e* 388 (M^+), 287 ($M^+ - 101$).

Anal. Calcd for $C_{24}H_{33}O_3F$: C, 74.19; H, 8.56; F, 4.87. Found: C, 74.00; H, 8.36; F, 5.25.

3-(2′β-Carbomethoxyvinylidene)-5α-androstan-17β-ol (4d).—A solution containing 150 mg of **4c**, 6 ml of methanol, 3 ml of methylene chloride, and 0.6 ml of concentrated hydrochloric acid was allowed to stand at room temperature for 20 hr. It was then poured into water and extracted with methylene chloride, washed with water to neutrality, and dried over anhydrous sodium sulfate. After evaporation the residue was crystallized from methanol–water, affording 110 mg of **4d**. An analytical sample was recrystallized from methanol to give mp 151–153°; $[\alpha]D$ +5°; λ_{max} 215–216 nm (log ε 4.16); ν_{max} 3240, 1960, 1725, 1710 (sh), and 1150 cm^{-1}; nmr 0.73 (18-H), 0.88 (19-H), 1.86 (17β-OH), 3.72 (methyl ester), 5.45 ppm (allenic H).

Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56; O, 13.39. Found: C, 76.91; H, 9.54; O, 13.56.

3-(2′β-Carboxyvinylidene)-5α-androstan-17β-ol (4e).—A mixture of 25 mg of **4c**, 5 ml of acetone, and 5 ml of sodium hydroxide (2%) in water was gently refluxed for 2 hr. After usual work-up there was isolated 19 mg of **4e**. Recrystallization from acetone afforded the analytical sample of **4e**: mp 210–215°; λ_{max} 219

nm (log ε 3.96); ν_{max} 3400, 1960, and 1690 cm^{-1}; nmr 0.73 (18-H), 0.91 (19-H), 5.34 ppm (22-allenic H); mass spectrum *m/e* 344 (M$^+$), 329 (M$^+$ − CH$_3$), 326 (M$^+$ − H$_2$O), 311 (M$^+$ − H$_2$O − CH$_3$), 301, 285.

3β,17β-Diacetoxy-3α-(3′-oxocyclopropen-1′-yl)-5α-androstane (5a).—Acid hydrolysis of 2.5 g of 2a under the conditions described for the preparation of 5c gave 2.25 g of 5a.[4] Three successive recrystallizations from acetone–hexane afforded the analytical sample: mp 132–134°; [α]D +8°; ν_{max} 1840, 1750, and 1730 cm^{-1}; nmr 0.78 (18-H), 0.91 (19-H), 2.28 (17-OAc), 2.10 (3-OAc), 8.32 ppm (cyclopropenyl H).

Anal. Calcd for $C_{26}H_{36}O_5$: C, 72.86; H, 8.47. Found: C, 72.52; H, 8.48.

3α-(3′-Oxo-1′-cyclopropen-1′-yl)-5α-androstane-3β,17β-diol (5b).—A solution of 200 mg of 2b, 2 ml of tetrahydrofuran, and 2.5 g of concentrated hydrochloric acid was stirred at room temperature for 1 hr. The usual extraction procedure gave 120 mg of crystals, which by recrystallizations from acetone afforded the analytical sample of 5b: mp 215–216°; [α]D +16°; λ_{max} 260–265 nmr (log ε 1.64) (MeOH); ν_{max} 3400, 1830, and 1580 cm^{-1}; nmr (100 MHz) (DMSO-d_6) 0.63 (18-H), 0.82 (19-H), 4.42 (d, *J* = 4 Hz, 17β-OH), 5.79 (3β-OH), 5.97 ppm (cyclopropenyl H).

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36; O, 13.93. Found: C, 76.87; H, 9.32; O, 13.46.

17α-(3′,3′-Difluoro-1′-cyclopropen-1′-yl)-3β,17β-dihydroxyandrostane Diacetate (7a).—Difluorocarbene addition to 6 g of 6, under the conditions mentioned above for the preparation of 2a, gave 3.5 g of 17α-difluorocyclopropene 7a, which recrystallized from methanol to afford the analytical sample: mp 138–139°; [α]D −57°; ν_{max} 3070, 1760, and 1740 cm^{-1}; nmr 0.82 (19-H), 0.95 (18-H), 2.00 (3β-OAc), 2.06 (17β-OAc), 4.60 (3α-H, unresolved m), 7.28 ppm (t, *J* = 2 Hz, difluorocyclopropenyl H).

Anal. Calcd for $C_{26}H_{36}O_4F_2$: C, 69.31; H, 8.05; F, 8.43. Found: C, 69.75; H, 7.98; F, 8.17.

17α-(3′,3′-Difluoro-1′-cyclopropen-1′-yl)-3β,17β-dihydroxy-5α-androstane (7b).—Alkaline hydrolysis of 1 g of 7a, as for the isolation of 2b, afforded 700 mg of 7b. Crystallization from acetone gave an analytical sample: mp 200°; [α]D −15°; ν_{max} 3390, 3180, and 1720 cm^{-1}; nmr (100 MHz) (acetone-d_6) 0.84 (18-H), 0.93 (19-H), 2.95 (2X-OH), 3.50 (3α-H, unresolved m), 7.65 ppm (t, *J* = 2 Hz, difluorocyclopropenyl H).

Anal. Calcd for $C_{22}H_{32}O_2F_2$: C, 72.09; H, 8.80; F, 10.37. Found: C, 72.33; H, 8.82; F, 10.53.

17α-(3′,3′-Difluoro-1′-cyclopropen-1′-yl)-3β,17β-dihydroxy-5α-androstane 3-Acetate (7c).—Selective acetylation of 2.8 g of 7b was achieved as above in the case of 2c, yielding after crystallization from acetone–hexane 1.28 g of the pure monoacetate 7c: mp 165–166°; ν_{max} 3350, 3050, 1715, and 1240 cm^{-1}; nmr 0.80 (18-H), 0.88 (19-H), 1.97 (3β-OAc), 2.83 (17β-OH, unresolved m), 4.60 (3α-H, unresolved m), 7.31 ppm (t, *J* = 2 Hz, difluorocyclopropenyl H).

Anal. Calcd for $C_{24}H_{34}O_3F_2$: C, 70.56; H, 8.39; F, 9.30. Found: C, 70.52; H, 8.46; F, 9.82.

17-(2′-α-Trifluoromethylvinylidene)-3β-hydroxy-5α-androstane Acetate (8a) and Its 21 Isomer 8b.—A mixture of 500 mg of 7c, 6.25 ml of methylene chloride (distilled over phosphorus pentoxide), and 346 mg of fluoramine reagent was stirred at room temperature for 1 hr. The reaction mixture was chromatographed over 25 g of Florisil. Elution with hexane–ether (98:2) afforded 70 mg of allene 8a. Crystallization from methanol gave an analytical sample: mp 128–129°; [α]D +7°; ν_{max} 1980, 1740, and 1240 cm^{-1}; nmr 0.861 (18-H), 0.85 (19-H), 1.98 (3β-OAc), 4.66 (3α-H, unresolved m), 5.33 ppm (21-H, unresolved m); mass spectrum *m/e* 410 (M$^+$).

Anal. Calcd for $C_{24}H_{33}O_2F_3$: C, 70.21; H, 8.10; F, 13.89. Found: C, 70.54; H, 8.42; F, 13.54.

Further elution with hexane–ether (98:2) gave 22 mg of 17β-fluoro-17α-(3′,3′-difluoro-1′-cyclopropen-1′-yl-(3β-hydroxy-5α-androstane acetate (7d). Recrystallization from methanol gave an analytical sample: mp 172–174°; [α]D +14°; ν_{max} 3090, 1730, and 1240 cm^{-1}; nmr 0.83 (18-H, 19-H), 2.01 (3β-OAc), 4.66 (3α, unresolved m), 7.33 ppm (t, *J* = 2 Hz, difluorocyclopropenyl H); mass spectrum *m/e* 410 (M$^+$).

Anal. Calcd for $C_{24}H_{33}O_2F_3$: C, 70.22; H, 8.10; F, 13.89. Found: C, 69.97; H, 8.29; F, 14.20.

Compound 8b was isolated in 1% yield from the mother liquors of 8a after tlc on silica gel in hexane–ethyl acetate (95:5). After crystallization from methanol, the analytical sample of 8b was obtained: mp 125–126°; [α]D +51°; ν_{max} 1980 and 1740 cm^{-1}; nmr 0.925 (18-H), 5.44 ppm (m, 21-H); mass spectrum *m/e* 410 (M$^+$), 395 (M$^+$ − CH$_3$), 350 (M$^+$ − HOAc), 335 (M$^+$ − HOAc − CH$_3$), 296.

Anal. Calcd for $C_{24}H_{33}O_2F_3$: C, 70.21; H, 8.10; F, 13.89. Found: C, 70.34; H, 7.95; F, 14.00.

3β-Acetoxy-17α-(3′-oxo-1′-cyclopropen-1′-yl)-17β-hydroxy-5α-androstane (9).—A mixture of 1 g of 7c in 20 ml of formic acid was stirred at room temperature for 1 hr. The mixture was then poured into water, extracted with ethyl acetate, and washed with sodium bicarbonate solution and then with water to neutrality. The organic layer was dried over anhydrous sodium sulfate. After evaporation of the solvent there was obtained 750 mg of 9. Recrystallization from acetone afforded the analytical sample: mp 187–189°; [α]D −42°; ν_{max} 3400, 1820, 1730, and 1570 cm^{-1}; nmr 0.81 (18-H), 0.92 (19-H), 1.97 (3β-OAc), 8.43 ppm (s, cyclopropenyl H).

Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.42; H, 8.83.

3β-Acetoxy-17-(2′-carboxyfluorovinylidene)-5α-androstane (8c).—To a solution of 9 (2.8 g) in 75 ml of anhydrous methylene chloride there was added 3.7 g of fluoramine. The reaction mixture was left at room temperature for 2 hr. Then 1.2 ml of anhydrous methanol was added and the mixture was evaporated to dryness *in vacuo*. The residue was crystallized from hexane to afford 2.29 g (81%) of 8c. Two successive recrystallizations from hexane provided the analytical sample: mp 175°; [α]D −36°; λ_{max} 226 nm (log ε 4.23); ν_{max} 1960, 1810, and 1730 cm^{-1}; nmr 0.83 (19-H), 0.93 (18-H), 2.00 (3β-OAc), 5.51 ppm (t, *J* = 4 Hz, 21-H).

Anal. Calcd for $C_{24}H_{33}O_3F$: C, 74.18; H, 8.56; F, 4.88. Found: C, 74.12; H, 8.29; F, 4.43.

17-(2′-Carbomethoxyvinylidene)-5α-androstan-3β-ol (8d).—To 100 mg of 8e in 2 ml of anhydrous methylene chloride and 4 ml of anhydrous methanol, a solution of 5 ml of sodium methoxide, 2% in methanol, was added. The mixture was left at room temperature for 3.5 hr. After treatment with acetic acid to neutrality, the reaction mixture was poured into water, extracted with ethyl acetate, and washed wih water to neutrality. The dried material was purified by chromatography on silica gel using benzene–methylene chloride–ether (45:45:10) as eluent, yielding 75 mg (79%) of 8d. The analytical sample was prepared by recrystallization from methanol: mp 89–90°; [α]D −81°; λ_{max} 222 nm (log ε 4.21); ν_{max} 3400, 1960, and 1730 cm^{-1}; nmr 0.80 (19-H), 0.90 (18-H), 3.71 (methyl ester), 5.6 ppm (t, *J* = 6 Hz, allenic H); mass spectrum *m/e* 358 (M$^+$), 343 (M$^+$ − CH$_3$), 340 (M$^+$ − H$_2$O).

Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56; O, 13.39. Found: C, 76.98; H, 9.61; O, 13.22.

20-Methoxy-21-carbomethoxy-5a-pregn-17(20)-en-3β-ol (10).—To a solution of 8d (250 mg) in 4 ml of anhydrous methylene chloride and 8 ml of anhydrous methanol, 10 ml of sodium methoxide, 2% in anhydrous methanol, was added. The reaction mixture was left at room temperature for 16 hr. After work-up as above 250 mg (95%) of 10 were obtained. Recrystallization from methanol afforded the analytical sample: mp 117–118°; [α]D +24°; ν_{max} 3400, 1750, and 1665 cm^{-1}; nmr 0.83 (19-H), 0.86 (18-H), 3.30 (21-H), 3.50 (20-OCH$_3$), 3.70 ppm (21-methyl ester).

Anal. Calcd for $C_{24}H_{36}O_4$: C, 75.36; H, 7.91. Found: C, 75.30; H, 7.86.

21-Carbomethoxy-3β-hydroxy-5α-pregnan-20-one (11a).—A solution containing 100 mg of 10, 10 ml of methanol, and 2 ml of hydrochloric acid (18%) was left at room temperature for 5 hr. It was poured into water and extracted with ethyl acetate, washed with water to neutrality, and dried over anhydrous sodium sulfate. After evaporation of the solvent, 98 mg (97%) of 11a was obtained. The analytical sample was obtained after recrystallization from methanol to show mp 143–145°; [α]D +104°; ν_{max} 3500, 1755, and 1720 cm^{-1}; nmr 0.63 (18-H), 0.80 (19-H), 3.43 (21-CH$_2$), 3.73 ppm (CO$_2$Me); mass spectrum *m/e* 376 (M$^+$), 361 (M$^+$ − CH$_3$), 358 (M$^+$ − H$_2$O), 233, 215.

Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 72.95; H, 9.45.

3β-Hydroxy-21-carboxy-5α-pregnan-20-one (11b).—To a solution of 50 mg of 11a in 10 ml of methanol, 25 mg of potassium carbonate in 2 ml of water was added. The mixture was refluxed for 15 min. Then it was poured into water and extracted with ether to remove the neutral components. The aqueous phase was then acidified with dilute hydrochloric acid to pH 2. The solution was extracted with chloroform, washed with water to neutrality, and dried over sodium sulfate. After evaporation of

the solvent *in vacuo* there was obtained 37 mg (60%) of **11b**: mp 105° dec; ν_{max} 3400, 1730, and 1710 cm^{-1}; nmr 0.54 (19-H), 0.73 (18-H), 3.35 ppm (21-CH_2); mass spectrum *m/e* 318 ($M^+ - CO_2$), 44 (CO_2).

3β-Hydroxy-5α-pregnan-20-one (11c).—A solution containing 25 mg of **11b** and 5 ml of 2% potassium hydroxide in 98% methanol was gently heated at reflux temperature for 3 hr. It was then poured into water, extracted with ethyl acetate, washed with water to neutrality, and dried over anhydrous sodium sulfate. After evaporation there was isolated 21 mg (95%) of 3β-hydroxy-5α-pregnan-20-one (**11c**). Recrystallization from methanol gave the pure sample of **11c**: mp 188–190°; $[\alpha]_D$ +115°; ν_{max} 3380 and 1705 cm^{-1}. This compound was shown to be identical with an authentic sample of **11c** by mixture melting point, ir, nmr, and tlc analysis.

20-Cyano-3β-acetoxy-5α-pregn-17(20)-ene-21-carboxylic Acid (12a) and 20-Cyano-3β-acetoxy-5α-pregn-17(20)-ene-21-carboxylic Acid (12b).—A mixture of 300 mg of **8c**, 6 ml of ethanol (96%), 3 ml of water, and 300 mg of potassium cyanide was refluxed for 1 hr. Then it was poured into water, acidified with dilute hydrochloric acid to pH 2, and extracted with ethyl acetate. The organic layer was washed to neutrality, dried over anhydrous sodium sulfate, and evaporated to dryness. The product was purified by preparative tlc, using chloroform–methanol (9:1). The less polar fraction (151 mg) corresponded to **12a**. Recrystallization from ethyl acetate afforded the pure sample: mp 196–197°; $[\alpha]_D$ ±0°; λ_{max} 223 nm (log ε 4.10); ν_{max} 3100, 2225, 1740, and 1250 cm^{-1}; nmr 0.70 (19-H), 0.89 (18-H), 2.20 (3β-OAc), 3.61 ppm (21-CH_2); mass spectrum *m/e* 413 (M^+), 353 (M^+ – HOAc), 338 (M^+ – HOAc – CH_3).

The second fraction corresponded to compound **12b** (90 mg). Recrystallization from ethyl acetate gave the pure sample: mp 228–229°; $[\alpha]_D$ ±0°; λ_{max} 223–224 nm (log ε 4.13); ν_{max} 3350, 2210, and 1725 cm^{-1}; nmr 0.77 (18-H), 0.86 (19-H), 3.63 ppm (21-CH_2); mass spectrum *m/e* 371 (M^+), 356 ($M^+ - CH_3$), 353 ($M^+ - H_2O$).

17-(2′β-Carboxyvinylidene)-5α-androstan-3β-ol (8e).—A solution of 60 mg of **8c** in 10 ml of acetone and 1 ml of sodium hydroxide (2%) in water was refluxed for 2 hr and poured into water. Extraction with ethyl acetate removed the neutral components. The aqueous phase was then acidified with dilute hydrochloric acid, extracted with ethyl acetate, washed with water to neutrality, and dried over sodium sulfate. After evaporation of the solvent 50 mg of **8e** was obtained. Recrystallization from acetone–methylene chloride afforded the analytical sample: mp 144–145°; $[\alpha]_D$ −29° (dioxane); λ_{max} 226 nm (log ε 3.98); ν_{max} 3250, 1960, and 1690 cm^{-1}; nmr 0.83 (19-H), 0.93 (18-H), 5.45 ppm (t, *J* = 4 Hz, 22-H); mass spectrum *m/e* 344 (M^+), 326 ($M^+ - H_2O$), 311 ($M^+ - H_2O - CH_3$).

Registry No.—**1a**, 10148-98-8; **1b**, 17006-64-3; **2a**, 19646-55-0; **2b**, 38616-25-0; **2c**, 38616-26-1; **2d**, 38616-27-2; **2e**, 38616-28-3; **3a**, 38616-29-4; **3b**, 19516-58-6; **4a**, 38616-31-8; **4b**, 38616-32-9; **4c**, 38616-33-0; **4d**, 38616-34-1; **4e**, 38616-35-2; **5a**, 19516-98-4; **5b**, 38616-37-4; **5c**, 38616-38-5; **5d**, 38616-39-6; **6**, 27741-55-5; **7a**, 21947-63-7; **7b**, 38616-51-5; **7c**, 34091-97-9; **7d**, 34091-98-0; **8a**, 34091-99-1; **8b**, 34092-00-7; **8c**, 34092-02-9; **8d**, 34092-03-0; **8e**, 34092-05-2; **9**, 34092-01-8; **10**, 34092-04-1; **11a**, 34092-06-3; **11b**, 38616-18-1; **11c**, 516-55-2; **12a**, 38400-05-4; **12b**, 38400-06-5; *N*-(2-chloro-1,1,2-trifluoroethyl)diethylamine, 357-83-5.

Transition Metal Catalyzed Reactions of Allene[1]

D. ROBERT COULSON

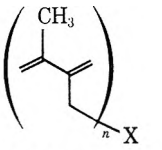
Contribution No. 1967 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898

Received January 12, 1973

Allene reacts with various amines or carbon acids in the presence of catalytic amounts of certain group VIII metal complexes to give high yields of derivatives of 2,3-dialkyl-1,3-butadienes (**1b–e**). Under the same conditions triethylsilane adds to allene, forming triethylallylsilane. Diels–Alder adducts of the dienes with maleic anhydride are also described. Possible mechanisms for the catalytic reactions are discussed.

Numerous reports of transition metal catalyzed reactions of 1,3-dienes with weak acids[2] or amines[3] have appeared in the literature. By contrast, only one report[4] has dealt with similar reactions of 1,2-dienes. In this report, Shier described the reactions of allene with acetic acid in the presence of palladium acetate. Of the several products isolated, the predominant one was 3-methyl-2-methylene-3-butenyl acetate (**1a**), formally resulting from a condensation of two molecules of allene with one of acetic acid.

Our work in this area resulted from a general interest in the transition metal catalyzed reactions of allene with amines. In the course of our investigations, a series of related reactions were discovered involving highly specific, catalytic condensations of allene with amines as well as with certain carbon acids. The resulting products (**1b–e**) have been shown to be of the



1a, X = $OCOCH_3$; *n* = 1
b, X = NR_2; *n* = 1
c, X = CR_3'; *n* = 1
d, X = NR; *n* = 2
e, X = CR_2; *n* = 2

same structural type as Shier's product, **1a**. As a result of the apparent generality of these reactions, our investigation was primarily directed toward developing the synthetic aspects of this area.

Results

Catalytic Reactions of Allene with Amines.—In the presence of various compounds of palladium or rhodium, *e.g.*, $PdCl_2$, $RhCl_3 \cdot 3H_2O$, $[P(Ph)_3]_4Pd$, or $[P(Ph)_3]_2Pd \cdot$olefin, allene and various amines reacted to give

(1) Part of this work was disclosed at the 163rd National Meeting of American Chemical Society, Division of Petroleum Chemistry, Symposium on "New Routes to Olefins," Boston, Mass., April 1972.

(2) (a) G. Hata, K. Takahashi, *et al.*, *J. Org. Chem.*, **36**, 2116 (1971); (b) E. S. Brown, and E. A. Rick, *Chem. Commun.*, 112 (1969); (c) E. J. Smutny, *J. Amer. Chem. Soc.*, **89**, 6793 (1967); (d) W. E. Walker, R. M. Manyik, *et al.*, *Tetrahedron Lett.*, **No. 43**, 3817 (1970).

(3) (a) S. Takahashi, T. Shibano, and N. Hagihara, *Bull. Chem. Soc. Jap.*, **41**, 454 (1968); (b) T. Mitseyusu, M. Hara, *et al.*, *Chem. Commun.*, 345 (1971).

(4) G. D. Shier, *J. Organometal. Chem.*, **10**, 15 (1967).

TABLE I

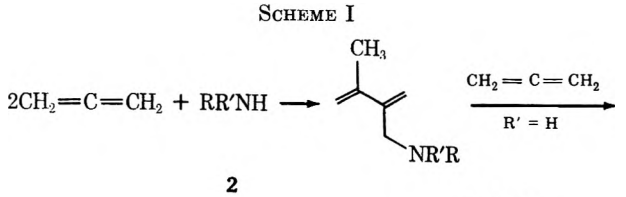
CATALYTIC CONDENSATIONS OF AMINES AND ALLENE[a]

Registry no.	Amine	Yield[c] of mono-dienyl-amine, %	Bp, °C (mm)	Yield[c] of bis-(dienyl)-amine, %	Bp, °C (mm)	Mole ratios of allene:amine:catalyst
7664-41-7	Ammonia	23	77.5–78 (100)	25	60 (0.4)	200:1200:1
	Ammonia[b]	2	77.5–78 (100)	50	60 (0.4)	200:1200:1
74-89-5	Methylamine	42	85.5–86.5 (100)	20	56–57.5 (0.3)	500:600:1
	Methylamine			58	46–57.5 (0.3)	1200:300:1
75-04-7	Ethylamine	29	47 (7)			500:200:1
	Ethylamine			60	49.5 (0.08)	800:200:1
75-31-0	Isopropylamine	44	30–33 (0.7)			500:200:1
107-10-8	Propylamine	30	54 (8)			580:230:1
75-64-9	*tert*-Butylamine	32	64–66 (11)			800:200:1
108-91-8	Cyclohexylamine	75	45 (0.4)			500:400:1
62-53-3	Aniline	12	76 (0.2)			500:200:1
768-94-5	Adamantane amine	75	108–113 (0.4)			500:200:1
124-40-3	Dimethylamine	70	136.5 (750)			250:600:1
110-68-9	*n*-Butylmethylamine	79	81–84 (7)			300:100:1
123-75-1	Pyrrolidine	78	71–74 (7)			500:200:1
110-89-4	Piperidine	79	71 (5.2)			500:200:1
110-91-8	Morpholine	41	60–61.5 (0.4)			500:200:1
100-60-7	*N*-Methylcyclohexylamine	67	80–81 (0.5)			500:200:1
109-89-7	Diethylamine	77	59–60.5 (7)			500:200:1
5459-93-8	*N*-Ethylcyclohexylamine	84	80–81 (0.4)			500:200:1
100-61-8	*N*-Methylphenylamine	62	90–90.5 (0.1)			500:200:1
141-43-5	β-Aminoethanol	37	62.5–63 (0.22)			500:200:1

[a] All the reactions were carried out under the conditions described for the preparation of 2 (R′ = H; R = CH_3) in the Experimental Section. [b] Temperature 140°. [c] Yields are based on the limiting component.

derivatives of 3-methyl-2-methylene-3-butenylamine (Scheme I).

SCHEME I



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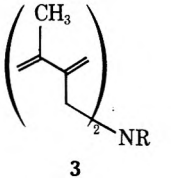


3

R = H, alkyl
R′ = H, alkyl, aryl

By employing ammonia or primary amines, both mono(dienyl)amines, 2, and bis(dienyl)amines, 3, were formed. Either product could usually be made the predominant product by varying the reaction temperature or mole ratio of the reactants. In most cases, the only side reaction observed was a competing, and usually negligible, homopolymerization of allene. Table I gives examples of the products obtained from these reactions.

The reactions could be easily performed by passing allene into a solution of the amine and catalyst in hexamethylphosphoramide at *ca.* 1-atm pressure. This solvent was chosen over several others because of a relatively greater ease of product separation. Temperatures of at least 70–90° were usually required for reasonable reaction times (<18 hr). When shorter reaction times were desired the reactions were conducted in sealed stainless steel vessels using lower boiling solvents, *e.g.*, tetrahydrofuran or benzene, and higher temperatures (*ca.* 100–140°).

Palladium complexes were generally superior to those of rhodium and most of the work described here involves the use of palladium catalysts. Of the several Pd(0) complexes tested, bis(triphenylphosphine)-(maleic anhydride)palladium[5] was used most frequently because of its high solubility and stability in air. With these catalysts, product–catalyst mole ratios of 75–100 were routinely achieved but values of 500–1000 could be easily reached, although at the expense of a decreased reaction rate.

It was observed that both Pd(0) and Pd(II) complexes were effective catalysts except when ammonia was employed in place of an amine. In this case, only Pd(0) complexes were found to be active.

In an attempt to gain some insight into the effects of reaction variables on these reactions, a brief study was made of the effect of changing the solvent and catalyst in the reaction of *n*-butylmethylamine with allene. Table II summarizes the results of this study.

The structural assignments of the products were based mainly on the results of studies of their physical properties. The properties found for 2 (R = CH_3; R′ = H) may be regarded as typical. The infrared spectrum[6] of this compound revealed a single strong absorption at 1607 cm^{-1}. The ultraviolet spectrum showed an absorption (λ_{max} 225 mμ, ε 17,200 in EtOH)

(5) S. Takahashi and N. Hagihara, *J. Chem. Soc. Jap., Pure Chem. Sect.*, **88**, 1306 (1967).

(6) The infrared[7] and ultraviolet[8] (EtOH) spectra of 2,3-dimethylbutadiene contain absorptions at 1600 cm^{-1} and λ_{max} 227 mμ, respectively.

(7) C. N. R. Rao, "Chemical Applications of Infrared Spectroscopy," Academic Press, New York, N. Y., 1963, p 149.

(8) W. J. Bailey and J. C. Goosens, *J. Amer. Chem. Soc.*, **78**, 2804 (1956).

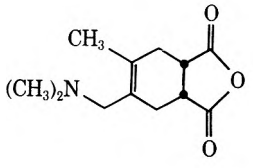
TABLE II
EFFECT OF SOLVENT AND CATALYST ON REACTION OF ALLENE WITH *n*-BUTYLMETHYLAMINE[a]

Registry no.	Catalyst	Solvent	Yield[c] of 2,[b] %
7647-10-1	$PdCl_2$	Benzene	83
	$PdCl_2$	Hexamethylphosphoramide	81
	$PdCl_2$	Acetonitrile	68
	$PdCl_2$	Tetrahydrofuran	41
16520-27-7	$PdCl_2 + P(Ph)_3$	Tetrahydrofuran	71
16520-27-7	$[P(Ph)_3]_2Pd \cdot MA$[d]	Tetrahydrofuran	98

[a] The reactions were run at 110° for 3 hr in an 80-cc stainless steel autoclave using 300 mmol of allene, 100 mmol of amine, 1 mmol of catalyst, and 25 ml of solvent. [b] R = CH_3; R′ = $CH_3(CH_2)_3$. [c] Yields are based on the amine and were determined by glpc analysis. [d] Maleic anhydride.

expected for a 2,3-dialkyl-1,3-diene.[6] A relatively simple nmr spectrum gave singlets corresponding to the NH (δ 0.60 ppm, exchangeable with D_2O), NCH_3 (2.21 ppm), olefinic CH_3 (1.82 ppm), and allylic methylene (3.27 ppm) groups. The olefinic hydrogens were assigned to a complex multiplet covering a range of δ 4.9–5.15 ppm. The corresponding bis(dienyl)amine **3** (R = CH_3) possessed similar spectral properties with the exceptions of an enhanced ultraviolet absorption at λ_{max} 222 mμ (ε 26,600 in EtOH) and the absence of an NH nmr absorption. All of the compounds described in Table I possessed similar spectral properties with generally predictable variations. Table III gives a compilation of the nmr spectral characteristics for all of these compounds.

Further verification of these structural assignments came from the reactions of the tertiary amines with maleic anhydride. Thus, **2** (R′ = R = CH_3) reacted with 1 equiv of maleic anhydride to give the expected Diels–Alder adduct, **4**. A similar reaction occurred



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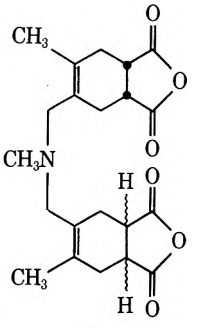

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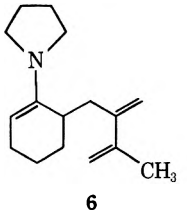
with **3** (R = CH_3), giving **5** as a mixture of syn and anti ring-junction isomers.

Although tertiary amines were found to be unreactive toward allene, enamines presented an exception. Thus, when 1-(1-cyclohexenyl)pyrrolidine was treated with allene under the usual conditions, the condensation product **6** was obtained in 34% yield.



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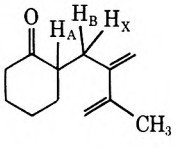

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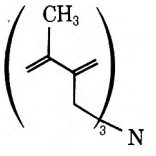
The structure of **6** was supported by its nmr spectrum, which revealed resonances attributable to an enamine hydrogen (δ 4.7–5.2 ppm, 4 H). The infrared spectrum indicated the presence of both the characteristic 1,3-diene unit (1592 cm^{-1}) and an enamine (1666 cm^{-1}). Furthermore, acidic hydrolysis of **6** gave a ketone to which structure **7** was assigned. This ketone had retained the 1,3-diene unit according to nmr analysis (δ 4.9–5.2 ppm, 4 H). Further information resulted from the observation of an unusual nmr resonance, assigned to H_X. This particular hydrogen appeared as a four-line pattern attributed to an ABX type spectrum (δ 3.33 ppm, $|J_{AX} + J_{BX}| = 17$ Hz). The unusual character of this resonance is probably due to the effect of an adjacent asymmetric center enhanced by the local field effect of the carbonyl group. Conformational preferences could also affect this resonance.

Attempts to prepare **8** directly from allene and ammonia were unsuccessful. However, by replacing the ammonia with **3** (R = H) and a trace of a radical trapping agent, phenothiazine, a material was obtained which appeared to be a sample of slightly impure **8**,



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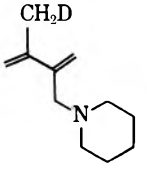
bp 94–96° (0.36 mm). All further attempts to purify this material induced its polymerization. The nmr spectrum of this material revealed the familiar pattern of absorptions at δ 5.43–5.13 (m, 3 H), 4.98 (m, 1 H), 3.20 (s, 2 H), and 1.84 (s, 3 H). None of the protons appeared to exchange with D_2O.

The formation of appreciable amounts of 1:1 allene–amine adducts was not observed in any of the reactions studied. For example, careful examination of the reaction products arising from the reaction of dimethylamine with allene revealed the formation of a *ca.* 1% yield of *N*,*N*-dimethylallylamine accompanied by a 70% yield of **2** (R = R′ = CH_3).

As part of a study of the reaction mechanism, *N*-deuteriopiperidine (>99% d_1) was treated with allene to give **9**.



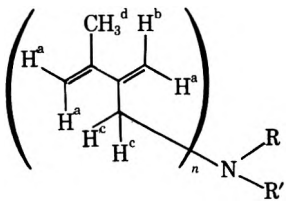
9

Nmr and mass spectral analysis revealed a total incorporation of 0.80 ± 0.05 deuterium atoms per molecule with 95 ± 3% of this amount located in the methyl group.

Catalytic Reactions of Allene with Carbon Acids.— In most respects, the reactions of allene with carbon acids were found to exactly parallel those found with amines (Scheme II). A singular exception to this generalization was the complete ineffectiveness of Pd(II) or Rh(III) complexes as catalysts. As in the case of the amines, Pd(0) complexes were found to be

TABLE III

NMR SPECTRAL DATA FOR MONO- AND BIS(DIENYL)AMINES (2 AND 3) (IN BENZENE)



Registry no.	Substituents R	R′	n	H^a	H^b	H^c	H^d	R	R′
38644-47-2	H	H	1	5.19–4.95 m	4.86 m	3.33 m	1.81 m	0.80 s	Same as R
38644-48-3	H		2	5.3–5.07 m	4.90 m	3.35 s	1.82 m	0.95 s	
38644-49-4			3	5.43–5.13 m	4.98 m	3.20 s	1.84 s		
38644-50-7	CH_3	H	1	5.15 m	4.90 m	3.27 m	1.82 m	2.21 s	0.60 s
38644-51-8	CH_3		2	5.40–5.00 m	4.89 m	3.05 s	1.95 m	2.20 s 0.99 t J = 7 Hz	
38644-52-9	C_2H_5	H	1	5.35–5.13 m	4.98 m	3.38 m	1.87 m	2.53 q J = 7 Hz 0.98 t J = 7 Hz	0.62 s
38644-53-0	C_2H_5		2	5.41–5.15 m	4.98 m	3.20 s	1.87 m	2.44 q J = 7 Hz 2.71 p J = 6.5 Hz	
38644-54-1	$(CH_3)_2CH$	H	1	5.37–5.12 m	4.98 m	3.41 s	1.87 m	0.99 d J = 6.5 Hz 2.62 t J = 7 Hz	0.72 s
38644-55-2	C_3H_7[c]	H	1	5.30–5.09 m	5.05 m	3.48 s	1.95 m	1.80–0.75 m	Obscured by R
38644-56-3	t-C_4H_9	H	1	5.31–5.07 m	4.91 m	3.31 m	1.85 m	0.99 s 2.0–0.75 m	0.55 s
38644-57-4	$(CH_2)_5CH$	H	1	5.35–5.1 m	4.98 m	3.45 s	1.88 m	2.65–2.1 m	Obscured by R
38644-58-5	C_6H_5[b]	H	1	5.31–5.01 m	5.01 m	3.83 m	1.94 m	7.32–6.32 m	Variable
38644-59-6	1-Adamantyl	H	1	5.56–5.15 m	5.01 m	3.45 s	1.91 m	2.15–1.8 m 1.75–1.45 m	0.55 s
38644-60-9	CH_3	CH_3	1	5.33–5.07 m	5.01 m	3.05 m	1.90 m	2.13 s	Same as R
38644-61-0	CH_3	n-C_4H_9	1	5.46–5.11 m	4.98 m	3.05 s	1.85 m	2.07 s	1.55–0.65 m 2.45–2.05 m
38644-62-1	$(CH_2)_2$	$(CH_2)_2$	1	5.52–5.12 m	5.01 m	3.23 s	1.88 m	1.64–1.47 m 2.62–2.20 m	Same as R
38644-63-2	$(CH_2)_3$	$(CH_2)_2$	1	5.60–5.14 m	5.01 m	3.06 s	1.87 m	1.76–1.15 m 2.50–2.15 m	Same as R
38644-64-3	$(CH_2)_2O$	$(CH_2)_2$	1	5.48–5.06 m	5.02 m	3.01 s	1.88 m	2.39–2.12 m 3.72–3.48 m	Same as R
38644-65-4	CH_3	$(CH_2)_5CH$	1	5.44–5.13 m	4.98 m	3.21 s	1.89 m	2.15 s	1.9–0.75 m 2.53–2.05 m
38644-66-5	C_2H_5	C_2H_5	1	5.17–5.49 m	4.95 m	3.18 m	1.89 m	0.93 t J = 7 Hz 2.45 q J = 7 Hz	Same as R
38644-67-6	CH_3[a]	C_6H_5	1	5.21–4.89 m	4.89 m	4.04 m	1.91 m	2.85 s	7.7–6.4 m
38644-68-7	C_2H_5	$(CH_2)_5CH$	1	5.54–5.17 m	4.97 m	3.27 m	1.90 m	1.0 t J = 7 Hz 2.48 q J = 7 Hz	2.0–0.85 m 2.75–2.2 m
38644-69-8	$HO(CH_2)_2$[b]	H	1	5.36–5.03 m	4.96 m	3.72–3.19 Obscured by R′	1.90 m	2.62 t J = 6 Hz 3.72–3.19 m	3.72–3.19 Obscured by H^c

[a] CD_3CN solution. [b] CCl_4 solution. [c] $CDCl_3$ solution.

the catalysts of choice. Consequently, in all of the work described here, bis(triphenylphosphine)(maleic anhydride)palladium was the only catalyst used. Table IV gives some results of the reactions that were performed with several carbon acids.

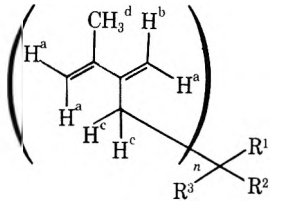
The structures assigned to **10** and **11** were based primarily on the evidence obtained from comparisons of their spectral properties with those of the previously discussed dienylamines. All of the carbon acid adducts possessed the spectral characteristics attributed to the presence of a 2,3-dialkyl-1,3-butadiene unit. In this respect, the spectral properties described for **10** (R = R′ = CO_2Et) in the Experimental Section may be regarded as typical for these compounds. The corre-

TABLE IV
CATALYTIC CONDENSATION REACTIONS OF CARBON ACIDS AND ALLENE[a]

Registry no.	Carbon acid	Yield of 10, %	Bp, °C (mm)	Yield of 11, %	Bp, °C (mm)	Mole ratios of acid:allene:catalyst
123-54-6	Acetylacetone	60[b]	90–92 (1.4)	<5		600:500:1
		<5		47	109.5 (0.5)	200:1000:1
141-97-9	Ethyl acetoacetate	58	89–89.5 (0.4)	<5		600:500:1
		<10		38	92 (0.05)	200:1000:1
105-53-3	Diethyl malonate	86[c]	80–80.5 (0.2)	0		100:100:1
105-56-6	Ethyl cyanoacetate	28	95.5 (0.35)	0		800:400:1
109-77-3	Malononitrile	47[d]	73 (0.5)	<5		600:500:1
		<5		73	100–101 (0.15)	200:500:1

[a] Unless otherwise noted, all of the reactions were carried out under the conditions described for the preparation of 10 ($R^1 = R^2 = CO_2Et$) in the Experimental Section at a temperature of 120°. Yields are based on the limiting reagent. [b] Reaction temperature 50°. [c] Reaction temperature 100°. [d] Reaction temperature 60°.

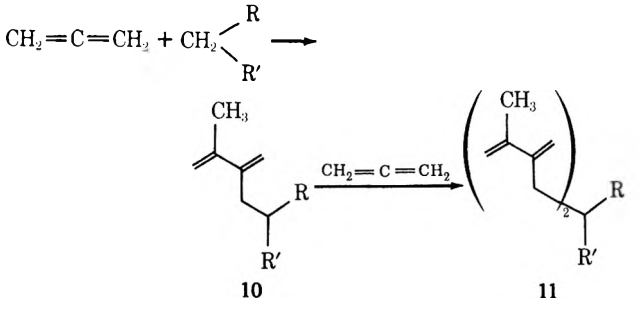
TABLE V
NMR SPECTRAL DATA FOR MONO- AND BIS(DIENYL)CARBON ACIDS (10 AND 11) (IN CCl_4)



Registry no.	Substituents R¹	R²	R³	n	H^a	H^b	H^c	H^d	R¹	R²	R³
38644-70-1	CH_3CO	CH_3CO[a]	H	1	5.22–4.76 m	5.22–4.76 m	2.75 d J = 7.5 Hz	1.96 s	2.06 s	2.06 s	3.83 t J = 7.5 Hz
38644-71-2	CH_3CO	CH_3CO		2	5.09 s 4.83 m 4.70 m	4.97 m	2.92 m	1.74 m	2.00 s	2.00 s	
38644-72-3	CH_3CO[a]	CO_2Et	H	1	5.07–4.92 m	4.90 m	2.75–2.6 m	1.87 m	2.10 s	1.22 t J = 7 Hz 4.10 q J = 7 Hz	3.67–3.39 m
38644-73-4	CH_3CO	CO_2Et		2	5.25–4.82 m	5.05 m	2.92 s	1.86 s	2.05 s	1.28 t J = 7 Hz 4.11 q J = 7 Hz	
38644-74-5	CO_2Et	CO_2Et	H	1	5.13 m	5.02 m	2.86 d J = 7.5 Hz	1.91 s	1.27 t J = 7 Hz 4.19 q J = 7 Hz	Same as R′	3.48 t J = 7.5 Hz
38644-75-6	CO_2Et	CN	H	1	5.25–4.90 m	5.02 m	3.18–2.25 m	1.90 m	1.28 t J = 7 Hz 4.18 q J = 7 Hz		3.77–3.42 m
38644-76-7	CN	CN	H	1	5.55–5.12 m 5.55–5.01 m	5.15 m 5.12 m	2.97 d J = 8 Hz	1.97 s			3.91 t J = 8 Hz
38644-77-8	CN	CN		2	5.55–5.3 m 5.12 m	5.12 m	2.86 s	1.97 s			

[a] Contains enol form; data given is for keto form.

SCHEME II



R, R′ = CN, CO_2Et, $COCH_3$

sponding bisdienes, **11**, differed primarily in that the ultraviolet absorptions were enhanced by the presence of an extra chromophore and the nmr spectrum lacked evidence for a methine hydrogen. Finally, a slight complication was introduced into the spectral interpretations of **10** (R = R′ = $COCH_3$ and R = $COCH_3$, R′ = CO_2Et), since these compounds contained substantial amounts of their respective enol forms, depending upon the solvent employed. Table V gives a compilation of the nmr spectral characteristics of these compounds, excluding the enol forms.

Because of the occurrence of side reactions, it was necessary to perform the allene condensations with acetylacetone and malononitrile at temperatures below 100°. When the reaction with malononitrile was performed above this temperature, the only product obtained was an intractable yellow solid. Although this material could not be adequately characterized, it seems reasonable to suggest that it arose from an intermolecular condensation of **10** (R = R′ = CN). In this regard, it should be noted that the dimerization of malononitrile to give 1,1,3-tricyano-2-amino-1-propene has been reported[9] to be catalyzed by tetrakis(triphenylphosphine)palladium. The side reaction is apparently suppressed when excess allene is employed. In this case a good yield of **11** (R = R′ = CN) may be obtained at 120° (see the last entry in Table IV). This finding supports the view that the side reaction is similar to the catalytic dimerization of malononitrile, since one would not expect **10** (R = R′ = CN) to undergo such a condensation.

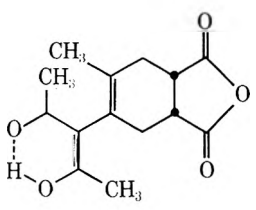
In the reaction of acetylacetone with allene, it was found that a material isomeric to **10** (R = R′ = CH_3CO) was obtained as the major product when the

(9) K. Schorpp, P. Kreutzer, and W. Beck, *J. Organometal. Chem.*, **37**, 397 (1972).

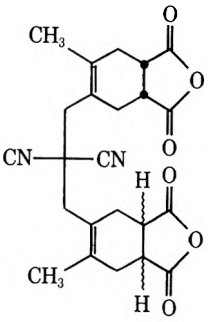
reaction was carried out above *ca.* 100°. This material was apparently formed from **10** (R = R′ = CH_3CO), since performing the reaction at lower temperatures (*ca.* 60°) gave good yields of **10** (R = R′ = CH_3CO). Upon isolation, this isomeric material proved to be an inseparable mixture of at least two compounds; therefore, the structures of these compounds remain unassigned.

Our apparent inability to prepare the compounds **11** (R = R′ = CO_2Et and R = CO_2Et; R′ = CN) may be the result of the instability of these compounds under the isolation conditions. The crude reaction mixtures gave evidence for product formation; however, rearrangements to complex mixtures appeared to occur on attempted distillation.

As with the amino dienes, maleic anhydride reacted smoothly with **10** and **11** to give the expected Diels–Alder adducts. Thus, **10** (R = R′ = $COCH_3$) and **11** (R = R′ = CN) gave the expected adducts **12** and **13**, respectively.

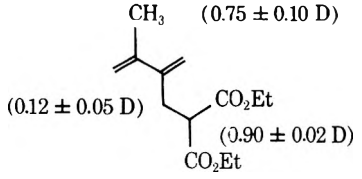


12

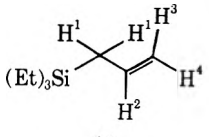


13

The reaction of allene with diethyl 2,2-dideuteriomalonate (>94% D_2) gave a labeled sample of **10** (R = R′ = CO_2Et). Mass spectral and nmr analysis revealed the following deuterium distribution.



Catalytic Reaction of Allene with Triethylsilane.— Numerous attempts were made to effect catalytic reactions between allene and other active hydrogen compounds. During this work, it was found that triethylsilane cleanly reacted with allene in the presence of bis(triphenylphosphine)(maleic anhydride)palladium to form triethylallylsilane (**14**).[10] The structure was



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assigned mainly on the basis of its nmr spectrum. A doublet at δ 1.55 (J_{12} = 8 Hz) was assigned to the allylic hydrogens. The olefinic protons, δ 4.6–6.2, displayed a pattern characteristic of a vinyl group.

(10) A. D. Petrov and V. F. Mironov, *Dokl. Akad. Nauk SSSR*, **75**, 707 (1950).

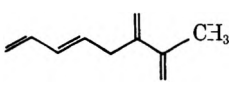
Discussion

Insufficient information is in hand to reasonably define any single mechanism for these catalytic reactions of allene. However, certain experimental facts shall be discussed which must be accommodated by any proposed mechanism.

It appears from the results of several experiments that the presence of either a Pd(0) or a Rh(I) species is necessary for catalysis to occur. The apparent activity of Pd(II) or Rh(II) complexes in the reactions of amines with allene is readily explained as resulting from the *in situ* reduction of these complexes by the amines. In support of this hypothesis, it was noted that palladium dichloride reacted with representative alkyl amines at temperatures of 80–100° to slowly deposit metallic palladium. If, as seems likely, the oxidation of the amines involves carbon–hydrogen bonds,[11] a similar oxidation pathway would not be available for ammonia, thus accounting for the observed inactivity of Pd(II) complexes in the ammonia–allene reactions.

The results of the deuterium-labeling experiments require a mechanism which places the active hydrogen of the amine or carbon acid predominantly in the olefinic methyl group of the product. In the case of the reaction of piperidine-d_1 with allene, all of the deuterium was found in the methyl group of the product. This finding is of little help in distinguishing between mechanisms, since all of the apparently reasonable mechanisms considered require this particular placement of hydrogen. However, the situation with the carbon acids is not so clear-cut. Thus, in the case of the reaction of allene with 2,2-dideuteriodiethyl malonate, some deuterium is found on the allylic methylene group. This does not appear to be the result of a slow exchange following product formation, although the uncertainty of the analytical method employed does leave some doubt. It may also be noted that this observed lack of significant exchange of **10** (R = R′ = CO_2Et) with 2,2′-dideuteriodiethyl malonate under typical reaction conditions rules out the possibility of the rapid, reversible formation of **10** (R = R′ = CO_2Et).

Apparently the presence of so-called "active hydrogen" compounds may not be necessary for the formation of products containing the characteristic 2,3-dialkyl-1,3-diene unit described here. In related work[12] reported recently, it was shown that butadiene reacts with allene in the presence of bis(triphenylphosphine)(maleic anhydride)palladium to give a 78% yield of **15**.



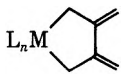
15

A possible mechanism for these reactions could involve the initial formation of a metal hydride, possibly by an oxidative addition of an amine or carbon acid to the metal. However, if such intermediates were formed, one would expect them to be reactive toward monoolefins. All attempts to observe such reactions have thus far failed.

(11) Compare with the oxidation of alcohols with palladium(II) salts: W. G. Lloyd, *J. Org. Chem.*, **32**, 2816 (1967).

(12) D. R. Coulson, *J. Org. Chem.*, **37**, 1253 (1972).

Alternative mechanisms not requiring a hydride intermediate could conceivably involve intermediates such as **16**, since metal–carbon bond cleavage of such



16

species with an amine or carbon acid would lead to the observed products. However, the evidence for such intermediates is purely circumstantial at this point.

The reaction of triethylsilane with allene obviously differs from the other reactions discussed here, since *only* a 1:1 addition product could be isolated. In this case an oxidative addition of the silane to the metal is likely to be a necessary step. This suggestion is corroborated by recent mechanistic studies[13] concerned with the catalytic additions of silanes to monoolefins.

Experimental Section

Melting points and boiling points are uncorrected. Nuclear magnetic resonance spectra were recorded at 60 MHz using a Varian Associates A-60A instrument. Chemical shifts are reported with tetramethylsilane (δ 0.00) as an internal standard. The proton integrations for all new compounds were found to be within ±5% of their theoretical values. The infrared spectra were recorded on pure liquids or KBr pellets of solids. All new compounds discussed previously but not described in this section gave satisfactory elemental analyses for carbon, hydrogen, and nitrogen, where applicable (within ±0.5 units of the calculated percentages).

***N*,3-Dimethyl-2-methylene-3-butenylamine, 2 (R′ = H, R = CH_3).**—A solution of allene (10 g, 250 mmol), methylamine (11 g, 300 mmol), and bis(triphenylphosphine)(maleic anhydride)-palladium (0.364 g, 0.5 mmol) in 25 ml of tetrahydrofuran was heated to 120° for 6 hr in an 80-cc stainless steel lined autoclave. The resulting solution was directly distilled, giving 5.8 g (42% yield) of *N*,3-dimethyl-2-methylene-3-butenylamine, **2** (R′ = H, R = CH_3): bp 85.5–86.5° (100 mm); ir 1607 cm^{-1} (C=C); uv (EtOH) λ_{max} 225 mμ (ε 17,200); nmr, see Table III.

Anal. Calcd for $C_7H_{13}N$: C, 75.6; H, 11.8; N, 12.6. Found: C, 75.45; H, 11.59; N, 12.60.

Reaction of *N*,*N*,3-Trimethyl-2-methylene-3-butenylamine, 2 (R = R′ = CH_3), with Maleic Anhydride.—A solution of **2** (6.9 g, 55 mmol) in 10 ml of benzene was added over 30 min to maleic anhydride (4.9 g, 50 mmol) in 30 ml of benzene. After standing for 18 hr the solution was directly distilled, giving 6.50 g of an oil, bp 151–152° (1.1 mm). This oil was purified by recrystallization from hot hexane, giving 3.30 g of white needles of **4**: mp 79–80°; ir 1775 and 1838 cm^{-1} (anhydride bands); nmr (benzene) δ 1.5 (s, 3 H, olefinic methyl), 1.8–2.2 (m, 8 H, *N*-methyl and methylene), 2.35–2.85 (m, 6 H, methylene and methine).

Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.65; H, 7.68; N, 6.28. Found: C, 64.48; H, 7.80; N, 6.49.

***N*-(3-Methyl-2-methylene-3-butenyl)piperidine, 2 [R = $(CH_2)_2$; R′ = $(CH_2)_3$].**—A solution of piperidine (10.0 ml, 100 mmol) and palladium chloride (0.177 g, 1 mmol) in 20 ml of hexamethylphosphoramide was warmed to 70°. Allene at *ca.* 1-atm pressure was allowed to be absorbed by the solution. After an initial slow rate of uptake the rate of absorption accelerated to *ca.* 20 ml/min. After 17 hr the absorption had essentially ceased and the dark solution was poured into 130 ml of water. The mixture was extracted with three 50-ml portions of pentane. The pentane extracts were combined, dried over magnesium sulfate, and distilled. A fraction was collected boiling at 71–75° (5 mm) and weighing 10.76 g. This material was identified as **2** [R = $(CH_2)_2$; R′ = $(CH_2)_3$] and corresponded to a 65% yield based on piperidine charged: ir 1608 cm^{-1} (1,3-diene); nmr, see Table III.

Anal. Calcd for $C_{11}H_{19}N$: C, 79.95; H, 11.59; N, 8.47. Found: C, 79.89; H, 11.51; N, 8.75.

***N*-[6-(2-Methyl-3-methylene-1,3-butadiene)-1-cyclohexenyl]-pyrrolidine (6).**—A mixture of *N*-(1-cyclohexenyl)pyrrolidine (15.1 g, 100 mmol), bis(triphenylphosphine)(maleic anhydride)-palladium (2.2 g, 3 mmol), and allene (10 g, 250 mmol) in 25 ml of tetrahydrofuran was heated to 120° for 6 hr in an 80-cc stainless steel pressure vessel. The resulting solution was distilled, giving 7.75 g (34% yield) of *N*-[6-(2-methyl-3-methylene-1,3-butadiene)-1-cyclohexenyl]pyrrolidine (**6**): bp 92–96° (0.2 mm); ir 1592 (C=C, 1,3-diene), 1633 cm^{-1} (C=C, enamine); nmr (benzene) 1.95–2.4 (m, 3 H, methylene + methine), 2.4–3.35 (m, 6 H, allylic methylene), 4.45 (t, 1 H, *J* = 4 Hz, enamine hydrogen), 4.78–5.25 (m, 4 H, olefinic).

Anal. Calcd for $C_{16}H_{25}N$: C, 83.05; H, 10.9; N, 6.05. Found: C, 82.65; H, 10.79; N, 5.64.

2-(3-Methyl-2-methylene-3-butenyl)cyclohexanone (7).—A solution of *N*-[6-(2-methyl-3-methylene-1,3-butadiene)-1-cyclohexenyl]pyrrolidine (1.15 g, 5 mmol) and concentrated hydrochloric acid (0.395 ml, 4.5 mmol) in 10 ml of methanol was stirred for 3 hr. The solution was then evaporated of solvent and the residue was extracted with pentane. The pentane layer was dried over magnesium sulfate and evaporated of solvent. The residual oil weighed 0.75 g. Glpc collection (retention time 14 min, 155°, 20% silicone gum nitrile; 8 ft × 0.25 in. column) afforded a pure sample of **7**: ir 1592 (C=C, 1,3-diene unit), 1709 cm^{-1} (C=O); nmr (CCl_4) δ 1.0–2.7 (m, 13 H, methylene and methyl), 3.03 (m, 1 H, methine), 4.9–5.2 (m, 4 H, C=C); derivative 2,4-dinitrophenylhydrazone, mp 117.8–118° from ethanol.

Anal. Calcd for $C_{18}H_{22}N_4O_4$: C, 60.35; H, 6.19; N, 15.62. Found: C, 60.0; H, 6.13; N, 15.56.

Diethyl (3-Methyl-2-methylene-3-butenyl)malonate (10) (R = R′ = CO_2Et).—A solution of diethyl malonate (30.6 ml, 200 mmol), allene (8 g, 200 mmol), and bis(triphenylphosphine)-(maleic anhydride)palladium (1.46 g, 2 mmol) in 25 ml of tetrahydrofuran was heated to 100° for 6 hr in an 80-cc stainless steel lined autoclave. The resulting solution was directly distilled giving 20.62 g (86% yield), bp 80–80.5° (0.2 mm), of **10** (R = R′ = CO_2Et): uv (EtOH) λ_{max} 232 mμ (ε 18,480); ir 1605 (1,3-diene), 1740 cm^{-1} (C=O); nmr, see Table V.

Anal. Calcd for $C_{13}H_{20}O_4$: C, 65.0; H, 8.38. Found: C, 64.64; H, 8.62.

Reaction of *N*-Deuteriopiperidine and Allene.—A solution of *N*-deuteriopiperdine[14] (>98% d_1) (5.0 ml, 50 mmol) and bis(triphenylphosphine)(maleic anhydride)palladium (0.364 g, 0.5 mmol) in 10 ml of hexamethylphosphoramide (redistilled) was placed under an atmosphere of allene at 75° with rapid stirring. Absorption of allene was allowed to proceed for 25 hr. The solution was then poured into 70 ml of water and extracted with 3 × 25 ml of pentane. The pentane layer was dried over $MgSO_4$ and filtered. The clear solution was distilled, giving 2.9 g (35% yield) of monodeuterated 2-methyl-3-(piperidinomethyl)-1,3-butadiene (**9**). Nmr analysis revealed a total of 0.78 ± 0.05 atoms of deuterium per molecule, all of which appeared to be on the methyl carbon. Mass spectral analysis gave d_0 17% and d_1 83%, in close agreement with the nmr analysis.

Reaction of Bis(2,3-dimethylenebutyl)dicyanomethane (12) with Maleic Anhydride.—A solution of maleic anhydride (2.16 g, 22 mmol) in 15 ml of benzene was added to a solution of **11** (R = R′ = CN) (2.27 g, 10 mmol) in 5 ml of benzene over 45 min with stirring. The solution was allowed to stand overnight, giving a white, crystalline mass which was filtered directly, giving 3.9 g of a white powder after washing with 3 × 15 ml of benzene. This powder could not be properly recrystallized but could be precipitated from methylene chloride by addition of ether. A white powder, 1.95 g, mp 217–218°, resulted. The formation of two stereoisomers is possible here and could account for the amorphous character of the product. The product was assigned the structure **13** on the following basis: ir 1775, 1840 cm^{-1} (anhydride); nmr (DMSO-d_6) δ 1.78 (s, 6 H, methyl), 2.2–2.6 (m, 8, methylene), 2.65–3.65 (m, 8 H, methylene and methine).

Anal. Calcd for $C_{23}H_{22}N_2O_6$: C, 65.4; H, 5.25; N, 6.63. Found: C, 65.92; H, 5.09; N, 6.47.

Attempted Preparation of Tris(3-methyl-2-methylene-3-butenyl)amine (8).—A solution of **3** (R = H) (8.85 g, 50 mmol), bis(triphenylphosphine)(maleic anhydride)palladium (0.364 g,

(13) (a) A. J. Chalk and J. F. Harrod, *J. Amer. Chem. Soc.*, **87**, 16 (1965); (b) L. H. Sommer, J. E. Lyons, and H. Fujimoto, *ibid.*, **91**, 7051 (1969); (c) J. W. Ryan and J. L. Speier, *ibid.*, **86**, 895 (1964).

(14) The *N*-deuteriopiperidine was prepared by heating *N*-deuteriopiperidinium deuteriochloride, obtained by exchange with D_2O, with freshly calcined calcium oxide.

0.50 mmol), and a trace of phenothiazine in 25 ml of tetrahydrofuran was charged to an 80-cc stainless steel presure vessel. Allene (6.0 g, 150 mmol) was added and the resulting mixture was heated to 120° for 6 hr. The solution was distilled directly, giving a middle fraction weighing 3.14 g, bp 94–96° (0.36 mm). Two other fractions (bp 93–97°) accounted for 3.52 g and the residue remaining in the distillation pot weighed 6.92 g. The middle fraction was analyzed by nmr; see Table III. Thus, the sample appeared to be *ca.* 90–95% pure **8**. All attempts to further purify this material resulted in polymer formation.

Separation of Products from Reaction of Acetylacetone with Allene.—A preparation of **10** (R = R′ = $COCH_3$) carried out at 120° according to the procedure described for the preparation of **10** (R = R′ = CO_2Et) gave a product containing *ca.* 70% of an unknown material. This product (10.0 g, >30 mmol) and maleic anhydride (5.44 g, 55.5 mmol) were allowed to stand for 4 days in 50 ml of benzene solution. The solution was then evaporated of solvent by rotary evaporation and the resulting green-yellow oil was treated with 55 ml of ether. Cooling to 0° gave crystal formation. Filtration gave 3.43 g of **12**. The filtrate was directly distilled, giving maleic anhydride (*ca.* 3.2 g) and a fraction of bp 61–65 (0.35 mm) (3.7 g) containing <5% maleic anhydride (0.32 mm) by nmr analysis.

A sample of this fraction was purified by preparative glpc (20% silicone gum nitrile column): ir 1674, 1650–1510 cm^{-1} (β-diketone, chelate); mass spectrum, parent peak at *m/e* 180 corresponding to $C_{11}H_{15}O_2$ (mol wt, 180.24); uv (EtOH) λ_{max} 271 mμ (ε 11,750) [note: **10** (R = R′ = $COCH_3$) possesses λ_{max} 275 mμ (ε 8350), enol form, and λ_{max} 223 mμ (ε 8000)]; nmr (CCl_4) δ 4.95 (m, 1.65 H), 4.87 (m, 0.30 H), 3.09 (m, 1.47 H), 2.90–2.70 (m, 0.60 H), 2.22–2.0 (m, 0.60 H), 1.79 (m, 0.85 H), 1.40 (m, 5.05 H).

Diels–Alder Reaction of (2,3-Dimethylenebutyl)diacetylmethane 10 (R = R′ = CH_3CO) with Maleic Anhydride.—A solution of maleic anhydride (4.9 g, 50 mmol) in 30 ml of benzene was added to **10** (R = R′ = $COCH_3$) (9.75 g, 55 mmol) in 25 ml of benzene. The solution was allowed to stand for 22.5 hr and was then evaporated of volatiles on a rotary evaporator (35°, 20 mm). The residue was a yellow oil. This oil, on mixing with 50 ml of ether, gave a white, crystalline solid. Filtration and washing of the solid gave 2.5 g of a white, crystalline solid, mp 122–123°. This compound is assigned the structure **12** on the following basis: ir 1775, 1838 cm^{-1} (anhydride); nmr (CD_3CN) δ 1.78 (s, 3 H, CH_3), 2.02 (s, 6 H, CH_3CO), 2.1–2.5 (m, 4 H, methylene), 3.08 (s, 2 H, methylene), 3.4–3.6 (m, 2 H, CHCO), 13.76 (s, 1 H, OH).

Anal. Calcd for $C_{15}H_{16}O_2$: C, 64.75; H, 6.51. Found: C, 65.35; H, 6.59.

Reaction of 2-Methyl-3-dimethylaminomethyl-1,3-butadiene (2, R = R′ = CH_3) with Maleic Anhydride.—A solution of 6.9 g (55 mmol) of 2-methyl-3-dimethylaminomethyl-1,3-butadiene in 10 ml of benzene under nitrogen was added with stirring over 30 min to 4.9 g (50 mmol) of maleic anhydride in 30 ml of benzene. The solution was allowed to stand for 18 hr and was then evaporated of volatiles on a rotary evaporator. The residue was directly distilled, giving 6.50 g of an oil, bp 151–152° (1.1 mm). This substance was further purified by recrystallization from hot hexane, giving 3.30 g of white needles, mp 79–80°. This compound was assigned the structure **4** on the basis of the following physical evidence: ir 1775, 1838 cm^{-1} (anhydride); nmr (benzene) δ 1.50 ppm (s, 3 H, methyl), 1.75–2.25 (m, 8 H, methyl and methylene), 2.25–2.9 (m, 6 H, methylene and methine).

Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.65; H, 7.68; N, 6.28. Found: C, 64.48; H, 7.71; N, 6.50.

Diels–Alder Reaction of Bis(2,3-dimethylenebutyl)methylamine (3, R′ = CH_3) with Maleic Anhydride.—A solution of 1.91 g (10 mmol) of **3** (R′ = CH_3) in 5 ml of benzene was added to 2.16 g (22 mmol) of maleic anhydride in 15 ml of benzene. The solution, after standing overnight, was evaporated of volatiles on a rotary evaporator (35°, 20 mm), giving a syrupy material. On mixing with 30 ml of ether the material solidified and the mixture was filtered, giving 3.62 g of a tan solid. This solid was recrystallized from benzene–hexane, giving 2.05 g of a microcrystalline material, mp 140–147°. This melting range is probably explainable by the fact that two stereoisomers are likely to be formed in this reaction. The structure assigned to this material, **5**, was found to be consistent with the following physical evidence: ir 1775, 1840 cm^{-1} (anhydride); nmr (benzene) δ 1.75 (s, 6 H, CH_3), 1.92 (s, 3 H, CH_3), 2.2–2.65 (m, 8 H, allylic methylene), 2.84 (s, 4 H, allylic methylene), 3.25–3.5 (m, 4 H, CHCO).

Anal. Calcd for $C_{21}H_{25}NO_6$: C, 65.15; H, 6.51; N, 3.62. Found: C, 65.42; H, 6.60; N, 3.52.

Catalytic Reaction of 2,2′-Dideuteriodiethyl Malonate with Allene.—A solution of 15.5 ml (100 mmol) of 2,2′-dideuteriodiethyl malonate,[15] >94% d_2, 0.182 g (0.25 mmol) of bis(triphenylphosphine)(maleic anhydride)palladium, and 4.0 g (100 mmol) of allene in 15 ml of dry tetrahydrofuran was placed in a 50-cc Carius tube and sealed. The tube was heated to 120° for 6 hr. The resulting mixture was directly distilled, affording a pure sample of deuterium-labeled diethyl (3-methyl-2-methylene-3-butenyl) malonate, bp 80° (0.2 mm). Nmr analysis of the sample in carbon tetrachloride provided the following distribution of deuterium, on the reasonable assumption that the ethyl substituents did not undergo hydrogen–deuterium exchange during the reaction: methyl group, 0.75 ± 0.10 D; methylene group, 0.12 ± 0.05 D; methine group, 0.90 ± 0.02 D. Within the limits of the measurement (±5% of the respective integration areas) there appeared to be no deuterium residing on the olefinic carbons.

A similar reaction was carried out in which the allene was replaced by a pure sample of diethyl (3-methyl-2-methylene-3-butenyl) malonate. Reisolation of the ester followed by nmr analysis showed that less than 0.05 D was present in either the methyl or the methylene group. Thus, within the limits of this method, essentially no exchange was found.

Triethylallylsilane (14).—A solution of allene (10 g, 250 mmol), triethylsilane (14.5 g, 125 mmol), and bis(triphenylphosphine)-(maleic anhydride)palladium in 25 ml of tetrahydrofuran was heated to 120° for 6 hr in an 80-cc stainless steel lined pressure vessel. The resulting solution was directly distilled, giving 9.4 g (48% yield) of **14**: bp 37° (3 mm); ir 1660 cm^{-1} (C=C); nmr (CCl_4) δ 0.25–1.30 (m, 15 H, ethyl), 1.55 (d, J_{12} = 8 Hz, 2 H, allylic hydrogens), 4.6–5.05 (m, 2 H, olefinic methylene), 5.4–6.2 (m, 1 H, J_{23} = 16 Hz, J_{24} = 8 Hz, olefinic methine).

Anal. Calcd for $C_9H_{20}Si$: C, 69.15; H, 12.89. Found: C, 69.71; H, 13.23.

Registry No.—**4**, 38644-78-9; *cis,cis*-**5**, 38644-79-0; *cis,trans*-**5**, 38644-80-3; **6**, 38644-81-4; **7**, 38644-82-5; **7** DNP, 38644-83-6; **8**, 38644-49-4; **9**, 38644-85-8; **12**, 38644-86-9; *cis,cis*-**13**, 38644-87-0; *cis,trans*-**13**, 38677-70-2; **14**, 17898-21-4; allene, 463-49-0; maleic anhydride, 108-31-6; *N*-(1-cyclohexenyl)pyrrolidine, 1125-99-1; *N*-deuteriopiperidine, 694-586; 2,2′-dideuteriodiethyl malonate, 4303-49-5; diethyl (3-methyl-2-methylene-3-butenyl)malonate, 38644-74-5; triethylsilane, 617-86-7.

Acknowledgment.—I thank Dr. R. V. Lindsey for his helpful suggestions and encouragement of this work.

(15) The diethyl 2,2-dideuteriomalonate was prepared from commercially available perdeuteriomalonic acid and ethanol-*O*-d_1.

α,α′-Dimetalations of Dimethylarenes with Organosodium Reagents. The Catalytic Effect of Certain Tertiary Amines[1]

GEORGE B. TRIMITSIS,* A. TUNCAY, R. D. BEYER, AND K. J. KETTERMAN

Department of Chemistry, Western Michigan University, Kalamazoo, Michigan 49001

Received January 15, 1973

It has been found that *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) exerts a marked catalytic influence on α,α′-dimetalations of certain dimethylarenes. Reaction of 1,2-, 1,3-, 1,6-, and 1,8-dimethylnaphthalene and *o*- and *m*-xylene with 2.1–4.0 molar equiv of *n*-amylsodium in the presence of TMEDA produced the corresponding α,α′ dianions in quantitative yield. 1,3- and 1,8-dimethylnaphthalene and *m*-xylene dianions were subjected to alkylation and/or carbonation and aldol condensation, to produce the expected α,α′-dicondensation products in high yield. 1,4-Dimethylnaphthalene and *p*-xylene could not be converted to their α,α′ dianions. The reactivity of the above dimethylarenes toward α,α′-dimetalation was established and arguments are presented to account for the observed results. The catalytic effect of certain substances other than TMEDA on metalations with *n*-amylsodium has been examined and the results are discussed.

Among the various transformations in organic chemistry, those leading to carbon–carbon bond formation have always been considered to be of the utmost fundamental interest and immense practical importance.[2] A large proportion of the carbon–carbon bond forming reactions proceed through carbanion intermediates:[2,3] aldol and Claisen condensations, Grignard reactions, alkylations of enolates and other anions, and metal acetylide reactions are just a few examples of such reactions.

Since most carbon acids are only weakly acidic,[4] the demand for strong bases capable of transforming such substrates to the corresponding carbanions under mild conditions and reasonably short reaction times is great. Among the strongest and most suitable bases presently available is the family of lithium alkyls,[5] which either alone or in conjunction with certain tertiary amine catalysts[6] have revolutionized the area of carbanion chemistry.

Although sodium and potassium alkyls[7] have been known for a long time to be much stronger bases than organolithium reagents, their use in the formation of carbanions has so far been relatively limited. The main reason for this is the high insolubility of organosodium and organopotassium reagents in hydrocarbon solvents, resulting in heterogeneous reaction mixtures and unacceptably low yield metalations even at high temperatures and prolonged reaction times.[8]

We have observed[1] that metalations with *n*-amylsodium, the most commonly used organosodium reagent, can be improved tremendously by performing these reactions in the presence of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA). Just as in the case of metalations with organolithium reagents,[6] this tertiary amine appears to have a profound catalytic effect on metalations with organosodium reagents.

The present report describes the use of this new base–catalyst system in the quantitative α,α′-dimetalation of certain dimethylnaphthalenes and xylenes, and the subsequent reaction of these dianions with representative electrophilic reagents to give a variety of α,α′-dicondensation products in high yield. In addition, the reactivity of the three isomeric xylenes as well as certain isomeric dimethylnaphthalenes toward α,α′ dianion formation has been studied and arguments are presented in order to explain the observed trends. Finally, the catalytic effect of certain substances other than TMEDA on metalations with *n*-amylsodium has been examined and the results are discussed.

Results

Formation of the *n*-Amylsodium–TMEDA Complex.—Addition of an approximately equimolar amount of TMEDA (see Experimental Section) to a suspension of *n*-amylsodium in hexane at −15° resulted in an apparent solubilization of the solid to give a bright blue solution. Centrifugation of a portion of this solution, however, gave a clear, supernatant liquid and a dark blue precipitate, indicating that the amine had a dispersing rather than a solubilizing effect on *n*-amylsodium in hexane.

The *n*-amylsodium–TMEDA mixture was found to be an exceedingly powerful metalating agent capable of quantitatively converting certain dimethylarenes to their α,α′ dianions at room temperature within 2 hr. The dimetalations of certain dimethylnaphthalenes and those of the three isomeric xylenes are described below.

Metalation of Certain Dimethylnaphthalenes.—The reactions of 1,2-, 1,3-, 1,4-, 1,6-, and 1,8-dimethylnaphthalene with *n*-amylsodium were studied under a variety of experimental conditions and their reactivities toward α,α′-dimetalation were compared. Of the five isomers examined, 1,3-dimethylnaphthalene was found to be the most reactive toward α,α′-dimetalation. Thus, treatment of this hydrocarbon at room temperature with 2.1–2.4 equiv of *n*-amylsodium[9] in the presence of 2 equiv of TMEDA for 2 hr produced the insoluble brick-red 1,3-dimethylnaphthalene dianion **1** (Scheme I) in practically quantitative yield, as evidenced by quenching the reaction mixture with deuterium oxide followed by nmr analysis of the deuterated product **2a**.

(1) For a preliminary account of part of this work, see G. B. Trimitsis, A. Tuncay, and R. D. Beyer, *J. Amer. Chem. Soc.*, **94**, 2152 (1972).

(2) W. Carruthers, "Some Modern Methods of Organic Synthesis," Cambridge University Press, London, England, 1971, pp 1–70.

(3) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, pp 492–816.

(4) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, pp 1–45.

(5) J. M. Mallan and R. L. Bebb, *Chem. Rev.*, **69**, 693 (1969).

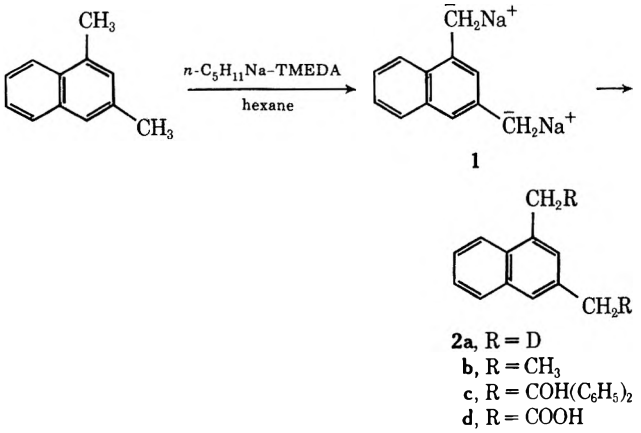
(6) (a) G. G. Eberhardt and W. A. Butte, *J. Org. Chem.*, **29**, 2928 (1964); (b) A. W. Langer, Jr., *Trans. N. Y. Acad. Sci.*, **27**, 741 (1965); (c) C. G. Screttas and J. F. Eastham, *J. Amer. Chem. Soc.*, **87**, 3276 (1965).

(7) R. A. Benkeser, D. J. Foster, and D. M. Sauve, *Chem. Rev.*, **57**, 867 (1957).

(8) A. A. Morton, E. L. Little, Jr., and W. O. Strong, Jr., *J. Amer. Chem. Soc.*, **65**, 1339 (1943).

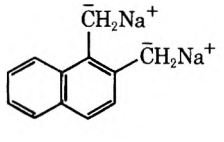
(9) The reaction of *n*-amyl chloride with sodium metal to give *n*-amylsodium proceeds to the extent of 70–80% yield, and the amount of base used in this experiment was that produced from 3 equiv of *n*-amyl chloride and excess sodium. For more details see Experimental Section.

SCHEME I



1,3-Dimethylnaphthalene dianion **1** was found to react quite readily at room temperature with electrophilic reagents to give α,α'-dicondensation products in high yield. For example, reaction with excess methyl iodide converted dianion **1** almost exclusively to 1,3-diethylnaphthalene (**2b**), as shown by vapor phase chromatographic (vpc) analysis of the crude reaction mixture. Only trace amounts of a second component, most likely the monoalkylation product, could be detected, and no starting material was recovered. Similarly, reaction of dianion **1** with 2.5 equiv of benzophenone gave the new carbonyl addition product **2c**, in 50% yield, while carbonation with excess solid carbon dioxide produced the new dicarboxylic acid **2d**, in 74% yield. Structural assignments for products **2c** and **2d** were based on C, H analyses and on spectral data (see Experimental Section).

Reaction of 1,2-, 1,6-, and 1,8-dimethylnaphthalene with *n*-amylsodium–TMEDA under conditions identical with those employed for the quantitative dimetalation of 1,3-dimethylnaphthalene, followed by deuteration with deuterium oxide and nmr analysis of the resulting products, showed the incorporation of 1.8 atoms of deuterium per molecule of 1,2- and 1,6-dimethylnaphthalene, and 1.5 atoms of deuterium per molecule of 1,8-dimethylnaphthalene, thereby indicating that only partial dimetalation of these substances had occurred under these conditions. Most interestingly, however, when the amount of *n*-amylsodium was increased to 3.5–4.0 equiv,[10] and the amount of TMEDA to 3.4 equiv, complete dimetalation was achieved in all three cases, to give α,α'-dimethylnaphthalene dianions **3**, **4**, and **5**, respectively, in quantitative yield, as shown by deuteration.



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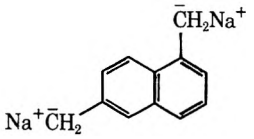
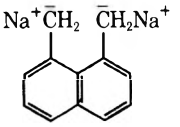


4

In addition to deuteration, 1,8-dimethylnaphthalene dianion **5** was found to undergo facile dicondensation reactions with a variety of typical electrophilic reagents. For example, treatment of **5** with 2.5 equiv of benzophenone afforded the new diol **6a**, in 52% yield, while reaction with excess carbon dioxide produced the new dicarboxylic acid **6b**, in 40% yield. The identity of products **6a** and **6b** was established by C, H analysis



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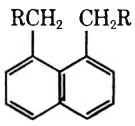


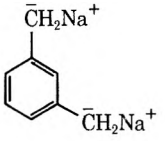
6a, R = $COH(C_6H_5)_2$
b, R = COOH

and by their nmr and ir spectra (see Experimental Section).

Unlike the isomeric naphthalenes discussed above, reaction of 1,4-dimethylnaphthalene with up to 4.0 equiv of *n*-amylsodium–TMEDA followed by deuteration resulted in the incorporation of only one deuterium atom per molecule of hydrocarbon, clearly indicating that 1,4-dimethylnaphthalene had been converted only to its monoanion.

Metalation of *o*-, *m*-, and *p*-Xylene.—The three isomeric xylenes had been previously dimetalated in low yield[8] by heating with *n*-amylsodium in octane for 3 hr. Their reactivity toward α,α'-dianion formation,[8] as indicated by subsequent carbonation of the reaction mixtures, was reported to be *m*-xylene $\cong$ *p*-xylene > *o*-xylene.

Reaction of *o*-, *m*-, and *p*-xylene with *n*-amylsodium in the presence of TMEDA under the conditions employed in the previous section established a completely different reactivity sequence for the above hydrocarbons and clearly showed that *m*-xylene was much more reactive toward α,α'-dimetalation than either of the other two isomers. Thus, reaction of *m*-xylene with 2.1–2.4 equiv of *n*-amylsodium[9] in the presence of 2.0 equiv of TMEDA in hexane at room temperature for 2 hr produced the insoluble α,α'-disodio-*m*-xylene **7** in



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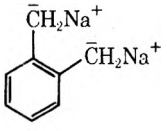


8

practically quantitative yield, as determined by subsequent quenching with deuterium oxide and quantitative nmr analysis. In addition treatment of dianion **7** with an excess of methyl iodide afforded almost exclusively 1,3-diethylbenzene, with only a minor amount of the monocondensation product 1-ethyl-3-methylbenzene being produced, as shown by vpc analysis of the crude reaction mixture.

Reaction of *o*-xylene with *n*-amylsodium–TMEDA under the above conditions followed by deuteration with deuterium oxide resulted in the incorporation of only 1.64 deuterium atoms per molecule of hydrocarbon. As in the case of 1,2-dimethylnaphthalene, however, when the amount of base was increased to 3.5–4.0 equiv[10] complete α,α'-dimetalation occurred to give dianion **8** in quantitative yield.

Finally it was found that unlike *m*- and *o*-xylene *p*-xylene failed to afford an α,α' dianion even when treated with 4.0 equiv of *n*-amylsodium in the presence of TMEDA. Instead, only α-monometalation occurred, as indicated by quenching the reaction mixture

(10) The amount of base used in these experiments was that produced from the reaction of 5.0 equiv of *n*-amyl chloride and excess sodium. For more details see footnote 9 and Experimental Section.

with deuterium oxide, followed by nmr analysis of the resulting product.

Next, an effort was made to investigate whether substances other than TMEDA might serve as catalysts in the α,α′-dimetalation of dimethylarenes by means of *n*-amylsodium in hydrocarbon solvents. For this purpose, the effect of 1,4-diazabicyclo[2.2.2]octane (DABCO), a tertiary amine which has been used extensively as a catalyst in metalations with organolithium reagents,[6a,11] and sodium *tert*-butoxide, which has been occasionally used to promote metalations with *n*-amylsodium,[12] were tested.

Reaction of *m*-xylene with 2.1–2.4 equiv of *n*-amylsodium[9] in the presence of 2.2 equiv of DABCO, under conditions identical with those described earlier, followed by treatment of the reaction mixture with an excess of methyl iodide afforded a mixture of products, consisting of starting material, 1-ethyl-3-methylbenzene, and 1,3-diethylbenzene in the ratio of 2.8:1.0:1.1.

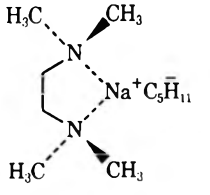
Similar results were obtained when dimethylation of *m*-xylene was attempted in the presence of sodium *tert*-butoxide as a catalyst. Thus, treatment of this hydrocarbon with 2.1–2.4 equiv of *n*-amylsodium[9] and 2.8 equiv of sodium *tert*-butoxide at room temperature for 2 hr, followed by methylation of the reaction mixture with excess methyl iodide, again afforded starting material, 1-ethyl-3-methylbenzene and 1,3-diethylbenzene, this time in a ratio of 1.0:1.1:4.6.

Finally, it was found that reaction of *m*-xylene or 1,3-dimethylnaphthalene with *n*-amylsodium under the above conditions, but in the *absence* of a catalyst, produced only low yield α-monometalation, and no dimetalation at all.

Discussion

Catalytic Effect of TMEDA on Metalations with *n*-Amylsodium.—The results described in the previous section clearly indicate that unlike DABCO and sodium *tert*-butoxide, TMEDA is an exceedingly effective catalyst in metalations of weak carbon acids by means of *n*-amylsodium.

Conceivably TMEDA can catalyze metalations with organosodium reagents in at least two different ways. First, it can coordinate with the sodium ion (structure **9**) and in so doing it can cause the large *n*-amylsodium



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aggregates to disintegrate into smaller particles, thereby providing a much larger surface area for the reaction to occur. That a peptizing action does indeed occur when TMEDA is added to the organosodium reagent is quite evident, since an *n*-amylsodium slurry in hexane appears as a true solution upon addition of TMEDA. As pointed out earlier, high-speed centrifugation of the reaction mixture afforded a dark blue precipitate and a clear supernatant layer, thereby confirming that the effect of TMEDA was to peptize rather than to solubilize the *n*-amylsodium aggregates in the hydrocarbon solvent.

In addition to its peptizing action, TMEDA may also catalyze metalations with *n*-amylsodium in another way. Complex formation between the sodium ions and TMEDA will undoubtedly help diffuse the polarizing power of the metal ion, thus weakening the carbon–sodium bond. As a result the carbanion will become more basic and therefore more reactive. Similar theories have been proposed in order to explain the catalytic effect of TMEDA and other tertiary amines on metalation reactions with organolithium reagents.[6]

The inability of DABCO to catalyze metalations with *n*-amylsodium is quite interesting, especially since this diamine has been found to be almost as effective[6a] in catalyzing metalations with alkyllithium reagents as TMEDA. The ineffectiveness of DABCO as a catalyst in metalations with *n*-amylsodium is most likely due to the fact that unlike TMEDA this diamine cannot act as a bidentate ligand.[13] Its coordinating power is therefore much lower than that of TMEDA, and its ability to disintegrate the tightly packed organosodium aggregates is considerably weaker. Although organolithium reagents also exist in a polymeric form[14] in hydrocarbon solvents, these compounds are much less ionic than organosodium compounds and the monomer units are held much less tightly in the aggregates. Consequently, even monodentate ligands such as DABCO and triethylamine have been shown to be capable of disrupting the polymeric alkyllithium species,[6c] thereby catalyzing metalations by means of these reagents.

Morton[12b] in 1955, and more recently Benkeser[12a] and his coworkers, have demonstrated that sodium *tert*-butoxide can serve as an effective catalyst in certain metalations with organosodium reagents. For example, it was found that, while treatment of *tert*-butylbenzene with *n*-amylsodium in nonane for 20 hr afforded only a 17% yield of ring metalation,[12a] an identical reaction in the presence of sodium *tert*-butoxide increased the yield of metalation to 70%. Under the reaction conditions employed during the present study the catalytic properties of sodium *tert*-butoxide in organosodium metalations were found to be slightly better than those of DABCO but definitely poorer than those of TMEDA.

Relative Reactivity of Isomeric Dimethylarenes toward α,α′-Dimetalation.—The fact that not all of the isomeric xylenes and dimethylnaphthalenes could be converted to their α,α′ dianions with equal facility is of particular interest and merits further discussion. Deuteration experiments during the present study clearly established that the ease of α,α′-dimetalation in the case of the xylenes is *m*-xylene > *o*-xylene ≫ *p*-xylene. This reactivity sequence is quite different from that reported by Morton[8] and his coworkers, who found *p*-xylene to be just as reactive as *m*-xylene toward α,α′-dimetalation, and *o*-xylene to be the least reactive of the three.

The reactivity sequence established during the

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(12) (a) R. A. Benkeser, T. F. Crimmins, and Wen-hong Tong, *J. Amer. Chem. Soc.*, **90**, 4366 (1968); (b) A. A. Morton, C. E. Claff, Jr., and F. W. Collins, *J. Org. Chem.*, **20**, 428 (1955); (c) A. A. Morton and A. E. Brachman, *J. Amer. Chem. Soc.*, **73**, 4363 (1951); (d) A. A. Morton, *Ind. Eng. Chem.*, **42**, 1488 (1950).

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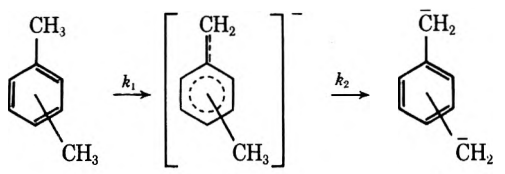
present study for the α,α'-dimetalation of the three isomeric xylenes can be best explained by means of a two-step mechanism as shown in Scheme II.

SCHEME II



10 11

According to this mechanism the hydrocarbon is envisioned to react first with 1 equiv of base to produce the benzylic monoanion **10**, which in turn reacts with a second molecule of base to form the dianion **11**. Undoubtedly, the negative charge in monoanion **10** will make ionization of the second methyl group much more difficult than that of the first ($k_1 > k_2$), and therefore k_2 will be the rate-determining step. Furthermore, the ease of ionization of the second methyl group is not expected to be the same for all three isomeric xylene monoanions, but instead should depend on the electron density accumulation on the carbon bearing each of the methyl groups. Since delocalization in benzylic anions such as **10** is known to result in the largest charge accumulation at the para position of the benzene ring, with the ortho and meta positions receiving progressively less charge,[15] it would reasonably follow that the tendency of the three isomeric xylene monoanion toward dianion formation would be in the order meta > ortho > para, a conclusion which is in excellent agreement with our experimental results.

Similar arguments can be proposed to account for the results obtained in the case of the five isomeric dimethylnaphthalenes. Their reactivity toward latteral dimetalation as determined in the present study was shown to be 1,3-dimethylnaphthalene > 1,2-dimethylnaphthalene ~ 1,6-dimethylnaphthalene > 1,8-dimethylnaphthalene ≫ 1,4-dimethylnaphthalene. Assuming that dianion formation proceeds through a monoanion such as that represented by structure **12**, the above results are, for the most part, in good qualitative agreement with Adamov's[16] self-consistent field (scf) calculations concerning the electron-density distribution in 1-methylnaphthalene monoanion **13**. These

12 13

calculations predict that charge accumulation in monoanion **13** decreases in the order α-carbon > C_4 > C_2 > C_7 > C_5 > C_6 > C_3 > C_8. On the basis of these electron-density distributions, the high reactivity of 1,3-dimethylnaphthalene and the low reactivity of 1,4-dimethylnaphthalene toward α,α'-dianion formation can be easily rationalized. The lower than expected reactivity of 1,8-dimethylnaphthalene toward α,α'-dianion formation is most likely due to the inability of the incipient 1,8-dimethylnaphthalene dianion to acquire a completely flat configuration because of steric interactions between the peri hydrogens, thereby rendering the transition state leading to the 1,8-dimethylnaphthalene dianion **5** somewhat less stable than that leading to the other dimethylnaphthalene dianions. Alternatively, the close proximity of the two negative charges may cause 1,8-dimethylnaphthalene dianion **5** and the transition state leading to it to be less stable than the other dimethylnaphthalene dianions.

Finally, the equal reactivity of 1,2- and 1,6-dimethylnaphthalene toward α,α'-dianion formation suggests that C_6 of monoanion **13** must bear much more negative charge than Adamov's[16] calculations would seem to indicate.

Conclusions

The introduction of TMEDA as a catalyst in metalations of weak carbon acids by means of *n*-amylsodium in hydrocarbon solvents is seen to exert a profound influence on the yield of these reactions. For the first time metalations with organosodium reagents are made to proceed in high yields, mild conditions, and short reaction times. Unlike TMEDA, sodium *tert*-butoxide was found to be only weakly effective as a catalyst in metalation reactions, while DABCO was found to be totally ineffective.

The reactivity of a number of isomeric dimethylarenes toward α,α'-dianion formation has been established and the observed results were explained on the basis of a two-step mechanism involving the conversion of the hydrocarbon into a monoanion, first, which subsequently reacts with a second equivalent of base to produce the dianion. The dominant influence of the negative charge of the monoanion toward dianion formation appears to have been either totally overlooked or greatly deemphasized in the past.[8]

Of all the dianion intermediates formed during the present study the most interesting from a synthetic and theoretical point of view is that derived from 1,8-dimethylnaphthalene. It should be noted that previous attempts to obtain this intermediate were unsuccessful.[17] We are presently investigating the reactions of this dianion with a number of difunctional electrophilic reagents, which are expected to produce a series of unusual cyclic products.

Experimental Section

General.—Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Vapor phase chromatographic (vpc) analyses were carried out on a Varian Aerograph, series 2700 gas chromatograph equipped with a thermal conductivity detector, and using helium as a carrier gas. A 5 ft × 0.25 in. column packed with 3% SE-30 on Varaport 30 was used. Infrared spectra (ir) were taken on a Beckman IR-8 infrared spectrophotometer. Nuclear magnetic resonance (nmr) spectra were obtained on a Varian Associates A-60 spectrometer. Chemical shifts, relative to internal tetramethylsilane, were measured to the center of a singlet or multiplet and are reported in parts per million. An IEC International, Size 2, Model K centrifuge was used. All organosodium reactions were carried out under a nitrogen atmosphere, in a Morton flask equipped with a high-speed stirrer (Stir-O-Vac), purchased from Lab-Line Instruments, Melrose Park, Ill.

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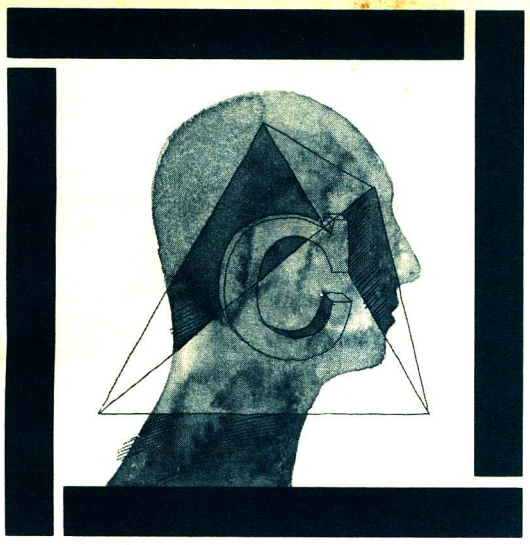

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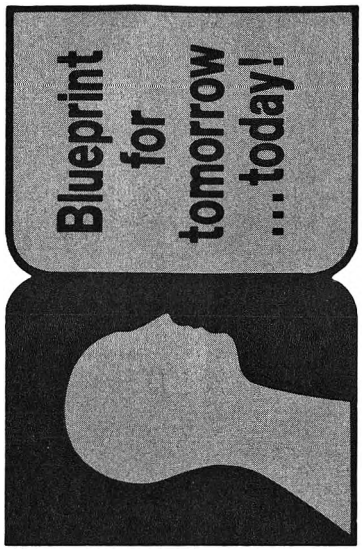

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Materials.—1,2- and 1,4-dimethylnaphthalene were purchased from Chemicals Procurement Laboratories, Inc., College Point, N.Y.

1,3-Dimethylnaphthalene was prepared essentially by the method of Canonne, *et al.*[18] 1,8-Dimethylnaphthalene was obtained by a modification of the method of Denisova, *et al.*,[19] as described below. *o*- and *m*-xylene were purchased from Matheson Coleman and Bell, Norwood, Ohio, while *p*-xylene was purchased from J. T. Baker Chemical Co., Phillipsburg, N. J. All three xylenes were distilled from sodium metal immediately before use. Sodium *tert*-butoxide was obtained from MSA Research Corporation, Evans City, Pa., and was used without further purification. Sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) was purchased from Aldrich Chemical Co., Inc., Milwaukee, Wis., as a 70% solution in benzene.

1,8-Bishydroxymethylnaphthalene.—Sodium bis(2-methoxyethoxy)aluminum hydride (0.638 mol) dissolved in 2200 ml of benzene was charged into a three-necked round-bottomed flask equipped with a heating mantle, a magnetic stirrer, an addition funnel, and a reflux condenser connected to a high-purity nitrogen tank by means of a T tube. Stirring was initiated and a solution of 62.4 g (0.255 mol) of 1,8-dimethyl naphthalate[19,20] in 650 ml of benzene was added dropwise at room temperature over a period of 40 min. The reaction mixture was then refluxed for 1.5 hr. After cooling to room temperature, 150 ml of water were cautiously added followed by 500 ml of 9 *N* HCl. The resulting precipitate was collected by filtration, washed with water, and dried to afford 33.2 g (69.4%) of 1,8-bishydroxymethylnaphthalene, mp 154–156° (lit.[19,21] mp 156.5–157°).

1,8-Dimethylnaphthalene.—A solution of 14.92 g (0.0793 mol) of 1,8-bishydroxymethylnaphthalene, prepared as described above, in 250 ml of methanol containing a few drops of concentrated hydrochloric acid and 0.91 g of palladium black was shaken with hydrogen at room temperature in a Parr low-pressure hydrogenator at 3.5 atm. After the theoretical amount of hydrogen was absorbed (12 min), the catalyst was removed by filtration and the solvent was evaporated. There was obtained 10.2 g (82%) of crude 1,8-dimethylnaphthalene: mp 57.5–59° and 61.5–62.5° after one recrystallization from methanol (lit.[19,21c] mp 63.5–64.5°); ir (CCl_4) 3040 (C=C) and 2980 cm^{-1} (C–C); nmr (CCl_4) δ 7.35 (m, 6 H, aromatic), and 2.88 (s, 6 H, CH_3).

Preparation of *n*-Amylsodium.—This reagent[22] was prepared by the slow addition of *n*-amyl chloride to a stirred (10,000–12,000 rpm) sodium dispersion in hexane at −15°. After all of the *n*-amyl chloride had been added, the mixture was stirred for an additional 0.5 hr to ensure complete reaction. A 70–80% yield of *n*-amylsodium formation was assumed.[23]

Effect of TMEDA on the Solubility of *n*-Amylsodium in Hexane.—*n*-Amylsodium was prepared as described above from 3.21 g (0.03 mol) of *n*-amyl chloride and 1.38 g (0.06 mol) of a sodium dispersion in 80 ml of dry hexane. Approximately one-half of the reaction mixture was transferred into a centrifuge tube and centrifuged for 5 min at 1500 rpm. A clear supernatant layer and a blue precipitate resulted. The remaining one-half of the reaction mixture was treated with 0.01 mol of TMEDA before it was centrifuged. Upon centrifugation this portion of the reaction mixture also afforded a clear supernatant liquid and a dark blue precipitate.

Formation of 1,3-Dimethylnaphthalene Dianion 1 by Means of *n*-Amylsodium in the Presence of TMEDA.—To a stirred (9,000–10,000 rpm) suspension of *n*-amylsodium prepared from 3.21 g (0.03 mol) of *n*-amyl chloride and 1.38 g (0.06 mol) of sodium in 80 ml of anhydrous hexane was added at −15°, over a period of 8 min, a solution of 1.56 g (0.01 mol) of 1,3-dimethylnaphthalene and 2.32 g (0.02 mol) of TMEDA in 15 ml of dry hexane. The cold bath was then removed and the reaction mixture was allowed to warm slowly to room temperature. Dimetalation was completed by stirring for an additional 2 hr at room temperature and the resulting brick-red, insoluble 1,3-dimethylnaphthalene dianion 1 was employed as described below.

Deuteration of Dianion 1.—A suspension of dianion 1 (0.01 mol) in hexane was prepared as described above and subsequently quenched with 10 ml of deuterium oxide. Water (50 ml) was then added to the reaction mixture, and the layers were separated. The organic layer was washed three times with 20-ml portions of 6 *N* hydrochloric acid, three times with 20-ml portions of aqueous saturated sodium bicarbonate, and once with 50 ml of water; it was then dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure to give 1,3-dimethylnaphthalene-d_2 (**2a**), as shown by quantitative nmr analysis, nmr (CCl_4) δ 7.40 (m, 6 H, aromatic), 2.50 (m, 2 H, CH_2D), and 2.32 (m, 2 H, CH_2D). Vpc analysis of the crude reaction mixture showed no impurities.

Alkylation of Dianion 1 with Methyl Iodide.—To a stirred suspension of 0.01 mol of dianion 1 in 80 ml of hexane at 1–5° was added 5.67 g (0.04 mol) of methyl iodide over a period of 8–10 min. The cold bath was then removed and the reaction mixture was allowed to stir (8000 rpm) for 45 min at room temperature. Water (50 ml) was then added, the layers were separated, and the organic layer was washed three times with 20-ml portions of 6 *N* hydrochloric acid, three times with 20-ml portions of aqueous saturated sodium bicarbonate, and once with 50 ml of water; it was then dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. Vpc analysis of the residue revealed the presence of two components in a ratio of 19:1. The predominant component was shown to be 1,3-diethylnaphthalene (**2b**), picrate mp 99–100° (lit.[24] mp 100.5°). No attempt was made to identify the minor component.

Condensation of Dianion 1 with Benzophenone.—To a stirred suspension of 0.01 mol of dianion 1 in 80 ml of hexane at room temperature was added dropwise a solution of 4.55 g (0.025 mol) of benzophenone in 50 ml of dry hexane. After 1 hr of stirring (8000 rpm) at room temperature 50 ml of water was added. The resulting yellow solid was collected by filtration, washed with water, and dried to afford 2.60 g (50%) of crude diol **2c**: mp 176–181° (several recrystallizations of the crude product **2c** from ethanol–water raised the melting point to 192–193°); ir (KBr) 3540 cm^{-1} (OH); nmr (DMSO-d_6) δ 7.33 (m, 26 H, aromatic), 5.48 (s, 1 H, CH_2COH), 5.39 (s, 1 H, CH_2COH), 3.83 (s, 2 H, CH_2COH), and 3.49 (s, 2 H, CH_2COH).

Anal. Calcd for $C_{38}H_{32}O_2$: C, 87.69; H, 6.16. Found: C, 87.61; H, 6.26.

Carbonation of Dianion 1 with Excess Solid Carbon Dioxide.—A suspension of 0.02 mol of dianion 1 in hexane was prepared in the usual manner and then syringed onto a large excess of moisture-free, solid carbon dioxide. The resulting slurry was allowed to stand overnight at room temperature; 300 ml of water was then introduced with stirring, the layers were separated, and the aqueous layer was washed twice with 50-ml portions of hexane and twice with 50-ml portions of ethyl acetate and acidified with 12 *N* HCl. Upon cooling (ice bath) the acidic solution afforded a yellow-white precipitate, which was collected by filtration and dried to give 3.62 g (74%) of crude 1,3-naphthalenediacetic acid (**2d**): mp 215–217°, and 224–225° after several recrystallizations from ethyl acetate–petroleum ether (bp 30–60°); ir (KBr) 3000 (OH) and 1700 cm^{-1} (C=O); nmr (DMSO-d_6) δ 7.65 (m, 6 H, aromatic), 4.05 (s, 2 H, CH_2COOH), and 3.76 (s, 2 H, CH_2COOH).

Anal. Calcd for $C_{14}H_{12}O_4$: C, 68.85; H, 4.91. Found: C, 69.03; H, 4.78.

Metalation and Subsequent Deuteration of 1,3-Dimethylnaphthalene with *n*-Amylsodium in the Absence of a Catalyst.—To a stirred (9,000–10,000 rpm) suspension of *n*-amylsodium prepared from 1.38 g (0.06 mol) of sodium and 3.21 g (0.03 mol) of *n*-amyl chloride in 80 ml of anhydrous pentane was added, at −15°, 1.56 g (0.01 mol) of 1,3-dimethylnaphthalene over a period of 5 min, and stirring was continued for 2 hr at room temperature. The reaction mixture was then quenched with 5 ml of deuterium oxide and processed as described above to give 1,3-dimethylnaphthalene-d_1 as shown by quantitative nmr analysis, nmr (CCl_4) δ 7.40 (m, 6 H, aromatic), 2.55 (s, 2.6 H, CH_2D and CH_3), and 2.36 (s, 2.4 H, CH_2D and CH_3).

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Formation of 1,2-, 1,6-, and 1,8-Dimethylnaphthalene Dianions 3, 4, and 5 and Subsequent Deuteration with Deuterium Oxide.—Treatment of 1.56 g (0.01 mol) of 1,2-, 1,6-, and 1,8-dimethylnaphthalene with *n*-amylsodium prepared from 2.30 g (0.10 mol) of sodium and 5.33 g (0.05 mol) of *n*-amyl chloride in the presence of 3.94 g (0.034 mol) of TMEDA under the same conditions used in the case of 1,3-dimethylnaphthalene produced dianions **3** (dark brown), **4** (dark red), and **5** (orange-brown), respectively, in quantitative yield, as shown by subsequent treatment of each reaction mixture with deuterium oxide followed by nmr analysis: nmr (CCl_4) for 1,2-dimethylnaphthalene-d_2, δ 7.53 (m, 6 H, aromatic), 2.45 (m, 2 H, CH_2D), and 2.37 (m, 2 H, CH_2D); nmr (CCl_4) for 1,6-dimethylnaphthalene-d_2, δ 7.48 (m, 6 H, aromatic), 2.60 (m, 2 H, CH_2D), and 2.45 (m, 2 H, CH_2D); nmr (CCl_4) for 1,8-dimethylnaphthalene-d_2, δ 7.36 (m, 6 H, aromatic) and 2.87 (m, 4 H, CH_2D).

When 1.56 g (0.01 mol) of 1,2-, 1,6-, and 1,8-dimethylnaphthalene was treated with *n*-amylsodium prepared from 1.38 g (0.06 mol) of sodium and 3.21 g (0.03 mol) of *n*-amyl chloride in the presence of 2.32 g (0.02 mol) of TMEDA followed by deuteration with deuterium oxide, 1.80 deuterium atoms were incorporated in each molecule of 1,2- and 1,6-dimethylnaphthalene, and 1.5 deuterium atoms were incorporated in each molecule of 1,8-dimethylnaphthalene, as established by nmr analysis.

Condensation of Dianion 5 with Benzophenone.—1,8-Dimethylnaphthalene dianion **5** (0.01 mol) was prepared as described above and subsequently treated with 4.55 g (0.025 mol) of benzophenone under conditions similar to those used in the case of 1,3-dimethylnaphthalene. There was obtained 2.75 g (52%) of crude diol **6a**: mp 177–181° and 198–199° after several recrystallizations of the crude product **6a** from ethanol; ir (KBr) 3540 cm^{-1} (OH); nmr ($CDCl_3$) δ 7.19 (m, 26 H, aromatic), 4.40 (s, 4 H, CH_2COH), and 2.30 (s, 2 H, CH_2COH).

Anal. Calcd for $C_{38}H_{32}O_2$: C, 87.69; H, 6.16. Found: C, 87.92; H, 6.30.

Carbonation of Dianion 5 with Excess Solid Carbon Dioxide.—Dianion **5** (0.01 mol) was carbonated with excess moisture-free solid carbon dioxide as described in the case of 1,3-dimethylnaphthalene dianion **1** to give 1.0 g (40%) of crude 1,8-naphthalenediacetic acid (**6b**), mp 229° dec. Compound **6b** was purified by recrystallization from ethyl acetate–petroleum ether (bp 30–60°): ir (KBr) 3000 (OH) and 1690 cm^{-1} (C=O); nmr (DMSO-d_6) δ 7.79 (m, 6 H, aromatic) and 4.18 (s, 4 H, CH_2COOH).

Anal. Calcd for $C_{14}H_{12}O_4$: C, 68.85; H, 4.91. Found: C, 68.57; H, 4.96.

Attempted Dimetalation of 1,4-Dimethylnaphthalene.—1,4-Dimethylnaphthalene (1.56 g, 0.01 mol) was treated with a mixture of *n*-amylsodium, prepared from 2.30 g (0.10 mol) of sodium and 5.33 g (0.05 mol) of *n*-amyl chloride, and 3.94 g (0.034 mol) of TMEDA. After 2 hr of stirring the reaction mixture was quenched with deuterium oxide and processed as described above. Nmr analysis of the crude reaction mixture showed that only one deuterium atom per molecule of 1,4-dimethylnaphthalene had been incorporated: nmr (CCl_4) δ 7.55 (m, 6 H, aromatic) and 2.58 (s, 5 H, CH_2D and CH_3).

Formation and Subsequent Deuteration of *m*-Xylene Dianion 7.—The green *m*-xylene dianion **7** was prepared by treating 5.30 g (0.05 mol) of *m*-xylene with *n*-amylsodium, prepared from 16.05 g (0.15 mol) of *n*-amyl chloride and 6.90 g (0.30 mol) of sodium, and 12.76 g (0.11 mol) of TMEDA under the conditions used for the formation of 1,3-dimethylnaphthalene dianion **1**. Subsequent quenching of the reaction mixture with 15 ml of deuterium oxide afforded *m*-xylene-d_2, as established by nmr analysis: nmr (hexane) δ 6.92 (m, 4 H, aromatic) and 2.20 (m, 4 H, CH_2D). Vpc analysis of the crude reaction mixture showed no impurities.

Alkylation of *m*-Xylene Dianion 7 with Excess Methyl Iodide.—Dianion **7** (0.05 mol) was prepared as outlined above and subsequently treated with 21.3 g (0.15 mol) of methyl iodide under the conditions used for the alkylation of 1,3-dimethylnaphthalene dianion **1**. Vpc analysis of the crude reaction mixture showed the presence of two peaks in the ratio of 15:1. The major component was shown by vpc and nmr analysis to be 1,3-diethylbenzene, while the minor component was identified as 1-ethyl-3-methylbenzene.

Metalation and Subsequent Alkylation of *m*-Xylene by Means of *n*-Amylsodium in the Presence of DABCO.—To a slurry of *n*-amylsodium prepared from 6.90 g (0.30 mol) of sodium and 16.05 g (0.15 mol) of *n*-amyl chloride was added 12.32 g (0.11 mol) of DABCO followed by 5.30 g (0.05 mol) of *m*-xylene. The reaction mixture was stirred for 2 hr at room temperature; it was then cooled to 5°; and 21.3 g (0.15 mol) of methyl iodide was added dropwise. The cold bath was removed and the reaction mixture was stirred for an additional 2 hr at room temperature and then processed in the usual manner. Vpc analysis of the crude reaction mixture showed the presence of *m*-xylene, 1-ethyl-3-methylbenzene, and 1,3-diethylbenzene in a ratio of 2.8:1.0:1.1.

Metalation and Subsequent Alkylation of *m*-Xylene by Means of *n*-Amylsodium in the Presence of Sodium *tert*-Butoxide.—*m*-Xylene (5.30 g, 0.05 mol) was treated with *n*-amylsodium prepared from 6.90 g (0.30 mol) of sodium and 16.05 g (0.15 mol) of *n*-amyl chloride, in the presence of 13.64 g (9.142 mol) of sodium *tert*-butoxide under the usual conditions. Methyl iodide (21.3 g, 0.15 mol) was then added as described above, and the reaction mixture was stirred for 2 hr at room temperature and then processed in the usual manner. Vpc analysis of the crude reaction mixture showed the presence of *m*-xylene, 1-ethyl-3-methylbenzene, and 1,3-diethylbenzene in a ratio of 1.0:1.1:4.6.

Metalation and Subsequent Alkylation of *m*-Xylene by Means of *n*-Amylsodium in the Absence of a Catalyst.—To a slurry of *n*-amylsodium prepared from 6.90 g (0.30 mol) of sodium and 16.05 g (0.15 mol) of *n*-amyl chloride in hexane was added 5.3 g (0.05 mol) of *m*-xylene and the reaction was allowed to stir at room temperature for 2 hr. Addition of 21.3 g (0.15 mol) of methyl iodide followed by the usual work-up and vpc analysis of the crude reaction mixture showed the presence of *m*-xylene with only trace amounts of 1-ethyl-3-methylbenzene. No 1,3-diethylbenzene could be detected.

Formation and Subsequent Deuteration of o-Xylene Dianion 8.—Treatment of 5.3 g (0.05 mol) of *o*-xylene with *n*-amylsodium prepared from 11.50 g (0.50 mol) of sodium and 26.75 g (0.25 mol) of *n*-amyl chloride in the presence of 20.30 g (0.175 mol) of TMEDA under the conditions described earlier afforded the green-brown *o*-xylene dianion **8**. Neutralization of the reaction mixture with 20 ml of deuterium oxide afforded o-xylene-d_2, as shown by vpc and nmr analysis: nmr (hexane) δ 6.95 (s, 4 H, aromatic) and 2.12 (m, 4 H, CH_2D).

When 5.3 g (0.05 mol) of *o*-xylene was treated with *n*-amylsodium prepared from 6.9 g (0.30 mol) of sodium and 16.05 g (0.15 mol) of *n*-amyl chloride in the presence of 12.76 g (0.11 mol) of TMEDA followed by deuteration with deuterium oxide, only 1.64 deuterium atoms were incorporated in each molecule of *o*-xylene, as shown by quantitative nmr analysis.

Attempted Dimetalation of *p*-Xylene.—*p*-Xylene (5.3 g, 0.05 mol) was treated with *n*-amylsodium prepared from 11.50 g (0.50 mol) of sodium and 26.75 g (0.25 mol) of *n*-amyl chloride in the presence of 20.30 g (9.175 mol) of TMEDA. The reaction mixture was stirred for 2 hr and was then neutralized with 20 ml of deuterium oxide. Nmr analysis of the crude product showed the incorporation of only one deuterium atom per molecule of *p*-xylene: nmr (hexane) δ 7.91 (s, 4 H, aromatic) and 2.21 (s, 5 H, CH_3 and CH_2D).

Registry No.—**1**, 36374-74-0; **2a**, 38645-27-1; **2b**, 38645-28-2; **2c**, 36374-75-1; **2d**, 36262-46-1; **3**, 38645-31-7; **4**, 38645-32-8; **5**, 38645-33-9; **6a**, 38677-69-9; **6b**, 38645-34-0; **7**, 36295-90-6; **8**, 38645-36-2; 1,8-dimethyl naphthalate, 81-84-5; 1,8-bishydroxymethylnaphthalene, 2026-08-6; 1,8-dimethylnaphthalene, 569-41-5; *n*-amylsodium, 1822-71-5; TMEDA, 110-18-9; benzophenone, 119-61-9; 1,3-dimethylnaphthalene, 575-41-7; 1,3-dimethylnaphthalene-d_2, 38669-44-2; 1,2-dimethylnaphthalene, 573-98-8; 1,6-dimethylnaphthalene 575-43-9; 1,2-dimethylnaphthalene-d_2, 38645-39-5; 1,6-dimethylnaphthalene-d_2, 38645-40-8; 1,8-dimethylnaphthalene-d_2, 38645-41-9; *m*-xylene, 108-38-3; *m*-xylene-d_2, 38645-42-0; *o*-xylene, 95-47-6; *o*-xylene-d_2, 38644-46-1.

Acknowledgment.—Support of this research by a Faculty Research Grant, Western Michigan University, and by the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged.

Oxidation of Organic Compounds with Cerium(IV). XVI. Relative Rates of Formation of Allyl, Benzyl, and *tert*-Butyl Radicals by Oxidative Cleavage of Alcohols[1]

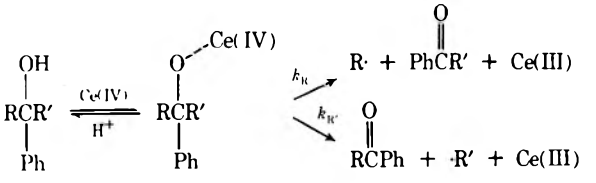
WALTER S. TRAHANOVSKY*[1d] AND DAVID B. MACAULAY

Department of Chemistry, Iowa State University of Science and Technology, Ames, Iowa 50010

Received September 27, 1972

Three tertiary alcohols, allylbenzylphenylmethanol, allyl-*tert*-butylphenylmethanol, and benzyl-*tert*-butylphenylmethanol, were synthesized from the appropriate ketone and Grignard reagent and oxidized in 75% aqueous acetonitrile at 80° by ceric ammonium nitrate. All three alcohols underwent oxidation cleavage to produce ketones and, from the yields of these ketones, it is calculated that the relative rates of formation of the allyl:benzyl:*tert*-butyl radicals by oxidative cleavage are 1:4.4:19.9–62.9.

As part of our study of the effect of structure on relative rates of oxidative cleavage of alcohols by cerium(IV), a reaction shown to be a one-electron process,[2] we wished to determine the relative rates of formation of allyl, benzyl, and *tert*-butyl radicals. These are very stable radicals, and previous results have shown that benzyl[2] and *tert*-butyl[3] radicals are cleaved very rapidly from the appropriate alcohols. We chose to measure these rates by oxidizing the appropriate tertiary alcohols and measuring the relative yields of the two possible ketones for several reasons. The relative rates of formation of radicals which are cleaved

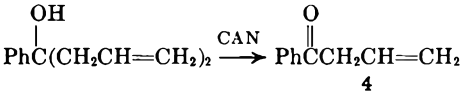


very rapidly cannot be measured accurately by determining the ratios of benzaldehyde to ketone from the oxidation of the appropriate secondary alcohols (alkylphenylmethanols), since the yields of ketones are very low.[3] Also, for radicals of varying sizes the extent of complex formation for the various alkylphenylmethanols would differ considerably[4] and this variation would have to be taken into account in order to determine relative rates of formation of these radicals. With the tertiary alcohols, only one complex is formed, which then undergoes oxidative cleavage in one of two ways. The phenyl group was chosen as one of the three groups of the tertiary alcohols, since phenyl ketones are resistant to oxidation.

Results

Three tertiary alcohols, allylbenzylphenylmethanol (**1**), allyl-*tert*-butylphenylmethanol (**2**), and benzyl-*tert*-butylphenylmethanol (**3**), were synthesized from the appropriate ketone and Grignard reagent and oxidized in 75% aqueous acetonitrile at 80° by ceric ammonium nitrate (CAN). The ketones produced were identified by glpc peak enhancement with authentic samples and by the nmr spectra of the product mixtures.

All of the ketones were well behaved except allyl phenyl ketone (**4**), which gave an ill-defined glpc peak. The material responsible for this peak was collected and had nmr and ir spectra consistent with a mixture of *cis*- and *trans*-1-propenyl phenyl ketones [nmr (CCl_4) δ 8.0–7.7 (m, 2), 7.5–7.2 (m, 3), 7.0–6.4 (m, 2), and 1.97 (d, J = 5 Hz, 3); ir strong bands at 1667 and 1622 cm^{-1}]. Apparently isomerization of **4** to these conjugated ketones occurred during the glpc analysis. An authentic sample of **4** was obtained by the CAN oxidation of diallylphenylmethanol. This reaction



is an excellent example of the synthetic utility of the oxidative cleavage reaction, since the only reported synthesis of this base-sensitive ketone is the hydration of 1-phenylbut-3-en-1-yne[5] and synthesis of it by other methods would be difficult.

From **1** and **2** >95% of the starting alcohol was accounted for but only 85–90% of the starting material was accounted for from **3**. The oxidations of **1** and **2** were very rapid but that of **3** was much slower. It is quite likely that oxidation of some of the benzyl phenyl ketone (**5**) to benzil, a known reaction,[2b] accounts for the missing material. Oxidation of a mixture of **5** and *tert*-butyl phenyl ketone (**6**) with CAN under the reaction conditions showed that **5** is consumed more rapidly than **6**, an expected result since **6** has no α-hydrogen atoms.

In Table I are presented relative yields of the various ketones obtained from oxidation of **1**, **2**, and **3**.[6] From the yields of ketones from **1** and **2**, it is seen that formation of the benzyl radical occurs 4.4 times faster and formation of the *tert*-butyl radical occurs 19.9 times faster than formation of the allyl radical. From these values, the calculated ratio of formation of *tert*-butyl to benzyl radicals is 4.5; however, the directly measured ratio (from **3**) is 8.7. Moreover, if it is

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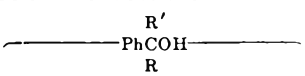
(6) In addition to the products listed in Table I, from **1** small amounts of benzyl alcohol and benzaldehyde were detected by their nmr signals and glpc peak enhancement with authentic samples, and there was ir and nmr evidence for benzyl nitrate. From **3**, small amounts of benzaldehyde and benzyl nitrate were detected by glpc analysis.

TABLE I

RELATIVE YIELDS OF PRODUCTS FROM THE CERIC AMMONIUM NITRATE OXIDATION OF VARIOUS TERTIARY METHANOLS[a]



Alcohol	R	R′	$PhCOCH_2Ph$	$PhCOCH_2CH{=}CH_2$	$PhCOC(CH_3)_3$
1	Allyl	Benzyl	(1)	4.4 ± 0.4[b]	
2	Allyl	*tert*-Butyl		19.9 ± 2.5[b]	(1)
3	Benzyl	*tert*-Butyl	8.7 ± 0.8[c]		(1)

[a] In 75% aqueous acetonitrile at 80°, 1/2[CAN] = [starting alcohol] = 0.0625 *M*. [b] Based on four runs; analyzed by nmr. [c] Based on three runs; analyzed by glpc.

assumed that all of the 15% material balance loss from **3** is due to the oxidation of **4**, then the *tert*-butyl to benzyl radical formation becomes 14.3. Thus, the relative rates of formation of the allyl:benzyl:*tert*-butyl radicals are 1:4.4:19.9–62.9.

Discussion

Bond-dissociation energies indicate that the *tert*-butyl radical is *ca.* 6 kcal/mol less stable than either the allyl or benzyl radicals[7] and thus predict that the *tert*-butyl radical should be less rapidly cleaved from appropriate alcohols than the allyl or benzyl radicals. Although the observed order of formation is not that expected from bond-dissociation energies, other radical reactions have shown the same behavior,[8,11] which has been explained by polar,[9,12] steric,[9,12,13] and conformational effects.[9]

Previous studies have shown that a fair amount of positive charge develops on the radical which is being formed in the transition state of a cerium(IV) oxidation cleavage of an alcohol.[2] There is evidence that the *tert*-butyl cation is significantly more stable than the allyl and benzyl cations[14] and thus a polar effect could account for the more rapid rate of formation of the *tert*-butyl group. The relief of steric strain could also account for the more rapid rate of formation of the *tert*-butyl radical,[12,13] but recent results[15] have shown that relief of steric strain in a radical reaction need not be important. It is also possible that the formation of the allyl and benzyl radicals is abnormally slow owing to conformational effects which restrict the vinyl and phenyl groups from stabilizing the incipient radical to the greatest possible extent. Currently, we are studying systems which we hope will enable us to determine the relative importance of these various effects.

The relative rate of formation of the *tert*-butyl radical indicated by the products of **3** is greater than that obtained from the study of **1** and **2**. The slower rate of oxidation of **3** is no doubt a result of severe steric crowding of the hydroxy group. This increased crowding could further enhance the cleavage of the *tert*-butyl group from **3** for steric reasons or retard the rate of cleavage of the benzyl group from **3** by restricting its conformations.

Experimental Section

Methods and Materials.—Most equipment and materials have been previously described.[1a] A 6 ft × 0.25 in. SE-52 on Fluorpak 80 column was used for glpc analysis. Elemental analyses were performed by Chemalytics, Inc., Tempe, Ariz.

Allylbenzylphenylmethanol (1).—To 2.48 g (102 mmol) of magnesium turnings in 170 ml of ether which was being stirred was added 5.8 g (76 mmol) of distilled allyl chloride (Matheson Coleman and Bell). Some heating was necessary to initiate the formation of the Grignard reagent. To this reagent was slowly added *ca.* 50% of 10.0 g (51 mmol) of benzyl phenyl ketone (Aldrich) in 40 ml of ether. Addition was discontinued when the yellow color which formed at the point of addition no longer faded. The mixture was allowed to stir overnight and was hydrolyzed with 250 ml of 20% ammonium chloride (NH_4Cl) solution. The ether solution was washed with saturated sodium chloride solution, dried ($MgSO_4$), and concentrated to give 6.4 g of a yellow oil which was converted to a colorless oil by chromatographing twice on silica gel columns using a 50:50 pentane–petroleum ether (bp 60–70°) mixture and benzene as eluents: nmr (CCl_4) δ 7.4–6.8 (m, 10), 6.0–4.8 (m, 3), 3.05 (s, 2), 2.9–1.8 (m, 2), and 1.9 (s, 1). *Anal.* Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.36; H, 7.51.

Allyl-*tert*-butylphenylmethanol (2).—To the Grignard reagent prepared from 1.85 g (76 mmol) of magnesium turnings and 5.27 g (69 mmol) of distilled allyl chloride in 200 ml of ether was added 7.50 g (46.3 mmol) of pivalophenone[16] (which had been purified by column chromatography) in 50 ml of ether. The mixture was stirred for 6 hr and then hydrolyzed with 125 ml of 20% NH_4Cl solution. After work-up and chromatography on a silica gel column using a 50:50 benzene–petroleum ether mixture as the eluent, a colorless oil (23% yield) was obtained: nmr ($CDCl_3$) δ 7.5–7.1 (m, 5), 5.4–4.8 (m, 3), 3.3–2.3 (m, 2), 1.95 (s, 1), and 0.92 (s, 9). *Anal.* Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.53; H, 9.84.

Benzyl-*tert*-butylphenylmethanol (3).—To the Grignard reagent prepared from 3.5 g (144 mmol) of magnesium turnings and 11.3 g (90 mmol) of distilled benzyl chloride (Baker) was added 7.5 g (46.3 mmol) of pivalophenone in 20 ml of ether. The mixture was stirred for 3 hr and then hydrolyzed with 300 ml of 20% NH_4Cl solution. After work-up and chromatography on a silica gel column using benzene as the eluent a white, crystalline solid (64% yield) was obtained: mp 50.0–51.5° (lit.[17] mp 50–51°); nmr (CCl_4) δ 7.5–6.8 (m, 10), 3.25 (AB quartet, J = 13 Hz, 2), 1.40 (s, 1), and 1.00 (s, 9).

Allyl Phenyl Ketone (4).—Diallylphenylmethanol was prepared by the addition of 125 mmol of methyl benzoate to the

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(8) Initially it was reported that *tert*-butyl radicals are formed much more rapidly in the β-scission of *tert*-alkoxy radicals than are benzyl radicals,[9] but later work[10] has shown that these results must be reexamined since competing chlorine atom chain reactions have been shown to complicate the results from the decomposition of *tert*-alkyl hypochlorites, especially when benzyl radicals are involved.

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(16) J. H. Ford, C. D. Thompson, and C. S. Marvel, *ibid.*, **57**, 2621 (1935).

(17) Ramart-Lucas, *Ann. Chim. Phys.*, [8] **30** 363 (1913).

Grignard reagent obtained from 250 mmol of allyl chloride. The crude product was purified by chromatography on a silica gel column using benzene as the eluent: nmr ($CDCl_3$) δ 7.4–7.0 (m, 5), 5.9–4.7 (m, 6), 2.50 (m, 4), and 2.14 (s, 1). To 2.96 g (15.8 mmol) of this alcohol in 25 ml of acetonitrile was added 18.95 g (34.6 mmol) of CAN in 20 ml of acetonitrile and 5 ml of water at 80°. After 10 min the initially formed deep red color faded to a light yellow. The mixture was cooled and 50 ml of water and 50 ml of ether were added. The ether layer was separated, washed with saturated NaCl solution, dried ($MgSO_4$), and concentrated. Distillation gave 3.7 mmol (23% yield) of a yellowish oil: bp 59–63° (0.04 mm) [lit.[5] bp 100–102° (0.5 mm)]; nmr ($CDCl_3$) δ 8.1–7.8 (m, 2), 7.6–7.2 (m, 5), 6.4–6.9 (m, 3), and 3.60 (m, 2).

Oxidation Procedure.—Typically, 0.625 mmol of the alcohol, 7.50 mmol of acetonitrile, and 1.25 ml of water were added to a flask equipped with a condenser and magnetic stirring bar. A quantity of 1.25 ml of 1.00 *M* CAN was added, the flask was immersed in an oil bath at 80°, and the solution was stirred. In the case of **1** and **2** an initial dark red color formed which faded to a light yellow after 4 min. In the case of **3** the initial color was bright yellow and it faded to a light yellow after 30 min. After the reaction was complete, the flask was cooled in a water bath and 8 ml of water and 8 ml of ether were added to it. The ethereal solution was washed three times with 8-ml portions of water, dried ($MgSO_4$), and concentrated. The products from **1** were determined by nmr analysis by integration of the signals for the methylene protons of **4** (δ 3.55, m), the benzylic protons of **5** (δ 4.15, s), and the benzylic protons of **1** (δ 3.05, s). In several runs, the total recovery was determined by the use of octadecane or *p*-di-*tert*-butylbenzene as standards. The products from **2** were determined by nmr analysis by integration of the signals for the methyl protons of **2** (δ 0.90, s), the methyl protons of **6** (δ 1.22, s), and the methylene protons of **4** (δ 3.55, m). In several cases, the total recovery was determined by the use of mesitylene as a standard. The products from **3** were determined by glpc analysis using benzophenone as a standard and correcting for thermal conductivity and extraction differences as previously described.[2b]

Stability of Benzyl Phenyl Ketone (5) and Pivalophenone (6) to the Oxidation Conditions.—To 0.193 g (1.00 mmol) of **5** and 0.163 g (1.00 mmol) of **6** in 24 ml of acetonitrile and 7.4 ml of water at 80° was added 0.60 ml of a 1.00 *M* CAN solution. After 30 min at 80°, the mixture was cooled and 0.1822 g of standard (benzophenone) was added. Ether and water (20 ml of each) were added and after extraction the ether layer was separated, washed three times with water, dried ($MgSO_4$), and concentrated. Analysis by glpc (correcting for extraction and thermal conductivity differences) showed 97% recovery of **4** and quantitative recovery of **5**.

Registry No.—**1**, 38400-73-6; **2**, 38400-74-7; **3**, 38400-75-8; **4**, 6249-80-5; **5**, 451-40-1; **6**, 938-16-9; allyl chloride, 107-05-1; benzyl chloride, 100-44-7; diallylphenylmethanol, 38400-77-0; cerium, 7440-45-1.

The Reaction of Oxo-Osmium(VI)–Pyridine Complexes with Thymine Glycols

L. R. SUBBARAMAN, JIJIE SUBBARAMAN, AND E. J. BEHRMAN*

Department of Biochemistry, The Ohio State University, Columbus, Ohio 43210

Received January 22, 1973

We have synthesized *trans*-thymine glycol, *trans*-thymidine glycol, and *trans*-1,3-dimethylthymine glycol by isomerization of the corresponding cis glycols. Both the cis and trans glycols react in aqueous buffer solutions, pH 7–10, with the Os(VI) species, $Os_2O_6py_4$ (formulated by Criegee as OsO_3py_2) to give the corresponding bis(pyridine) *cis*-osmate (VI) esters. The 3-chloropyridine and 3-picoline osmate(VI) esters were also made. Kinetic studies show that the reactions are first order in Os(VI) and in substrate, and inverse first order in pyridine. The rate of reaction increases with increasing pH, but the apparent order in hydroxyl ions is less then one. Labeling experiments with ^{18}O show that ester formation takes place without cleavage of the C–O bond. We also report some observations on the equilibria of the Os(VI) species which suggest a pH-dependent monomer–dimer interconversion and concurrent ligand dissociation.

The radiolysis of nucleic acids, particularly their pyrimidine components, has received a good deal of attention. The recent elegant work of Téoule and Cadet[1] has provided a clearer picture of the course of events for thymine. Twenty-three products of the radiolysis of thymine have been identified. Under typical conditions 25% of the final products are the *cis*- and *trans*-thymine glycols (5,6-dihydroxy-5,6-dihydrothymine). Criegee and his coworkers have shown that the compound then thought to be $OsO_3(pyridine)_2$, among other Os(VI) species, reacts with glycols to form bis(pyridine) osmate(VI) esters.[2] We have shown that these bis(pyridine) esters, in contrast to the uncomplexed esters, are of sufficient hydrolytic stability to allow their easy manipulation in aqueous systems.[3,4] In continuation of our goals of developing selective reactions for the characterization of nucleic acids, we have undertaken this study, which may aid the recognition by electron-microscopic techniques[5,6,7a] of those thymine residues in a DNA molecule damaged by radiolysis. Oxo-osmium species have also been used recently in X-ray diffraction analyses of transfer RNA.[7b]

Results and Discussion

Structure and Equilibria.—Criegee and coworkers[2] formulated the product of the reaction of osmium tetroxide and pyridine in the presence of ethanol as OsO_3py_2. Griffith and Rossetti[8a] have recently presented good spectroscopic evidence which suggests that this compound in the solid state is actually the dimer, $Os_2O_6py_4$, with trans O=Os=O osmyl groups

(1) J. Cadet and R. Téoule, *Biochim. Biophys. Acta*, **238**, 8 (1971); R. Téoule and J. Cadet, *Chem. Commun.*, 1269 (1971).

(2) R. Criegee, B. Marchand, and H. E. Wannowius, *Justus Liebigs Ann. Chem.*, **550**, 99 (1942).

(3) L. R. Subbaraman, J. Subbaraman, and E. J. Behrman, *Bioinorg. Chem.*, **1**, 35 (1971).

(4) L. R. Subbaraman, J. Subbaraman, and E. J. Behrman, *Inorg. Chem.*, **11**, 2621 (1972).

(5) M. Beer and E. N. Moudrianakis, *Proc. Natl. Acad. Sci. U. S.*, **48**, 409 (1962).

(6) A. V. Crewe, J. Wall, and J. Langmore, *Science*, **168**, 1338 (1970).

(7) (a) R. M. Henkelman and F. P. Ottensmeyer, *Proc. Natl. Acad. Sci. U. S.*, **68**, 3000 (1971); R. F. Whiting and F. P. Ottensmeyer, *J. Mol. Biol.*, **67**, 173 (1972). (b) R. W. Schevitz, M. A. Navia, D. A. Bantz, G. Cornick, J. J. Rosa, M. D. H. Rosa, and P. B. Sigler, *Science*, **177**, 429 (1972); S. H. Kim, G. Quigley, F. L. Suddath, A. McPherson, D. Sneden, J. J. Kim, J. Weinzierl, P. Blattmann, and A. Rich, *Proc. Natl. Acad. Sci. U. S.*, **69**, 3746 (1972); *Science*, **179**, 285 (1973).

(8) (a) W. P. Griffith and R. Rossetti, *J. Chem. Soc., Dalton Trans.*, 1449 (1972). (b) Griffith reports privately that the 640-cm^{-1} band was indeed observed in the ir and that its omission in ref 8a is an error.

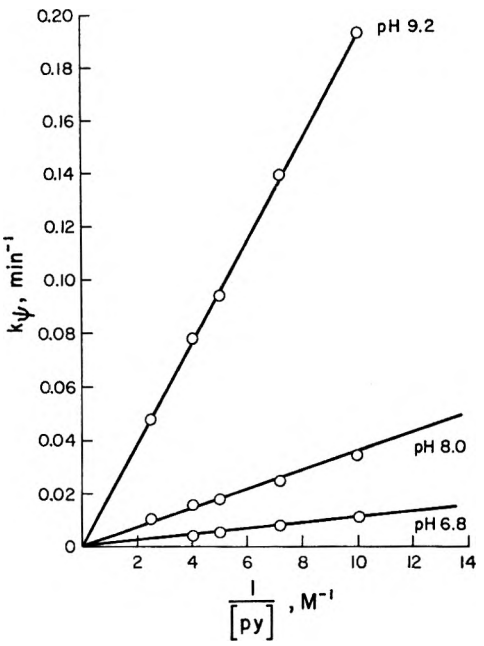
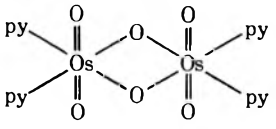


Figure 1.—Variation of k_ψ with pyridine concentration, 15°: [Os(VI)] 4–5 × 10^{-4} M, calculated as OsO_3L_2, λ 304 nm, [*cis*-thymine glycol] 3.2 × 10^{-2} M.

and two oxygen bridges, analogous to the structure demonstrated by X-ray crystallography for $Os_2O_6(NO_2)_4$.[9] We confirm the results of Griffith and



Rossetti. The ir spectrum (KBr) of the complex formed with pyridine is in agreement with their data except that we observe an additional strong band at 645 cm^{-1} which they report only in the Raman spectrum.[8b] The complexes formed with 3-picoline or 3-chloropyridine in place of pyridine are similar in exhibiting strong bands near 830 and near 640 cm^{-1}. We have found, however, evidence for a monomer–dimer equilibrium. The molecular weight of a 0.39 wt % solution in water was 810 ± 40 at 37.5° by vapor phase osmometry (Galbraith Laboratories) and 803 ± 20 and 782 ± 25 at 21.3° by equilibrium ultracentrifugation using a partial specific volume of 0.696. The formula weight for $Os_2O_6py_4$ is 793. Since our kinetic studies were carried out in buffer solutions over the pH range 7–10, equilibrium ultracentrifugation was also carried out in 0.08 M sodium carbonate buffer, pH 9.4. Under these conditions, a 0.39 wt % solution of the Os(VI) species gave a number average molecular weight of 746 ± 25; a 0.0975 wt % solution in the same buffer gave a number average molecular weight of 523 ± 13. Although these data do not yield a consistent equilibrium constant for the dimerization process on the basis of any of the simple assumptions that we have used, they do suggest complete dissociation to the monomeric species at sufficiently low concentrations. Our kinetic work, for example, has been carried out at a concentration of about 0.02 wt %.

We have also measured the dissociation of pyridine and 3-picoline from the corresponding Os(VI) species as a function of pH. These data are summarized in Table I. We note that approximately constant values

TABLE I
EQUILIBRIA OF $OsO_3 \cdot L_2$ SYSTEMS, 15°[a]

10^3[$OsO_3 \cdot L_2$], M[b]	L	pH	10^4[L_0], M	10^4[L_a], M	K[c]
5.154	Pyridine	7.45	1.44	1.10	40.46
4.764	Pyridine	8.05	2.77	2.13	43.35
4.764	Pyridine	9.45	10.81	8.32	39.62
4.506	Pyridine	10.15	17.46	13.44	41.50
4.492	3-Picoline	7.9	3.78	1.15	35.46
4.492	3-Picoline	9.15	13.76	4.16	39.20
4.438	3-Picoline	9.95	23.92	7.25	38.40

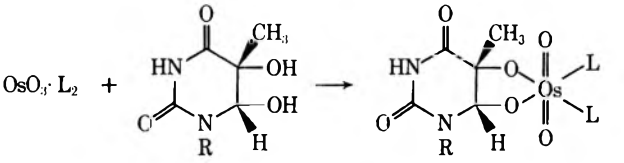
[a] $\mu \approx 0.15$ M, carbonate and phosphate buffer. [b] These concentrations are calculated on the basis of the monomeric species $OsO_3 \cdot L_2$. [c] $K = ([L_a]\{[L_a] + [L_0]\})/(\{[OsO_3 \cdot L_2] - ([L_a] + [L_0])\}[OH^-])$. $[L_0]$ and $[L_a]$ are the free ligand concentrations in the organic and aqueous phases, respectively. These were determined by partitioning the ligand between ether and the aqueous phase (see Experimental Section).

for K are obtained on the assumption of an equilibrium of the type given by

$$OsO_3L_2 + HO^- \rightleftharpoons (OsO_3 \cdot L \cdot OH)^- + L$$

This may be regarded as confirmatory evidence for the model which assumes substantially complete dissociation of the dimer to the monomeric species. We have written the monomer here and elsewhere as OsO_3L_2, but it may well exist as the hydrate $OsO_2(OH)_2L_2$. We have not considered the dissociation of the second ligand to give, for example, a species such as $(OsO_3 \cdot H_2O \cdot OH)^-$ since these solutions undergo no observable decomposition after several days in air at room temperature and since it has been shown[4,10,11] that pyridine-free Os(VI) oxide species are not stable under these conditions.

Kinetics.—$OsO_3 \cdot L_2$, where L represents pyridine, 3-picoline, or 3-chloropyridine, reacts with *cis*-thymine glycol and its derivatives to give the corresponding bis(ligand) osmate(VI) esters in good yield (see Experimental Section). These compounds have already been synthesized by another route.[5]



With limiting concentrations of $OsO_3 \cdot L_2$ and in the presence of added ligand, plots of log $(A_\infty - A_0/A_\infty - A_t)$ *vs.* time were linear for about 80% of the reaction. The slopes of these lines, which give k_ψ, the pseudo-first-order rate constant, were unaffected when the initial concentration of $OsO_3 \cdot L_2$ was varied in the range 2.5–5 × 10^{-4} M. If free ligand was not added, the reaction was complete within the time of mixing. The pseudo-first-order rate constant varied linearly with the first power of the substrate concentration. At constant substrate concentration, k_ψ increased with increasing pH and showed an inverse first-order dependence on ligand concentration (Figure 1). k_ψ was unaffected by halving carbonate buffer

(9) L. O. Atovmyan and O. A. L'yachenko, *J. Struct. Chem.*, **8**, 143 (1967).

(10) J. Périchon, S. Palous, and R. Buvet, *Bull. Soc. Chim. Fr.*, 982 (1963).

(11) J. F. Cairns and H. L. Roberts, *J. Chem. Soc. C*, 640 (1968).

TABLE II

REACTION OF THYMINE AND THYMIDINE GLYCOLS WITH PYRIDINE AND SUBSTITUTED PYRIDINE COMPLEXES OF Os(VI) AT 15° [a]

Registry no.	Substrate	pH[c]	$10^2 k_{obsd}$ min^{-1} [b] 3-Picoline[d] system	Pyridine system	3-Chloropyridine system
1431-06-7	*cis*-Thymine glycol	10.25	69.2	208	
	cis-Thymine glycol	9.25	20.0	60.20	
	cis-Thymine glycol	8.05	2.0	10.70	836.6 (pH 7.9)
	cis-Thymine glycol	6.85		3.30	91.75 (pH 6.5)
1124-84-1	*trans*-Thymine glycol	10.25		13.20	
	trans-Thymine glycol	9.25		3.62	
	trans-Thymine glycol	8.05		0.69	
38645-22-6	*cis*-Thymidine glycol	9.25		18.23	
38645-23-7	*cis*-1,3-Dimethylthymine glycol	10.20		45.67	
	cis-1,3-Dimethylthymine glycol	9.25	5.62	14.36	
	cis-1,3-Dimethylthymine glycol	8.0		2.66	

[a] [Os(VI) complex] = 4–5 × 10^{-4} *M* calculated as the monomer, OsO_3L_2; [L] = 0.08–0.6 *M*; [substrate] = 8–32 × 10^{-3} *M*; λ 304 nm, μ 0.14–0.15 *M*. [b] k_{obsd} = slope of k_ψ *vs.* 1/[L] plots divided by [S], or the slope of k_ψ *vs.* [S] plots multiplied by [L]; see text. [c] The fluctuation in pH in all runs was within ±0.05 pH units. [d] The k_2 values (M^{-1} min^{-1}) evaluated from intercepts of plots of k_ψ *vs.* 1/[3-pic], with *cis*-thymine glycol as substrate were 0.28 (pH 8.05), 0.47 (pH 9.25), and 1.25 (pH 10.25); for *cis*-1,3-dimethylthymine glycol, 0.12 (pH 9.25).

concentration at constant pH and ionic strength. Table II shows that the reactivity for the Os(VI) complexes decreased in the order OsO_3(3-chloropyridine)$_2$, OsO_3(pyridine)$_2$, OsO_3(3-picoline)$_2$ and also gives the numerical results as a function of pH and substrate. *cis*-1,3-Dimethylthymine glycol, which does not ionize appreciably in the pH range investigated, shows the same pH dependence as *cis*-thymine glycol.

Cis–Trans Isomerization of the Glycols.—Criegee, *et al.*,[2] reported that OsO_3(pyridine)$_2$ as well as $(KO)_2(CH_3O)_4Os$ and $KO(AcO)_3Os{=}O$ react in general only with acyclic 1,2-diols and with cyclic cis 1,2-diols. Other diols, including most trans 1,2-diols, did not react with the exception of *trans*-1,2-cyclohexanediol and *trans*-1,2-cycloheptanediol. Model-building with *trans*-thymine glycol shows that one cannot expect to form a cyclic osmate ester from this rigid compound. Nevertheless, we observed that *trans*-thymine glycol (Table I), *trans*-thymidine glycol, and *trans*-1,3-dimethylthymine glycol all react slowly with OsO_3(pyridine)$_2$. The product is in each case the cis ester as shown by the identity of the ir spectra. Since we have observed that the trans glycols isomerize to the cis glycols in the absence of Os(VI) species (see also Shugar[12]), we interpret the conversion of the *trans*-thymine glycol to the *cis*-osmate ester as the sum of the following reactions.

$$\text{trans glycol} \rightleftharpoons \text{cis glycol}$$

$$\text{cis glycol} + OsO_3\cdot py_2 \longrightarrow \text{bis(pyridine) } cis\text{-osmate ester}$$

The isomerization of the *cis*- to the *trans*-thymine glycols has been previously reported,[12,13] but the corresponding reactions of the thymidine and 1,3-dimethylthymine glycols (see Experimental Section) are new.

We have no clues to the mechanism of these interesting transformations aside from our qualitative observation that the reactions are base catalyzed and that 1,3-dimethylthymine glycol is not prevented from undergoing the isomerization. Hahn and Wang have recently suggested a possible pathway for the thymine glycols[14] which is, however, not consistent with our finding of apparently similar isomerizations for thymidine and 1,3-dimethylthymine.

Mechanism.—We outline below a mechanism which fits the data as we have them. We realize, however, that the study of the Os(VI)–pyridine–hydroxyl ion system is incomplete.

$$Os_2O_6L_4 \rightleftharpoons 2OsO_3L_2 \quad (1)$$

$$OsO_3\cdot L_2 + HO^- \overset{K}{\rightleftharpoons} (OsO_3\cdot L\cdot OH^-) + L \quad (2)$$

$$OsO_3\cdot L_2 + S \xrightarrow{k_2} \text{product} \quad (3)$$

$$(OsO_3\cdot L\cdot HO^-) + S \xrightarrow{k_1} (OsO_3\cdot L\cdot OH\cdot S^-) \xrightarrow[L]{\text{fast}} \text{product} + HO^- \quad (4)$$

Here S is the substrate and the product is the bis(ligand) osmate(VI) ester.

If we assume essentially complete dissociation of the dimer to monomeric species under the kinetic conditions, the rate law for this process is

$$v = k_1[OsO_3\cdot L\cdot HO^-][S] + k_2[OsO_3\cdot L_2][S] \quad (5)$$

The total Os(VI) species is given by

$$[Os(VI)]_{total} = [OsO_3\cdot L\cdot OH^-] + [OsO_3\cdot L_2] \quad (6)$$

We omit any ligand-free Os(VI) species for the reasons already discussed and also because the data show a clean inverse dependence on the first power of the ligand. Substituting for $[OsO_3\cdot L\cdot OH^-]$ from the equilibrium expression (eq 2), we get

$$[Os(VI)]_{total} = \frac{K[OsO_3\cdot L_2][OH^-]}{[L]} + [OsO_3\cdot L_2] \quad (7)$$

$$[OsO_3\cdot L_2] = \frac{[Os(VI)]_{total}[L]}{K[OH^-] + [L]} \quad (8)$$

(12) D. Barszcz, Z. Tramer, and D. Shugar, *Acta Biochim. Pol.*, **10**, 9 (1963).

(13) S. Iida and H. Hayatsu, *Biochim. Biophys. Acta*, **213**, 1 (1970).

(14) B. S. Hahn and S. Y. Wang, *J. Amer. Chem. Soc.*, **94**, 4764 (1972).

This expression may be simplified for the reaction conditions we have used because our data show that the $K[OH^-]$ term (see Table II) is negligible in comparison with the ligand term in the denominator of eq 8. Thus

$$[OsO_3 \cdot L_2] \simeq [Os(VI)]_{total} \quad (9)$$

With limiting concentrations of the Os(VI) species, k_ψ, the pseudo-first-order rate constant, is given by

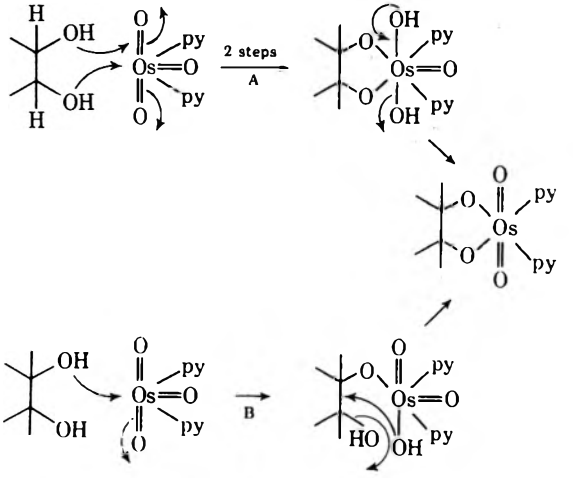
$$v = k_\psi [Os(VI)]_{total} \quad (10)$$

Thus

$$k_\psi = \frac{k_1 K [S][OH^-]}{[L]} + k_2[S] \quad (11)$$

Equation 11 predicts that a plot of k_ψ *vs.* $1/[L]$ will be linear with a slope given by $k_1K[S][OH^-]$ and an intercept equal to $k_2[S]$.

The data show that the k_1 term is large compared with the k_2 term. Indeed, k_2 was measurable only for the 3-picoline system (footnote *d*, Table II). This is also consistent with the reactivity order for the ligand complexes, 3-chloropyridine > pyridine > 3-picoline, and implies rate-limiting nucleophilic attack by the glycol on the osmium species. Two pathways can be written for a mechanism of this type which differ in the nature of the fast ring closure.



Experiments with ^{18}O-labeled glycerol were carried out to distinguish between these pathways. Glycerol labeled (2.2 ± 0.1 atom %) at positions 1 and 2 with ^{18}O was allowed to react with $OsO_3(pyridine)_2$. The bis(pyridine) osmate ester was reductively hydrolyzed. The glycerol was reisolated and found to contain 2.4 ± 0.1 atom % ^{18}O. Pathway A predicts 2.2 ± 0.1 atom % ^{18}O, whereas pathway B predicts no more than 1.4 ± 0.1 atom % ^{18}O. Our finding is thus consistent with pathway A and eliminates pathway B from consideration.

pH Dependence.—Equation 11 predicts first-order dependence on $[OH^-]$. Table I shows, however, that, although the rate of reaction increases with pH, the order in $[OH^-]$ is only about one half. We can account for this in a qualitative way by our observation that the isomerization of the *cis*- to the *trans*-thymine glycol is base catalyzed. Since the trans glycol is converted to the product ester more slowly than the cis glycol (Table I), these reactions will reduce the apparent $[OH^-]$ dependence of eq 10 to some value less than one. We have insufficient data for a quantitative treatment.

Studies at higher pH values are further complicated by ionization of the substrates which have approximate pK_a' values of 10.8[13] (*cis*-thymine glycol) and 10.7[15] (*cis*-thymidine glycol), the base-catalyzed ring cleavage of the glycols,[13,15] and, at very high concentrations of base, cleavage of the esters to the osmate ion.[4]

Experimental Section

Reagents.—Reagent grade pyridine, 3-picoline, and 3-chloropyridine were purified by distillation over KOH. Sources for other chemicals follow: thymine and thymidine, Sigma Chemical Co.; osmium tetroxide, Varlacoid Chemical Co.; dimethyl sulfoxide-d_6, Norell Chemical Co.; tetramethylsilane, Aldrich Chemical Co.; other chemicals were of reagent grade and were obtained from the usual commercial sources. Phosphate buffers were used in the pH range 6–8 and carbonate buffers in the pH range 9–10. Stock solutions of the various pyridines were made up in buffer. Stock solutions of thymine glycol derivatives and of Os(VI) complexes were prepared in double distilled deionized water and stored at 5°

Analyses.—Ultraviolet spectra were measured using a Perkin-Elmer Model 202 instrument, ir spectra on a Perkin-Elmer Model 237B or 457 grating instrument, and nmr spectra on a Varian Associates Model T-60 instrument (60 MHz) at 35° using dimethyl sulfoxide-d_6 as solvent and tetramethylsilane as internal standard. Mass spectra were obtained on a Finnigan Model 1015 S/L instrument. Equilibrium ultracentrifugation was carried out using a Spinco Model E analytical ultracentrifuge equipped with electronic speed control and RTIC temperature control. Runs were carried out at 40,000 rpm using interference optics, a double-sector cell, 12-mm path length with sapphire windows. Partial specific volumes were determined pycnometrically. The pyridine, 3-picoline, and 3-chloropyridine content of the Os(VI) compounds was determined by the method of Ang.[16] Paper chromatography of the osmate esters was carried out on Whatman #1 paper using ethyl acetate:2-propanol:water, 75:16:9 (v/v) (solvent A) and 1-butanol:water, 86:14 (v/v) (solvent B). Standard osmate(VI) esters were prepared by the reaction of OsO_4 with thymine or thymidine in the presence of various ligands as previously described.[3] Elementary analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Kinetics.—Kinetic runs were conducted by spectrophotometry in 1-cm capped silica cells. Reactions were started by the addition of substrate and were followed by the increase in absorbance at 304 nm where we observed the maximum difference between $OsO_3 \cdot L_2$ and the osmate(VI) esters. Reactions were run under pseudo-first-order conditions with the substrate in at least tenfold excess over the Os(VI) species. The ionic strength was between 0.14 and 0.15 *M*.

Os(VI) Complexes with Pyridine and Substituted Pyridines.—Complexes of the general formula $Os_2O_6 \cdot L_4$, where L represents a monodentate ligand such as pyridine, were prepared by a slight modification of Criegee's method.[2] Osmium tetroxide (0.5 g) was dissolved in 8 ml of CCl_4. Pyridine (2 ml), 3-picoline (2.2 ml), or 3-chloropyridine (2.5 ml) was added followed by 1.9 ml of absolute ethanol as reducing agent. The mixture was allowed to stand at room temperature for 18 hr. The precipitated material was filtered, washed several times with CCl_4, and dried under vacuum. Ir: (KBr) $Os_2O_6(pyridine)_4$, 830, 645 cm^{-1}; $Os_2O_6(3\text{-picoline})_4$, 835, 635 cm^{-1}; $Os_2O_6(3\text{-chloropyridine})_4$, 837, 640 cm^{-1}. Compare ref 8.

$Os_2O_6(pyridine)_4$ is identical with the material prepared by Badger's method[17] and reported to be $OsO_4(pyridine)_2$.

Anal. Calcd for $Os_2O_6(pyridine)_4$: pyridine, 39.92. Found: 39.56. Calcd for $Os_2O_6(3\text{-picoline})_4$: 3-picoline, 43.88. Found: 43.79. Calcd for $Os_2O_6(3\text{-chloropyridine})_4$: 3-chloropyridine, 48.79. Found: 48.32. These complexes consumed 2 equiv of iodide per atom of osmium corresponding to reduction of Os(VI) to Os(IV) when titrated according to the method described for osmate(VI) esters.[4]

Osmate(VI) Esters.—$Os_2O_6(pyridine)_4$ (2.5×10^{-4} mol) and *cis*-thymine glycol (5×10^{-4} mol) were mixed in 10 ml of a 1 *M*

(15) S. Iida and H. Hayatsu, *Biochim. Biophys. Acta*, **228**, 1 (1971).
(16) K. P. Ang, *Anal. Chem.*, **38**, 1411 (1966).
(17) G. M. Badger, *J. Chem. Soc.*, 456 (1949).

aqueous solution of pyridine. The dark brown solution was allowed to stand overnight and then evaporated to dryness. The brown powder was washed several times with diethyl ether and dried under vacuum. The same product was obtained when Os_2O_6(pyridine)$_4$ and *cis*-thymine glycol were allowed to react in water. The 3-picoline and 3-chloropyridine esters were prepared in the same way. In all cases the yield was about 98%. These esters were identical with the esters prepared from osmium tetroxide, the ligand, and thymine.[3]

***cis*-Thymine Glycol.**—This material was synthesized by the procedure of Baudisch and Davidson.[18] It was recrystallized from 95% ethanol to yield white crystals: mp 214–215° (lit.[13,18,19] 216, 220, 215°); ir (KBr) 3350, 3425 (OH), 3238 (NH), 1738, 1700, 1668 (C=O), 1230, 1172, 1088, 1052, 987, 933 cm^{-1}; nmr (DMSO-d_6) δ 1.27 (s, 3, 5 -CH_3), 4.32 (t, 1, J = 5 Hz, 6 -H), 5.23 (s, 1, 5 -OH), 5.97 (d, 1, J = 5 Hz, 6 -OH), 8.07 (d, broad, 1, J = 5 Hz, 1 -NH), and 9.93 (s, broad, 1, 3 -NH). The nmr data are in good accord with those reported by Chabre, *et al.*,[20] except that the quartet for H-6 is not sufficiently resolved in our work and appears as a triplet. The uv spectrum in carbonate buffer, pH 9.85, showed a broad peak between 220 and 230 nm (ϵ 2350). The cis glycol was also prepared by performic acid oxidation of thymine. There are precedents[21] for the formation of the cis glycol by peracid oxidation, although the usual product is the trans glycol. A mixture of 5 g of powdered thymine, 45 ml of 90% formic acid, and 9 ml of 30% H_2O_2 was kept at 40° until all of the peroxide had been consumed (about 66 hr). The solution was evaporated to dryness under reduced pressure; 100 ml of water was added to the solid residue; and the mixture was again taken to dryness. This residue was then heated with 100 ml of water at 98° for 1 hr. The solution was cooled in an ice bath, whereupon 1.5 g of unreacted thymine separated. The filtrate, containing the thymine glycol, was evaporated to dryness under reduced pressure and the residue was recrystallized from ethanol to yield 3.5 g (55%) of *cis*-thymine glycol identical with the material prepared by the Baudisch and Davidson procedure.[18] *cis*-Thymine glycol was also prepared for comparison in small amounts by hydrolysis of the bis(pyridine) osmate ester of thymine.

***trans*-Thymine Glycol.**—The trans glycol was prepared by isomerization of the cis glycol. One gram of the cis glycol was refluxed in 80 ml of water for 8 hr. Chromatography in solvent A showed only two spots corresponding to the two glycols. Heating beyond 9 hr resulted in the appearance of two additional spots, which are ring-cleavage products as shown by their reaction with Ehrlich's reagent (*p*-dimethylaminobenzaldehyde) in the absence of alkali. These appear on paper chromatograms at R_f values corresponding to the additional spots reported by Shugar.[12] The trans glycol was separated by preparative chromatography in solvent A on Schleicher and Schull Orange Ribbon paper (thick, high capacity). The R_f ratio of the trans to cis isomer was 1.5 ± 0.05. The glycols were located on chromatograms by their uv absorption and by their characteristic color changes following the NaOH–Ehrlich's reagent spray (yellow to pink to blue).[22] The isomers were distinguished from one another by the fact that the cis but not the trans reacted with the periodate–benzidine reagent[23] and by the fact that the cis isomer had zero mobility in solvent A if the paper was impregnated with borate.[24] It was eluted with water, crystallized from 95% ethanol, and rechromatographed to remove traces of the cis isomer to give a white solid in about 14% yield: mp softens 166–168°, 218–219° dec; ir (KBr) 3351, 3412 (OH), 3202 (NH), 1744, 1714, 1695 (C=O), 1280, 1163, 1097, 970 cm^{-1}; nmr (DMSO-d_6) δ 1.25 (s, 3, 5 -CH_3), 4.39 (t, 1, J = 5 Hz, 6 -H), 5.84 (s, 1, 5 -OH), 6.15 (d, 1, J = 5 Hz, 6 -OH), 8.05 (d, broad, 1, J = 5 Hz, 1 -NH), and 9.95 (s, broad, 1, 3 -NH). These data are virtually identical with those reported by Cadet and Téoule[1] (nmr) and by Téoule[25] (ir). The nmr data, published by Hahn and Wang[14] are in error; all δ values should be reduced by 0.32. Compare also the ir assignments of Nofre, *et al.*,[26] and the nmr assignments of Rouillier, *et al.*[27] The uv spectrum in carbonate buffer, pH 9.85, showed a peak at 221 nm (ϵ 1635 at 230 nm).

Anal. Calcd for $C_5H_8N_2O_4$: C, 37.52; H, 5.04; N, 17.50. Found: C, 37.55; H, 5.23; N, 17.41.

***cis*-Thymidine Glycol.**—This compound was synthesized by the permanganate oxidation of thymidine.[15] The glycol was separated from the other components of the oxidation mixture by preparative chromatography on Schleicher and Shull Orange Ribbon paper using Solvent B. The R_f ratio of thymidine to its cis glycol was 2.75. The glycol was eluted from the paper with water and crystallized from methanol–ether mixtures to give a white solid: mp softens 134–138°, 190–191° dec (lit.[15,28] mp 191–193°, 189–190°); ir (KBr) 1742, 1694 cm^{-1} (C=O); nmr (DMSO-d_6) δ 1.23 (s, 3, 5 -CH_3), 4.75 (s, 1, 6 -H), 5.46 (s broad, 1, 5 -OH), 6.05 (multiplet, 1, 6 -OH), and 10.00 (broad, 1, 3 -NH). (Compare ref 15, 28.)

***trans*-Thymidine Glycol.**—*cis*-Thymidine glycol (200 mg) was dissolved in 16 ml of water and refluxed for 8 hr. The trans and cis isomers were separated by preparative paper chromatography in solvent B. The compounds were located by their uv absorption and by the NaOH–Ehrlich's reagent spray. The yield of trans glycol was about 5%. Both isomers reacted with the periodate–benzidine reagent. The R_f ratio of the trans to the cis isomer was 1.8; mp 195–197° dec; ir (KBr) 1700 cm^{-1} (C=O); nmr (DMSO-d_6) δ 1.31 (s, 3, 5 -CH_3), 4.70 (s, 1, 6 -H), 5.76 (s broad, 1, 5 -OH), 5.93 (multiplet, 1, 6 -OH), and 10.25 (broad, 1, 3 -NH).

The mass spectrum (75 eV) gave peaks at m/e 259 (M − OH)$^+$, 160 (MH − deoxyribosyl)$^+$, 117 (deoxyribosyl)$^+$.

1,3-Dimethylthymine.—This compound was prepared in 96% yield following the procedure described by Davidson and Baudisch[29] for the synthesis of 1,3-dimethyluracil. Crystallization from 95% ethanol gave white needles: mp 152° (lit.[30] mp 153°); ir (KBr) 1705, 1670, 1645 cm^{-1} (C=O); nmr (DMSO-d_6) δ 1.82 (s, 3, 5 -CH_3), 3.2–3.3 (two s, 6, 1- and 3 -CH_3), and 7.6 (s, 1, 6 -H).

***cis*-1,3-Dimethylthymine Glycol.**—The glycol was synthesized from 1,3-dimethylthymine following the procedure of Baudisch and Davidson[18] for thymine glycol. The material was obtained in 84% yield as an uncrystallizable gum after drying over P_2O_5. The material did not react with periodate: ir (neat) 3375 (OH), 1725, 1662 (C=O), 1185, 1137, 1050 cm^{-1} (CO); nmr (DMSO-d_6) δ 1.33 (s, 3, 5 -CH_3), 3.0 (two s, 6, 1- and 3 -CH_3), 4.5 (d, 1, J = 5 Hz, 6 -H), 5.15 (broad, 2, 5- and 6 -OH).

Anal. Calcd for $C_7H_{12}N_2O_4$: C, 44.67; H, 6.43; N, 14.89. Found: C, 44.44; H, 6.53; N, 14.97.

***trans*-1,3-Dimethylthymine Glycol.**—*cis*-1,3-Dimethylthymine glycol (420 mg) was dissolved in 34 ml of water and refluxed for 5.5 hr. The trans and cis isomers were separated by preparative paper chromatography in solvent B. The compounds were located by their uv absorption. The R_f ratio of the cis to the trans isomer was 1.2. The yield of trans glycol was about 54% and it was obtained as a gum after drying over P_2O_5: ir (neat) 3400 (OH), 1650 (C=O), 1185, 1056 cm^{-1} (CO); nmr (DMSO-d_6) δ 1.28 (s, 3, 5 -CH_3), 3.0 (two s, 6, 1- and 3 -CH_3), 4.55 (s, 1, 6 -H), 3.76 (broad, >2, 5- and 6 -OH, H_2O).

Anal. Calcd for $C_7H_{12}N_2O_4 \cdot {}^1/_2H_2O$: C, 42.64; H, 6.99; N, 14.21. Found: C, 42.52; H, 6.70; N, 14.32.

Oxygen-18 Measurements.—Osmium tetroxide (1.18×10^{-4} mol) was mixed with 8.83×10^{-4} mol of allyl alcohol in 2.5 ml of 3.3 ± 0.1 atom % $H_2{}^{18}O$ in a closed container under air. Under these conditions, the osmate ester initially formed hydrolyzes with 100% Os–O bond cleavage to give glycerol and an Os(VI) species which is reoxidized to osmium tetroxide by oxygen.[4] The osmium thus cycles until all of the allyl alcohol is consumed. After 11 days at room temperature, the black precipitate was coagulated by warming and then filtered. The precipitate was discarded. The filtrate containing glycerol was evaporated under a stream of air to about 0.1 ml. Water was added and the evaporation was repeated twice in order to remove any remaining

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(28) P. Howgate, A. S. Jones, and J. R. Tittensor, *J. Chem. Soc. C*, 275 (1968).
(29) D. Davidson and O. Baudisch, *J. Amer. Chem. Soc.*, **48**, 2382 (1926).
(30) T. B. Johnson and S. H. Clapp, *J. Biol. Chem.*, **5**, 49 (1908).

traces of allyl alcohol. A sample was analyzed by mass spectrometry as previously reported.[4] The remainder was diluted to 2 ml with ordinary water and then treated with excess Os_2O_6(pyridine)$_4$ and a trace of free pyridine. After standing overnight, the solution was filtered. The filtrate was dried under a stream of air to give the brown bis(pyridine) osmate ester of glycerol. This ester was reductively hydrolyzed to glycerol in water in the presence of a 2–3-fold excess of $NaHSO_3$ at room temperature for 30 min. The mixture was analyzed by measurement of the mass spectrum at m/e 61, 62, and 63 using the calculations described by Biemann.[31] Suitable blanks were run with $NaHSO_3$ alone.

Dissociation Constants for $OsO_3 \cdot L_2$.—The distribution coefficient of pyridine and 3-picoline between buffer and diethyl ether was determined at 15°. The pyridine concentration in the organic phase was measured at 256 nm after transfer to 0.1 N H_2SO_4 using ϵ 5200. 3-Picoline was measured at 263 nm (ϵ 5560). The distribution coefficient, $D = [L_0]/[L_a]$, where the subscripts refer to the organic and aqueous phases, was found to be 1.3 ± 0.02 (pyridine) and 3.3 ± 0.05 (3-picoline). When Os_2O_6(pyridine)$_4$ was equilibrated between equal volumes of buffer and ether, it was found that no detectable quantities of Os(VI) species were extracted into the organic phase, as shown by the lack of absorption in the 300–350-nm region. The degree of dissociation of the ligand from the Os(VI) species could thus be measured from the quantity of ligand in the ether phase and the distribution coefficient. The dissociation constants were calculated from the relationship

$$K = \frac{[OsO_3 \cdot L \cdot OH^-][L_a]}{[OsO_3 \cdot L_2][HO^-]}$$

using $K_w = 5 \times 10^{-15}$.[32] If we can assume no dissociation of the second ligand (see text), then

$$[OsO_3 \cdot L \cdot OH^-] = [L_a] + [L_0]$$

$$[OsO_3 \cdot L_2] = [OsO_3 \cdot L_2]_{initial} - ([L_a] + [L_0])$$

in the absence of added ligand.

Registry No.—Os-3-picoline dimer, 38641-67-7; Os–3-picoline monomer, 38669-79-3; Os–pyridine dimer, 38641-68-8; Os–pyridine monomer, 38669-80-6; Os–3-chloropyridine dimer, 38677-68-8; Os–3-chloropyridine monomer, 38669-81-7; *trans*-thymidine glycol, 38645-24-8; 1,3-dimethylthymine, 4401-71-2; *trans*-1,3-dimethylthymine glycol, 38645-26-0.

Acknowledgment.—We thank the National Science Foundation for support (GB-21267), Dr. George Serif for his help in determining the mass spectra, Mr. John Ragazzo for some of the ir spectra, and Dr. Kirk Aune for the ultracentrifugal data.

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A Comparison of Lithium Aluminum Hydride and Diborane in the Reduction of Certain 3-Indolylglyoxamides

RUDDY LITTELL AND GEORGE R. ALLEN, JR.*

Lederle Laboratories, A Division of American Cyanamid Company, Pearl River, New York 10965

Received December 13, 1972

The utility of lithium aluminum hydride ($LiAlH_4$) and diborane for the preparation of tryptamines from 3-indolylglyoxamides, including certain 4-trifluoromethyl derivatives, has been studied. Three distinctions in the behavior of these reducing agents toward the glyoxamides have been observed. (1) Diborane allows elaboration of the tryptamine side chain without concomitant reduction of trifluoromethyl substituents, whereas these groups are converted into methyl substituents by $LiAlH_4$ when reducing conditions are sufficiently vigorous to give the tryptamine. (2) Reduction of the glyoxamides with diborane may be accompanied by reduction of the indolic enamine triad to give indolines, an event not seen with $LiAlH_4$. (3) 1-Alkyl-3-indolylglyoxamides are converted into the corresponding tryptamines by diborane, whereas $LiAlH_4$ reduction gives 1-alkyl-3-indolylglycolamines. The formation of a 3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indole (**4**) was observed in the $LiAlH_4$ reduction of 5-methoxy-*N*,*N*,2-trimethyl-4-(trifluoromethyl)-3-indolylglyoxamide (**3c**). Diborane reduction of 3-indolecarboxylic acid (**16b**) and its ethyl ester **16a** gave skatole (**17**) as the major product.

Application of the Nenitzescu reaction[1] to 2-trifluoromethyl-1,4-benzoquinone and alkyl 3-aminocrotonates constitutes a convenient preparation of certain 4-trifluoromethylindoles.[2] The availability of these last substances prompted us to prepare the 4-trifluoromethyl congeners of biologically significant tryptamines, and the procedure of Speeter and Anthony[3] seemed to be the most direct way to achieve this objective. In this method an indole which is unsubstituted at the 3 position is converted into a 3-glyoxamide, reduction of which gives the tryptamine. Lithium aluminum hydride ($LiAlH_4$) is the usual reagent for this reduction, but the use of borane has been reported on one occasion.[4] In this paper we compare the effect of these two reducing agents on certain 3-indolylglyoxamides, including the 4-trifluoromethyl derivatives.

The required amides of Table I were prepared readily from 5-methoxy-2-methyl-4-trifluoromethylindole (**1**)[2] by the usual technique (see Scheme I).[3] Reduction of the N^b,N^b-dimethylglyoxamide **3c** with $LiAlH_4$ in boiling tetrahydrofuran (THF) for 48 hr gave the 4-methyltryptamine **2** and the 3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indole **4**. The former product is identical with that obtained by $LiAlH_4$ reduction of 5-methoxy-2,4,N^b,N^b-tetramethyl-3-indolylglyoxamide,[5] and its formation constitutes another example of the conversion of a trifluoromethyl substituent into a methyl group by $LiAlH_4$. Such conversions were observed earlier for a 6-trifluoromethylindole,[6] another 4-trifluoromethylindole,[2] and a benzotrifluoride.[7] A

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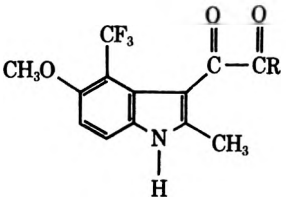
TABLE I

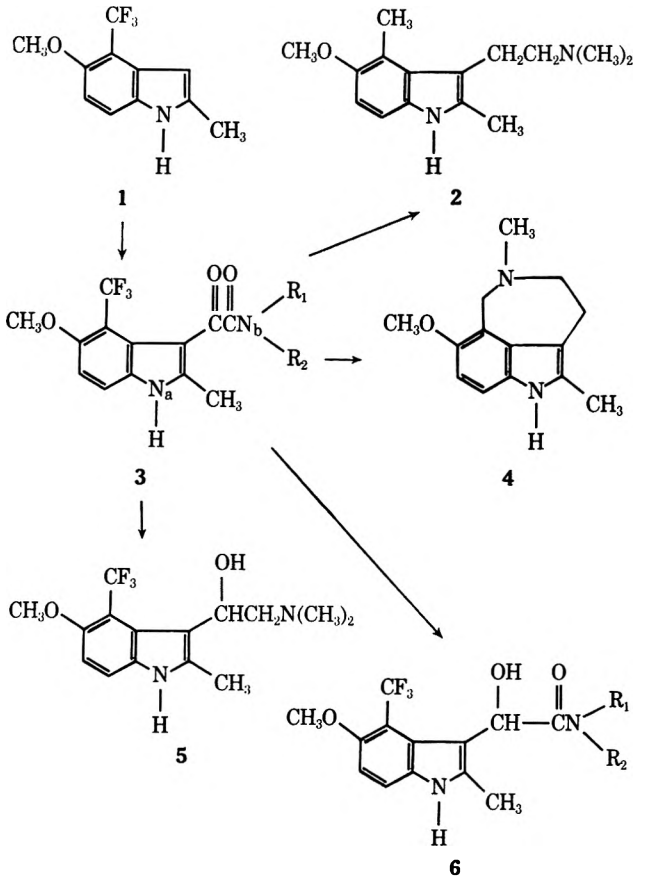
5-METHOXY-2-METHYL-4-TRIFLUOROMETHYL-3-INDOLYLGLYOXAMIDES



Registry no.	No.	R	Yield, %	Recrystn solvent	Mp, °C	Formula[a]	Analyses, % Carbon Calcd	Carbon Found	Hydrogen Calcd	Hydrogen Found	Fluorine Calcd	Fluorine Found	Nitrogen Calcd	Nitrogen Found
7664-41-7	3a	NH_2	90	MeOH	274–276 dec	$C_{13}H_{11}F_3N_2O_3$	52.00	51.85	3.69	3.64	18.98	19.06	9.33	9.21
74-89-5	3b	$NHCH_3$	75	MeOH	290–291 dec[b]	$C_{14}H_{13}F_3N_2O_3$	53.50	53.71	4.17	4.22	18.14	18.59	8.91	8.76
109-89-7	3c	$N(CH_3)_2$	80	Acetone–hexane	212–213	$C_{15}H_{15}F_3N_2O_3$	54.88	54.99	4.60	4.40	17.36	16.86	8.54	8.57
2878-14-0	3d	$NHCH_2C(CH_3)=CH_2$	75	Acetone	222–224	$C_{17}H_{17}F_3N_2O_3$	57.62	57.45	4.84	4.98	16.09	16.48	7.91	8.01
123-75-1	3e		72	Aqueous MeOH	227–229[b]	$C_{17}H_{17}F_3N_2O_3$	57.62	57.57	4.84	4.68	16.09	16.17	7.91	7.76
283-24-9	3f		64	Aqueous MeOH	262–264[b]	$C_{21}H_{22}F_3N_2O_3$[c]	61.75	61.33	5.68	5.83	13.96	14.13	6.86	6.55

[a] Except as noted the 4-trifluoromethylindolyl-3-glyoxamides had uv max 219–221, 280, 299–300 mμ (ε 25,000–30,100, 10,100–14,000, 12,600–14,100) and ir max 6.10–6.20, 6.30–6.32 μ. [b] Final purification accomplished by sublimation. [c] Uv max 219, 270, 288 mμ (ε 27,300, 14,600, 16,300).

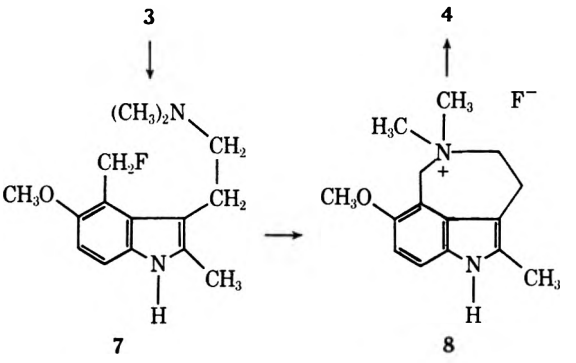
SCHEME I



recent report emphasizes that these reductions are facilitated by the presence of *o*- or *p*-amino and hydroxy functions.[8] The methoxy group in **3** presumably exerts a similar influence.

1*H*-Azepino[5,4,3-*cd*]indole (**4**) apparently results from the intramolecular quaternization of the benzyl fluoride **7**, which arises by stepwise reduction of the trifluoromethyl group in **3c**.[7] The reductive demethylation of the postulated intermediate quaternary salt **8** to give **4** (Scheme II) is amply supported in the literature. Three such examples are the conversion of

SCHEME II



strychnine methosulfate into strychnidine[9] and demethylation of two quaternary derivatives in the gelsemine class of alkaloids.[10]

Amino alcohol **5** resulted when **3c** was submitted to $LiAlH_4$ reduction under less vigorous conditions (4–16 hr, 23°). However, microanalyses on the product indicate that even these conditions are sufficient to cause partial reduction of the trifluoromethyl group. In the instance of the unsubstituted (**3a**) and N^b-methallyl (**3d**) glyoxamides, reduction with $LiAlH_4$ in boiling THF for 5–180 min gave the corresponding glycolamide **6**. Surprisingly, the pyrrolidine-derived glyoxamide **3e** suffered side-chain cleavage to regenerate **1** when exposed to $LiAlH_4$ in THF for 10 min–24 hr.

The inability to convert the 4-trifluoromethyl-3-indolylglyoxamides into the corresponding tryptamines by reduction with $LiAlH_4$ under a variety of conditions prompted us to investigate the utility of diborane for this reduction. At the outset of our study, limited

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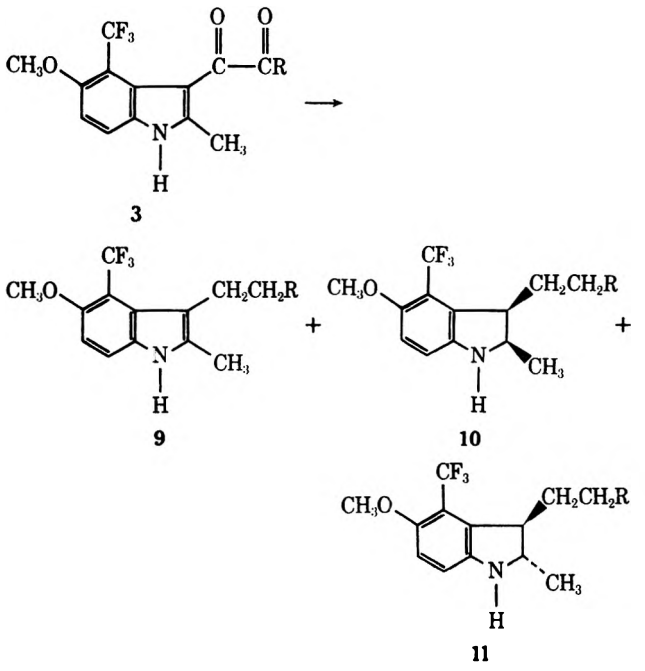
(9) G. W. Kenner and M. A. Murray, *J. Chem. Soc.*, 406 (1950).

(10) (a) N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience, New York, N. Y., 1956, p 788. (b) A referee suggested the possibility that **8** may also function as the immediate precursor for **2** (reductive debenzylation), as well as **4** (reductive demethylation).

evidence indicated that this reagent would behave in the manner predicted by theoretical considerations. Thus, the utility of diborane for the selective reduction of a 2-acylindole-3-carboxaldehyde into a 2-acyl-3-indolylmethanol had been demonstrated by Remers and coworkers.[11] Subsequently, while our work was in progress, Biswas and Jackson reported the conversion of N^b-methyl-3-indolylglyoxamide into the corresponding tryptamine using diborane as the reducing agent.[4]

We find that this reagent reacts with the N^b,N^b-dimethylglyoxamide **3c** to give 34% of the corresponding tryptamine **9c**, which was isolated as an adduct with borane (see Scheme III). Treatment of the adduct with 1-octene in xylene liberated the tryptamine. The hydrogenolysis of the trifluoromethyl group seen in the $LiAlH_4$ reductions of **3c** is not evident with diborane. A second important distinction exists in the behavior of $LiAlH_4$ and B_2H_6 toward glyoxamide **3c**. The latter reagent also gave two indoline products, which differ only in the stereochemical relationship of the groups at the 2 and 3 positions. The major (37%) isomer is that in which the substituents are cis oriented, *e.g.*, **10c**, whereas the trans isomer **11c** constituted 10% of the reaction product. These structural assignments are based on spectral evidence, the indoline nucleus being required by the ultraviolet spectra (see Experimental Section). The geometrical relation of the 2 and 3 substituents was determined from the nmr spectra of **10a** and **11a** and appropriate decoupling experiments. The chemical shift (δ 1.35) of the 2-methyl doublet in the spectrum of the major isomer is at lower field than that (δ 1.01) in the spectrum of the minor isomer. This paramagnetic shift is characteristic of cis-oriented alkyl substituents. Decoupling experiments provided conclusive evidence. Irradiation at the 2-methyl resonance of **10c** reduced the two-proton quintet to a doublet having $J_{2,3}$ = 7.5 Hz, indicating a dihedral angle near 0° and a cis juxtaposition of the 2 and 3 hydrogens. A similar decoupling experiment with **11c** collapsed the two-proton quartet to a single line, suggesting a dihedral angle near 90°, which necessitates a trans relation of the 2 and 3 hydrogens.

SCHEME III

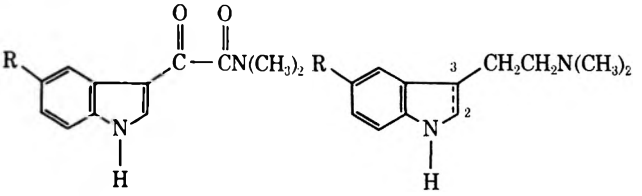


c, R = $N(CH_3)_2$
e, R = pyrrolidinyl
f, R = 3-azabicyclo[3.2.2]nonane

Reduction of the 3-azabicyclo[3.2.2]nonane-derived glyoxamide **3f** with diborane also gave a ternary mixture, nmr spectral analysis of which indicated it to contain the indole **9f** and indolines **10f** and **11f** in a ratio of 4:3:3. Separation of this mixture by partition chromatography was only partially successful; however, samples of the cis (**10f**) and trans indoline (**11f**) were isolated. The spectral properties of **10f** and **11f** were consonant with the assigned structures (see Experimental Section).

Reduction of the pyrrolidine derivative **3e** gave a mixture from which the tryptamine **9e** was isolated as the borane adduct; treatment of this adduct with 1-octene in boiling xylene then gave **9e**. The nmr spectrum of the remaining crude product indicated it to consist mostly of the cis indoline **10e**.

Extension of the borane reduction procedure to other 3-indolylglyoxamides indicates that this method for the preparation of indoline analogs of tryptamines is not general. Although reduction of *N,N*-dimethyl-3-indolylglyoxamide (**12a**) with borane gave primarily the indoline derivative **13a**, a similar reduction of the 5-methoxy congener **12b** gave 73% of the tryptamine **13b**, which was isolated as the borane adduct.



12a, R = H
b, R = OCH_3

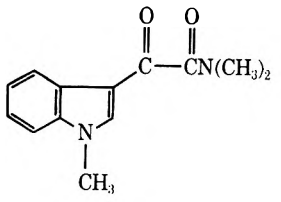
13a, R = H; C_2-C_3 = CH_2CH_2
b, R = OCH_3; C_2-C_3 = CH=CH

The above examples illustrate two distinctions in the reduction of 3-indolylglyoxamides by $LiAlH_4$ and diborane: (1) diborane permits reduction of the glyoxamide grouping without concomitant reduction of the trifluoromethyl substituent; (2) reduction of the glyoxamide moiety with the electrophilic diborane may be accompanied by reduction of the enamine triad,[12] a side reaction not observed with the nucleophilic $LiAlH_4$. A third distinction in the behavior of these reducing agents toward 3-indolylglyoxamides has also been observed.

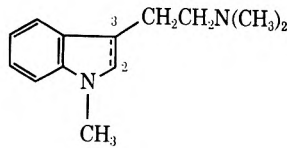
Thus, it has long been recognized that $LiAlH_4$ reduction of 1-alkyl-3-indolylglyoxamides, *e.g.*, **14**, affords 3-indolylhydroxylamines analogous to **5**.[3] However, diborane reduction of one such glyoxamide, **14**, efficiently reduced the side chain to the ethylamine, giving tryptamine **15a** (24%) and its 2,3-dihydro derivative **15b** (21%) as borane adducts. The isolation of **15b** constitutes the first example wherein a 1-alkylindoline has been detected among the products derived from

(11) W. A. Remers, R. H. Roth, and M. J. Weiss, *J. Amer. Chem. Soc.*, **86**, 4612 (1964).

(12) (a) J. A. Marshall and W. S. Johnson, *J. Org. Chem.*, **28**, 421 (1963); (b) I. J. Borowitz and G. J. Williams, *ibid.*, **32**, 4157 (1967); (c) J. W. Lewis and A. A. Pearce, *J. Chem. Soc. B*, 863 (1969).



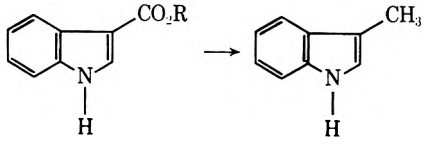
14



15a, $C_{2,3}$ = CH=CH
b, $C_{2,3}$ = CH_2CH_2

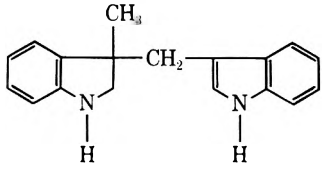
diborane reduction of a 1-alkylindole, even though earlier reports indicate that such products are not observed with 1,3-disubstituted[4] or 1,2,3-trisubstituted indoles.[13]

The susceptibility of the 3-indolylglyoxamides to reduction by diborane prompted us to study the behavior of other unstudied electrophilic indoles toward this reagent. Ethyl 3-indolylcarboxylate (**16a**) gave skatole (**17**) as the only product following treatment with diborane for 48 hr. However, a similar reduction of 3-indolecarboxylic acid (**16b**) gave **17** (49%) and the 3,3′ dimer **18** (8%). The last substance is identical



16a, R = C_2H_5
b, R = H

17



18

with one dimer which Biswas and Jackson found among the reduction products of 3-indolecarboxaldehyde,[4] and its isolation in the present instance is accommodated by their rationalization of its formation from the aldehyde.

Experimental Section

Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. Ultraviolet spectra were determined in methanol solution with a Cary recording spectrophotometer, and infrared spectra were determined in potassium bromide disks with a Perkin-Elmer Model 21 spectrophotometer. Proton magnetic resonance spectra were determined with a Varian A-60D spectrometer in the indicated solvent using tetramethylsilane as an internal standard. Evaporations were carried out under reduced pressure.

5-Methoxy-*N*,*N*,2-trimethyl-4-(trifluoromethyl)-3-indoleglyoxamide (3c).—The following experiment illustrates the general procedure used to prepare the glyoxamides of Table I (*cf.* footnote 3).

To a solution of 6.0 g (26.2 mmol) of 5-methoxy-2-methyl-4-(trifluoromethyl)indole in 150 ml of ether at 0° was added dropwise over 20 min 6.0 ml of oxalyl chloride. After stirring at 0° for 1 hr the bright orange solution of glyoxyl chloride was filtered. The filtrate was stirred in 600 ml of ether and saturated with gaseous dimethylamine. The resulting white solid was collected, washed with water, and dried to give 6.70 g (80%) of pale yellow powder, mp 208–210°. Characterization of this substance and the other 3-indolylglyoxamides is given in Table I.

3-(2-Dimethylaminoethyl)-5-methoxy-2,4-dimethylindole (2) Succinate and 3,4,5,6-Tetrahydro-7-methoxy-2,5-dimethyl-1*H*-azepino[5,4,3-*cd*]indole (4).—A solution of 6.5 g (20 mmol) of 5-methoxy-*N*,*N*,2-trimethyl-4-(trifluoromethyl)-3-indolylglyoxamide in 500 ml of THF containing 5.0 g (130 mmol) of $LiAlH_4$ was heated at reflux for 4 days. After the reaction mixture was cooled, it was treated with 32 ml of potassium sodium tartrate solution (650 mg/ml); filtration removed the inorganic salts. The solvent was evaporated, and the residue was dissolved in ethyl acetate, washed with saturated $NaHCO_3$ and with water, dried over $MgSO_4$, and evaporated to give an oil which crystallized in acetone to furnish 800 mg (17%) of white powder, mp 205–207°. Several crystallizations from acetone gave the pure azepinoindole **4**: mp 213–215°; uv max 230, 288, 300 mμ (ε 27,600, 8510, 8050); nmr (DMSO-d_6) δ 2.20 (s, 3, CCH_3), 2.40 (s, 3, NCH_3), 2.83 (m, 4, $-CH_2CH_2-$), 3.68 (s, 3, OCH_3), 3.94 (s, 2, NCH_2 aryl), 6.64 (d, 1, J = 9.0 Hz, 8-H), 6.99 (d, 1, J = 9.0 Hz, 9-H), 10.48 (s, 1, NH).

Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.17; O, 6.95; mol wt, 230.30. Found: C, 73.30; H, 8.19; N, 11.91; O, 7.48; mol wt, 230.

The filtrate from collection of the original crystalline material was evaporated to give 3.00 g of an oil. This oil was treated with a solution of 1.44 g (12 mmol) of succinic acid in 10 ml of methanol. The solution was stirred for several minutes, diluted with ether, and filtered to give 2.90 g (38%) of crystals, mp 120–124° dec. Crystallization of this material from acetone furnished pure **2** succinate as white crystals: mp 133–135°; uv max 224, 278, 297 mμ (ε 34,200, 9500, 7200); nmr (DMSO-d_6) δ 2.30 (s, 4-CH_3), 2.39 (s, $HO_2CCH_2CH_2CO_2H$), 2.46 (s, 2-CH_3), 2.50 [s, $N(CH_3)_2$], 2.84 (m, $-CH_2CH_2-$), 3.72 (s, 3, OCH_3), 6.74 (1, d, J = 9.0 Hz, 6-H), 7.00 (1, d, J = 9.0 Hz, 7-H), 9.56 (s, 2, CO_2H), 10.55 (s, 1, NH).

Anal. Calcd for $C_{15}H_{22}N_2O \cdot C_4H_6O_4$: C, 62.62; H, 7.74; N, 7.69; F, 0.00. Found: C, 62.96; H, 7.94; N, 7.53; F, 0.00.

3-(2-Dimethylamino-1-hydroxyethyl)-5-methoxy-2-methyl-4-(trifluoromethyl)indole (5).—A solution of 7.50 mg (2.3 mmol) of 5-methoxy-*N*,*N*,2-trimethyl-4-(trifluoromethyl)-3-indoleglyoxamide (**3c**) in 20 ml of THF was treated with 165 mg (4.35 mmol) of $LiAlH_4$. The mixture was stirred at room temperature for 4 hr, and the excess hydride was decomposed by addition of water. The mixture was filtered, and the filtrate was evaporated. The residue was dissolved in methylene chloride; this solution was dried over magnesium sulfate and evaporated. Trituration of the residue with ether gave 400 mg (55%) of white crystals: mp 125–127°; uv max 228, 305 mμ (ε 26,900, 10,800); ir 3.00 (sh), 3.15, 6.16, 6.36 μ; nmr ($CDCl_3$, DMSO-d_6) δ 2.35 [s, 6, $N(CH_3)_2$], 2.56 (s, 3, 2-CH_3), 2.35–2.75 (underlying m, CH_2), 3.66 (s, 1, OH), 5.28 (dd, 1, $J_{1,2}$ = 10.0 Hz, $J_{1,2}$ = 3.0 Hz, CHOH), 6.80 (d, 1, J = 9.0 Hz, 6-H), 7.38 (d, 1, J = 9.0 Hz, 7-H), 10.35 (s, 1, NH).

A salt with fumaric acid was prepared by dissolution of 410 mg (1.32 mmol) of material in 2 ml of methanol and addition of 156 mg (1.35 mmol) of fumaric acid. The solid that was precipitated by addition of ether was recrystallized from methanol–ether to give crystals, mp 146–147° dec.

Anal. Calcd for $C_{15}H_{19}N_2O_2 \cdot {}^1/_2C_4H_4O_4$: C, 54.54; H, 5.65; F, 15.22; N, 7.48. Found: C, 54.97; H, 5.74; F, 13.72; N, 7.43.

5-Methoxy-2-methyl-4-(trifluoromethyl)-3-indoleglycolamide (6a).—A solution of 1.4 g (4.65 mmol) of 5-methoxy-2-methyl-4-(trifluoromethyl)-3-indoleglyoxamide and 600 mg (16 mmol) of $LiAlH_4$ in 140 ml of THF was heated at reflux for 5 min. Water was added, inorganic material was removed by filtration, and the filtrate was evaporated. Crystallization of the residue from acetone–hexane gave 370 mg (26%) of crystals, mp 160–162°. Two recrystallizations from the same solvents gave the analytical sample as white crystals: mp 166–167°; uv max 215, 305 mμ (ε 28,500, 11,000); ir max 3.10, 5.96, 6.16, 6.35 μ; nmr ($CDCl_3$) δ 2.36 (s, 3, 2-CH_3), 3.86 (s, 3, OCH_3), 4.12 (broad, OH), 5.45 (s, 1, CHOH), 6.85 (m, 3, NH_2, 6-H), 7.38 (d, 1, J = 8 Hz, 7-H), 10.5 (s, 1, NH).

Anal. Calcd for $C_{13}H_{13}F_3N_2O_3$: C, 51.82; H, 4.67; F, 18.85; N, 9.27. Found: C, 52.02; H, 4.41; F, 18.22; N, 9.29.

5-Methoxy-2-methyl-*N*-(2-methallyl)-4-(trifluoromethyl)-3-indoleglycolamide (6d).—A solution of 920 mg (2.6 mmol) of 5-methoxy-2-methyl-*N*-(2-methallyl)-4-(trifluoromethyl)-3-indoleglyoxamide and 190 mg (5 mmol) of $LiAlH_4$ in 30 ml of THF was stirred at room temperature for 3 hr. Water was added, the inorganic material was removed by filtration, and the filtrate was evaporated. Addition of ether and filtration

(13) S. A. Monti and R. R. Schmidt, *Tetrahedron*, **27**, 3331 (1971).

gave 365 mg of product, mp 164–167°. Crystallization from acetone–hexane gave the analytical sample: mp 182–183°; uv max 225, 305 mμ (ε 28,000, 11,200); ir max 3.07, 6.10, 6.35, 9.30 μ; nmr (DMSO-d_6) δ 1.70 (s, 3, C=CCH$_3$) 2.30 (s, 3, 2-CH$_3$), 3.71 (m, 2, –CH$_2$–), 4.81 (s, 2, =CH$_2$), 5.35 (d, 1, J = 5.0 Hz, CHOH), 5.55 (d, 1, J = 5.0 Hz, CHOH), 6.95 (d, 1, J = 9.0 Hz, 6-H), 7.45 (d, 1, J = 9.0 Hz, 7-H), 7.80 (t, 1, J = 6.5 Hz, NHCH$_2$), 11.30 (s, 1, NH).

Anal. Calcd for $C_{17}H_{19}F_3N_2O_3$: C, 57.30; H, 5.37; F, 15.99; N, 7.86. Found: C, 57.19; H, 5.65; F, 15.70; N, 7.93.

5-Methoxy-2-methyl-4-(trifluoromethyl)indole (1).—A solution of 710 mg (2.0 mmol) of 1-[5-methoxy-2-methyl-4-(trifluoromethyl)-3-indoleglyoxyloyl]pyrrolidine (**3e**) and 300 mg (8 mmol) of LiAlH$_4$ in 70 ml of THF was stirred at room temperature overnight. Water was added, the inorganic precipitate was removed by filtration, and the filtrate was evaporated. Crystallization of the residue from acetone–hexane gave 110 mg (24%) of white crystals, mp 121–123°. This material was identical with known 5-methoxy-2-methyl-4-(trifluoromethyl)indole (**1**)[2] by the usual criteria. A similar reaction conducted for 10 min at room temperature gave 27% of **1**.

Reduction of 5-Methoxy-*N*,*N*,2-trimethyl-4-(trifluoromethyl)-3-indoleglyoxamide (3c) with Diborane.—A solution of 2.3 g (7.0 mmol) of **3c** in 160 ml of THF and 30 ml (30 mmol) of 1.0 *M* borane in THF was heated at reflux for 2 hr and cooled, and the excess borane was cautiously decomposed with water. After evaporation of solvent the residue was dissolved in ether, washed twice with saturated saline, dried, and evaporated. Ether was added and 750 mg (34%) of 3-(2-dimethylaminoethyl)-5-methoxy-2-methyl-4-(trifluoromethyl)indole borane, mp 164–166° dec, was collected by filtration. A sample from a similar experiment with mp 166–168° dec was recrystallized from dichloromethane–hexane to give the analytical specimen: mp 180–181°; dec; uv max 230, 308 mμ (ε 26,000, 11,000); ir max 3.00, 4.25–4.40, 6.17, 6.37 μ; nmr (CDCl$_3$ + DMSO-d_6) δ 2.42 (s, 3, 2-CH$_3$), 2.64 [s, 6, N(CH$_3$)$_2$], 2.64–3.33 (m, –CH$_2$CH$_2$–), 3.86 (s, 3, OCH$_3$), 6.88 (d, 1, J = 8.0 Hz, 6-H), 7.42 (d, 1, J = 8.0 Hz, 7-H), 10.4 (s, 1, NH).

Anal. Calcd for $C_{15}H_{19}F_3N_2O\cdot BH_3$: C, 57.34; H, 7.06; N, 8.92. Found: C, 57.42; H, 7.34; N, 9.01.

The filtrate from the above ether trituration was evaporated to give 1.80 g of yellow oil, which was heated at reflux temperature with 10 ml of 20% hydrochloric acid solution for 1 hr. The cooled reaction mixture was washed with ether, rendered strongly alkaline with sodium hydroxide, and extracted again with ether. The ethereal solution was washed with saline, dried, and evaporated to give 1.00 g of yellow oil. Vpc using 5% SE-30 on Chromosorb W showed this material to be a binary mixture, 22% having a retention time of 2.5 min and 78% being eluted at 3.2 min.

Chromatography on diatomaceous silica using the system heptane–ethyl acetate–methanol–water (90:10:17:4) separated the two components.[14] The product eluted at peak-hold-back volume 3.5 (V_m/V_s = 2.27) was evaporated to give 122 mg (6%) of *trans*-3-(2-dimethylaminoethyl)-5-methoxy-2-methyl-4-(trifluoromethyl)indoline (**11a**) as a colorless oil: uv max 248, 325 mμ (ε 7600, 3500); ir 3.10, 6.20 μ; nmr (CDCl$_3$) δ 1.01 (d, 3, J = 7 Hz, 2-CH$_3$), 1.73 (m, 2, –CH$_2$CH$_2$N<), 2.20 [s, 6, N(CH$_3$)$_2$], 2.39 (m, –CH$_2$CH$_2$N<), 3.12 (m, 1, 3-H), 3.46 (s, 1, NH), 3.60 (9, 1, J = 7 Hz, 2-H), 3.82 (s, 3, OCH$_3$), 6.74 (s, 2, aryl H).

Anal. Calcd for $C_{15}H_{21}F_3N_2O$: C, 59.59; H, 7.00; F, 18.85; N, 9.27. Found: C, 59.35; H, 6.68; F, 18.85; N, 8.99.

The fraction eluted at peak-hold-back volume 4.6 was evaporated to give 350 mg (17%) of *cis*-3-(2-dimethylaminoethyl)-5-methoxy-2-methyl-4-(trifluoromethyl)indoline (**10a**) as yellow crystals: mp 92–94°; uv max 248, 325 mμ (ε 7800, 3900); ir 3.20, 6.25 μ; nmr (CDCl$_3$) δ 1.33 (d, 3, J = 7 Hz, 2-CH$_3$), 1.92 (m, 2, –CH$_2$CH$_2$N<), 2.17 [s, 6, N(CH$_3$)$_2$], 2.34 (m, –CH$_2$CH$_2$N<), 3.28 (m, 1, 3-H), 3.65 (b, 1, NH), 3.83 (s, 3, OCH$_3$), 3.90 (q, 1, 2-H), 6.68 (s, 2, aryl H).

Anal. Calcd for $C_{15}H_{21}F_3N_2O$: C, 59.59; H, 7.00; F, 18.85; N, 9.27. Found: C, 59.36; H, 6.64; F, 19.13; N, 9.20.

3-(2-Dimethylaminoethyl)-5-methoxy-2-methyl-4-(trifluoromethyl)indole (9c).—A solution of 200 mg of 3-(2-dimethylaminoethyl)-5-methoxy-2-methyl-4-(trifluoromethyl)indole borane in 2 ml of xylene and 2 ml of octene-1 was heated at reflux temperature for 4 hr, cooled, and diluted with hexane to give 80 mg of white powder. Crystallization of material from a similar experiment from acetone–hexane gave white crystals, mp 145–147°. Sublimation at 0.5 mm and 110° furnished crystals: mp 146–148°; uv max 229, 306 mμ (ε 22,500, 9300); ir 2.95, 6.13, 6.32 μ; nmr (DMSO-d_6) δ 2.2 [s, N(CH$_3$)$_2$], 2.36 (s, 2-CH$_3$), 2.08–3.00 (underlying m, CH$_2$CH$_2$), 3.82 (s, 3, OCH$_3$), 6.90 (d, 1, J = 9.0 Hz, 6-H), 7.45 (d, 1, J = 9.0 Hz, 7-H), 11.15 (s, 1, NH).

Anal. Calcd for $C_{15}H_{19}F_3N_2O$: C, 60.00; H, 6.38; F, 19.00; N, 9.33. Found: C, 60.27; H, 6.25; F, 19.27; N, 9.33.

***cis*- (10f) and *trans*-3-{2-[5-Methoxy-2-methyl-4-(trifluoromethyl)-3-indolinyl]ethyl}-3-azabicyclo[3.2.2]nonane (11f).**—A solution of 2.50 g (61.4 mmol) of 3-[5-methoxy-2-methyl-4-(trifluoromethyl)-3-indolylglyoxyloyl]-3-azabicyclo[3.2.2]-nonane (**3f**) and 20 ml of 1 *M* borane in THF was diluted with 150 ml of THF and heated at reflux temperature for 3 hr. The solution was evaporated, and the residue was distributed between ether and water. The ether layer was washed with saline, dried, and evaporated to give 2.00 g (~85%) of a yellow oil: nmr (DMSO-d_6) *inter alia* δ 1.01 (d, J = 7.0 Hz, 2-CH$_3$ in trans indoline), 1.25 (d, J = 7.0 Hz, 2-CH$_3$ in cis indoline), 2.36 (s, 2-CH$_3$, indole **9f**), 3.72 (s, OCH$_3$ of indolines), 3.82 (s, OCH$_3$ of indole **9f**), 5.52 (b, NH of indolines), 6.70, 6.79 (d, J = 9.0 Hz, 6-, 7-H of indolines), 6.93, 7.45 (d, J = 9.0 Hz, 6-, 7-H of indole), 10.95 (s, NH of indole); integration of the nmr trace indicated the ratio of **9f**:**10f**:**11f** to approximate 4:3:3.

Partial separation of material from a similar reduction was achieved by partition chromatography on diatomaceous silica using heptane–2-methoxyethanol (1:1) as the solvent system. The indoline products were eluted at peak hold-back-volumes 2.2 and 2.5 (V_m/V_s = 1.65). Isolation of pure material was achieved only after repeated rechromatography of each peak. The less polar fraction contained the trans isomer **11f**, which was sublimed to give yellow crystals: mp 113–116°; uv max 240, 320 mμ (ε 7600, 4000); ir max 2.95, 3.09, 6.20 μ; nmr (CDCl$_3$) δ 1.16 (d, J = 6.5 Hz, 2-CH$_3$), 3.80 (s, OCH$_3$), 6.70 (s, 2, aryl H), and a series of multiplets at δ 1.25–3.76.

Anal. Calcd for $C_{21}H_{29}F_3N_2O$: C, 65.93; H, 7.66; F, 14.90; N, 7.32. Found: C, 66.22; H, 7.66; F, 14.90; N, 7.32.

The more polar material was recrystallized from acetone–hexane to give the cis isomer **10f** as yellow crystals: mp 108–110°; uv max 246, 322 mμ (ε 8200, 3800); ir max 2.95, 3.10, 6.25 μ; nmr (CDCl$_3$) δ 1.40 (d, J = 6.5 Hz, 2-CH$_3$), 3.80 (s, OCH$_3$), 3.88 (q, J = 7.0 Hz, 2-H), 6.70 (s, 2, aryl H), and a series of multiplets at δ 1.25–3.77.

Anal. Found: C, 66.02; H, 7.70; F, 15.09; N, 7.28.

5-Methoxy-2-methyl-3-[2-(1-pyrrolidinyl)ethyl]-4-(trifluoromethyl)indole (9e) Borane.—A solution of 1.80 g (5.1 mmol) of 1-[5-methoxy-2-methyl-4-(trifluoromethyl)-3-indoleglyoxyolyl]-pyrrolidine (**3e**) in 140 ml of THF and 15 ml of 1.0 *M* borane in THF was heated at reflux for 4 hr and cooled, and the excess borane was decomposed with water. After evaporation of solvents, the residue was dissolved in benzene and this solution was washed with water, dried, and evaporated.

Crystallization of the crude residue from ether–hexane gave 330 mg of pale yellow powder, mp 162–164°. The mother liquor was chromatographed on 100 g of silica gel.[15] Elution with dichloromethane–hexane (9:1) gave an additional 300 mg (36% total product, mp 166–170°).

The analytical specimen was obtained from a similar experiment by crystallization from ether–hexane to give white plates: mp 174–176°; uv max 232, 308 mμ (ε 27,000, 10,000); ir max 2.99, 4.25–4.30, 6.13, 6.35 μ; nmr (CDCl$_3$ + DMSO-d_6) δ 2.00 (m, –CH$_2$CH$_2$– of pyrrolidine), 2.45 (s, 2-CH$_3$), 2.45–3.42 (m, –CH$_2$CH$_2$N, –CH$_2$NCH$_2$–), 3.85 (s, 3, OCH$_3$), 6.84 (d, 1, J = 9.0 Hz, 6-H), 7.40 (d, 1, J = 9.0 Hz, 7-H), 10.75 (s, 1, NH), and 3 H in the 1.0–3.0 region (BH$_3$).

Anal. Calcd for $C_{17}H_{24}F_3N_2O\cdot BH_3$: C, 60.00; H, 7.11; N, 8.24. Found: C, 59.91; H, 6.83; N, 8.28.

Further elution of the column with dichloromethane–ether (8:2) gave 750 mg (43%) of a mixture of the borane adducts of indolines **10e** and **11e** as a yellow oil, uv max 250, 330 mμ, ir

(14) The support is that material marketed under the trademark Celite by the Johns-Manville Co. A complete description of this technique as developed by Mr. C. Pidacks is given by M. J. Weiss, R. E. Schaub, G. R. Allen, Jr., J. F. Poletto, C. Pidacks, R. B. Conrow, and C. J. Coscia, *Tetrahedron*, **20**, 357 (1964).

(15) A product of the Davison Chemical Co., Baltimore, Md., with mesh size 100–200.

max 4.20, 6.30 μ. Chromatography of this material on diatomaceous silica using a heptane–ethyl acetate–methanol–water (90:10:17:4) system gave 600 mg of oil at peak hold-back-volume 4.0 (V_m/V_s = 2.47); tlc of this material in heptane–ethyl acetate (1:1) and acetone–acetic acid–methanol–benzene (5:5:20:100) showed two spots. Partial separation was effected by preparative chromatography on silica gel using heptane–ethyl acetate (1:1). A fraction containing 240 mg was isolated as a yellow oil: uv max 246, 325 mμ (ε 8200, 3600); ir max 3.02, 4.25, 6.25 μ; nmr ($CDCl_3$) δ 1.40 (d, 3, J = 7.0 Hz, 2-CH_3), 3.80 (s, 3, OCH_3), 6.72 (s, 2, aryl H), and 1.15–4.00 (series of multiplets). This spectral data suggests the material to be the borane adduct of cis isomer **10e**.

5-Methoxy-2-methyl-3-[2-(1-pyrrolidinyl)-ethyl]-4-(trifluoromethyl)indole (9e).—A solution of 800 mg of 5-methoxy-2-methyl-3-[2-(1-pyrrolidinyl)ethyl]-4-(trifluoromethyl)indole borane in 10 ml of xylene and 4 ml of *n*-octene-1 was heated at reflux for 3 hr, cooled, diluted with heptane, and filtered to give 510 mg of pink crystals, mp 145–150°. The product was purified by crystallization from acetone–water and sublimation at 130° to give white crystals: mp 152–154°; uv max 228, 305 mμ (ε 25,200, 10,000); ir max 2.95, 6.13, 6.32 μ; nmr (DMSO-d_6) δ 1.68 (m, 4, $-CH_2CH_2-$ of pyrrolidine), 2.36 (5,3,2-CH_3), 2.36–4.67 (underlying m, $-CH_2CH_2N<$, $-CH_2NCH_2-$), 3.81 (s, 3, OCH_3), 6.92 (d, 1, J = 9.5 Hz, 6-H), 7.47 (d, 1, J = 9.5 Hz, 7-H), 11.20 (s, 1, NH).

Anal. Calcd for $C_{17}H_{21}F_3N_2O$: C, 62.56; H, 6.49; F, 17.47; N, 8.48. Found: C, 62.87; H, 6.65; F, 17.41; N, 8.71.

3-(2-Dimethylaminoethyl)indoline (13a).—A solution of 2.16 g (10 mmol) of *N,N*-dimethyl-3-indoleglyoxamide[16] in 150 ml of THF and 40 ml of 1.0 *M* borane in THF was heated at reflux for 2.5 hr and cooled. The excess borane was cautiously decomposed with water. After evaporation of the solvents, the residue was dissolved in ether, and this solution was washed with water, dried, and evaporated to give 2.10 g of colorless oil.

The crude oil was heated at reflux temperature with 12 ml of 20% HCl for 1.5 hr. The cooled solution was washed once with ether, rendered strongly alkaline with NaOH, and extracted with ether. The ether solution was washed twice with water, dried, and evaporated to give 1.10 g of colorless oil; vpc at 142° on a 6 ft 3.8% SE-30 on Diatoport S column showed this material to be 95% **13a** (retention time 4.4 min) and 5% 3-(2-dimethylaminoethyl)indole (retention time 6.5 min; identical with that of a known sample).

Purification was effected by chromatography on diatomaceous silica using a heptane–ethyl acetate–methanol–water (90:10:17:4) solvent system. The fraction with peak hold-back-volume 3.25 (V_m/V_s = 2.44) was evaporated to give 800 mg of amber oil, uv max 242, 293 mμ (ε 5900, 2300), ir max 3.05, 6.20 μ. This material formed a picrate, mp 158–160°.

Anal. Calcd for $C_{12}H_{18}N_2 \cdot C_6H_3N_3O_7$: C, 51.55; H, 5.05; N, 16.70. Found: C, 51.28; H, 5.16; N, 16.93.

3-(2-Dimethylaminoethyl)-5-methoxyindole (13b) Borane.—A solution of 2.46 g (10 mmol) of 5-methoxy-*N,N*-dimethyl-3-indoleglyoxamide[17] in 50 ml of THF and 35 ml of 1.0 *M* borane in THF was heated at reflux temperature for 3 hr and cooled, and the excess borane was decomposed with water. After evaporation the residue was dissolved in ether, washed with water, dried, and evaporated to give 2.90 g of white plates. This material was recrystallized twice from dichloromethane–hexane to give 1.20 g of crystals: mp 124–125°; uv max 222, 278, 298, 308 mμ (ε 23,000, 5800, 4650, 3350); ir max 2.90, 4.22, 4.40, 6.15, 6.30 μ.

Anal. Calcd for $C_{13}H_{18}N_2O \cdot BH_3$: C, 67.26; H, 9.12; N, 12.07. Found: C, 67.04; H, 9.43; N, 11.97.

An additional 500 mg (73% total) of product was obtained by chromatographing the first mother liquor on 50 g of silica gel and eluting with ether–dichloromethane (1:4).

The same compound, mp 123–125°, was prepared by similar treatment of 3-(2-dimethylaminoethyl)-5-methoxyindole[17] with borane.

Reduction of 1,*N,N*-Trimethyl-3-indoleglyoxamide (14).—A solution of 2.20 g (9.6 mmol) of crude 1,*N,N*-trimethyl-3-indoleglyoxamide (**14**) (prepared in the usual way[3] from 1-methylindole, oxalyl chloride, and dimethylamine, and obtained as a homogeneous oil) and 30 ml of 1 *M* borane in THF was heated at reflux temperature for 3 hr. The usual isolation procedure gave 1.90 g of colorless oil, which was chromatographed on 100 g of silica gel. Elution with dichloromethane gave 500 mg (24%) of white crystals, mp 84–86°. Two crystallizations from ether gave pure 3-(2-dimethylaminoethyl)-1-methylindole (**15a**) borane: mp 90–92°; uv max 223, 288 mμ (ε 35,500, 5500); ir max 4.25, 4.32, 4.41, 6.15 μ; nmr ($CDCl_3$) δ 1.0–3.0 (broad, BH_3), 2.58 [s, 6, $N(CH_3)_2$], 3.06 (broadened s, 4, $-CH_2CH_2N<$), 3.62 (s, 3, NCH_3), 6.80 (s, 1, 2-H), 7.22 (m, 2, 5-, 6-, and 7-H), 7.55 (m, 1, 4-H).

Anal. Calcd for $C_{13}H_{18}N_2 \cdot BH_3$: C, 72.23; H, 9.79; N, 12.96. Found: C, 72.48; H, 9.64; N, 13.13.

Continued elution of the column with ether–dichloromethane (1:4) gave 450 mg (21%) of 3-(2-dimethylaminoethyl)-1-methylindoline (**15b**) borane as a white solid, mp 92–94°. Two recrystallizations of this solid from ether–hexane gave white crystals: mp 98–99°; uv max 250, 295 mμ (ε 12,500, 6100); ir max 2.35, 6.25 μ; nmr ($CDCl_3$) δ 1.67–2.37 (m, $-CH_2CH_2N<$), 2.65 (s, NCH_3), 2.71 [s, $-N(CH_3)_2 \cdot BH_3$], 2.71 (underlying m, 3-H), 2.89 (m, 2-CH_2), 3.20 (m, $-CH_2CH_2N<$), 6.35–7.20 (m, 4, aryl H).

Anal. Calcd for $C_{13}H_{20}N_2 \cdot BH_3$: C, 71.57; H, 10.62; N, 12.84. Found: C, 71.73; H, 10.41; N, 12.78.

3-Methylindole (17).—A solution of 2.82 g (15 mmol) of ethyl 3-indolecarboxylate (**16a**) in 50 ml of THF and 50 ml of 1.0 *M* borane in THF was heated at reflux for 48 hr. Examination of the reaction mixture by tlc and vpc showed the presence of a single product having R_f values and retention times corresponding to those of skatole.

3-Methylindole (17) and 3-(3-Indolylmethyl)-3-methylindoline (18).—A solution of 2.42 g (15 mmol) of 3-indolecarboxylic acid (**16b**) in 100 ml of THF and 50 ml of 1 *M* borane in THF was heated at reflux for 4 hr and cooled, and the excess reagent was decomposed with water. After evaporation of the solvents, the residue, 1.6 g of malodorous oil, was dissolved in ether and extracted three times with 25-ml portions of 6 *N* HCl and the ether was dried and evaporated to give 965 mg (49%) of skatole (**17**) as white crystals, mp 75–79°. The structure was confirmed by comparison of its nmr spectrum with that of an authentic sample.

The combined acid washes were extracted with $CHCl_3$ and the $CHCl_3$ extracts were combined, washed with saturated $NaHCO_3$, dried, and evaporated to 250 mg of tan oil. This material was chromatographed on diatomaceous silica using a heptane–methanol (1:1) system. The fraction eluted at peak hold-back-volume 4.0 (V_m/V_s = 2.38) was evaporated to give 150 mg (8%) of 3-(3-indolylmethyl)-3-methylindoline (**18**) as odorless, pink crystals, mp 121–123°. Recrystallization from acetone–hexane, followed by sublimation at 115°, gave the pure sample: mp 132–134° (lit.[4] mp 132–134°); uv max 225, 284, 292 mμ (ε 29,800, 9600, 9200); ir max 2.90, 3.02, 6.08, 6.22 μ; nmr ($CDCl_3$) δ 1.33 (s, 3, CH_3), 3.00 (s, 2, $-CH_2$), 3.09 (d, 1, J = 9.0 Hz, 2-H of indoline), 3.22 (s, 1, NH of indoline), 3.50 (d, 1, J = 9.0 Hz, 2-H of indoline), 6.42–7.67 (m, 8, aryl), 7.80 (broad s, NH of indole).

Anal. Calcd for $C_{15}H_{18}N_2$: C, 82.40; H, 6.92; N, 10.68; mol wt, 262. Found: C, 82.33; H, 6.70, N, 10.52; mol wt, 262.

Registry No.—**1**, 16052-63-4; **2** succinate, 38179-35-0; **3a**, 23340-79-6; **3b**, 23340-80-9; **3c**, 23340-81-0; **3d**, 38662-06-5; **3e**, 23340-83-2; **3f**, 23340-84-3; **4**, 38662-09-8; **5**, 38662-10-1; **5** fumarate, 38662-46-3; **6a**, 38662-11-2; **6d**, 38662-12-3; **9c**, 23340-82-1; **9c** borane, 38662-14-5; **9e**, 23340-85-4; **9e** borane, 38662-16-7; **10a**, 38662-47-4; **10e** borane, 38662-48-5; **10f**, 38677-72-4; **11a**, 38662-49-6; **11f**, 38661-77-7; **13a**, 38662-17-8; **13a** picrate, 38662-18-9; **13b** borane, 38662-23-6; **14**, 38662-19-0; **15a** borane, 38662-20-3; **15b** borane, 38662-21-4; **16a**, 776-41-0; **16b**, 771-50-6; **17**, 83-34-1; **18**, 38662-24-7; oxalyl chloride, 79-37-8; *N,N*-dimethyl-3-indoleglyoxamide, 4545-06-6; 5-methoxy-*N,N*-dimethyl-3-indoleglyoxamide, 2426-20-2; $LiAlH_4$, 16853-85-3; diborane, 19287-45-7.

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Acknowledgment.—Spectral data, partition chromatography, and microanalyses were furnished by Messrs. W. Fulmor, C. Pidacks, and L. Brancone and their associates, respectively. The assistance of Mr. G. O. Morton in interpreting the nmr spectra is especially noteworthy.

The Influence of Aggregate Composition on Relative Reactivities of Alkyllithiums

WARREN PEASCOE AND DOUGLAS E. APPLEQUIST*

Department of Chemistry, University of Illinois, Urbana, Illinois 61801

Received December 1, 1972

Studies of the competitive metalation of indene by *tert*-butyllithium and isopropyllithium in pentane have shown that the reactions are first order in alkyllithium and that the relative reactivities of the two alkyllithiums depend upon the compositions of the aggregates in the mixture, pure *tert*-butyllithium tetramer being an order of magnitude less reactive than *tert*-butyllithium in mixed aggregates with isopropyllithium.

An important clue to the mechanism of any reaction of an organolithium compound could be the relationship of the rate of that reaction to the stabilities or inherent basicities of the organolithiums. The latter may be assumed to bear some relationship to the aqueous acidities (pK_a) of the corresponding hydrocarbons, and, in part by such an assumption, Cram[1] has combined various kinds of kinetic and equilibrium data into an internally consistent scale ("MSAD scale") of hydrocarbon acidities. We have sought correlations of MSAD acidities with the rates of the simplest possible organolithium reactions, and here report the results of some such studies on the metalation of the acidic hydrocarbon indene by two alkyllithium compounds.

In this study, a limiting amount of indene was added to a mixture of two alkyllithiums in pentane at room temperature. After a reaction period of 1–2 hr, the reaction was quenched with D_2O and the extent of deuterium incorporation in each of the resulting alkanes was determined by quantitative infrared analysis. If undeuterated alkane arose exclusively from the reaction of RLi with indene, then the relative rates of reaction of the two alkyllithiums with indene were thus determined. The determination of the relative rate constants (k/k') from the data using eq 1 requires

$$\frac{d(RLi)}{d(R'Li)} = \frac{k(RLi)^m}{k'(R'Li)^n} \quad (1)$$

assumption or prior determination of values for the exponents m and n. The literature reveals fractional orders for the very similar metalation of fluorene in benzene[2] and for metalation of triphenylmethane in THF.[3] Other reactions of alkyllithiums sometimes exhibit fractional order[4] or first order[5] or are reactions with induction periods.[5a,6]

The determination of the reaction orders m and n in a competitive study such as this one is complicated by the fact that if a fractional order arises from the commonly accepted mechanism (eq 2), and if the two

$$(RLi)_n \overset{K}{\rightleftharpoons} nRLi$$
$$RLi + \text{substrate} \xrightarrow[k]{\text{slow}} \text{product} \quad (2)$$

lithium reagents in the competitive mixture have formed a statistical array of mixed aggregates, then analysis of the data using eq 1 will give constant values for k/k' only for $m = n = 1$, regardless of the fact that the rate law for reaction of an isolated RLi would be of fractional order.[7] The values of "k/k'" thus obtained will not be the ratios of rate constants for the proton-abstraction steps, but will be related to the dissociation constants of the aggregates (eq 3), where

$$\left(\frac{k}{k'}\right)_{obsd} = \left(\frac{K}{K'}\right)^{\frac{1}{n}}\left(\frac{k}{k'}\right) \quad (3)$$

K and K' are the equilibrium constants for the two alkyllithiums in the first step of mechanism 2. Competitive rate studies thus cannot be interpreted in purely kinetic terms if mechanism 2 is operative *and* if the alkyllithiums have formed a statistical mixture of aggregates.

In the present work it has been found that alkyllithiums in pentane react with indene in a process which is first order in alkyllithium, not fractional order, so that mechanism 2 is not operative here. Rather, indene apparently reacts directly with the undissociated RLi aggregate. The means by which the true first-order dependence was established was to investigate

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(7) A simple proof was presented by D. E. Applequist and D. F. O'Brien, *J. Amer. Chem. Soc.*, **85**, 743 (1963), that the ratio of two monomeric alkyllithium species in such a statistical array is directly proportional to the ratio of the total stoichiometric concentrations of the two alkyllithium compounds.

competitive reactions of a mixture of *tert*-butyllithium and isopropyllithium which were freshly mixed and therefore had not had time to form mixed aggregates.[8] Only the assumption of first-order reactions ($m = n = 1$) in alkyllithium gave constant values of $k_{t\text{-PrLi}}/k_{t\text{-BuLi}}$ from integrated forms of eq 1, as shown in Table I.

TABLE I

CALCULATED VALUES OF $k_{i\text{-PrLi}}/k_{t\text{-BuLi}}$ FOR VARIOUS VALUES OF m (ORDER IN i-PrLi) AND n (ORDER IN t-BuLi) WITH VARIOUS INITIAL MIXTURES OF HOMOGENEOUS AGGREGATES OF i-PrLi AND t-BuLi[b,c]

$X_{t\text{-BuLi}}$[a]	$m = 1$ $n = 1$	$m = 1/2$ $n = 1/2$	$m = 1/4$ $n = 1/4$	$m = 2$ $n = 2$	$m = 1/4$ $n = 1$
0.843	11.3	3.8	2.2	112	54
0.572	15.1	9.1	7.3		107
0.215	13.6	21	26	6.5	114
0.151	11.5	23	32		146

[a] Stoichiometric mole fraction of t-BuLi in the alkyllithium mixture. [b] The estimated maximum errors in the calculated ratios (from experimental errors) are 25–50%. [c] All alkyllithium mixtures were allowed to stand together for 18 min before addition of indene.

Since both t-BuLi and i-PrLi in their homogeneous aggregates (tetramers in the case of t-BuLi and a mixture of tetramers and perhaps hexamers in the case of i-PrLi)[9] react with indene by processes first order in alkyllithium, it seems safe to infer that mixed aggregates of these two alkyllithiums also react by such first-order processes. It was next of interest to determine the effect upon $k_{t\text{-PrLi}}/k_{t\text{-BuLi}}$ of allowing the mixture of alkyllithiums to stand long enough[8] to form a statistical mixture of aggregates before the indene was added. The results of a set of such experiments are shown in Table II.

TABLE II

RATIO OF PSEUDO-FIRST-ORDER RATE CONSTANTS AS A FUNCTION OF THE TIME THE ALKYLLITHIUMS WERE ALLOWED TO STAND PRIOR TO ADDITION OF INDENE[a]

Time, hr	$k_{i\text{-PrLi}}/k_{t\text{-BuL}}$
0.3	15 ± 4
11	3.2 ± 0.4
24.8	1.9 ± 0.4
42.8	1.6 ± 0.2
93	1.3 ± 0.2

[a] The mole fraction of t-BuLi was 0.572 in these runs.

The conclusion from the data of Table II is that the relative reactivities of the two alkyllithiums in the reaction with indene are markedly dependent upon the composition of the aggregate which reacts with the indene. It is clear that *tert*-butyllithium in its homogeneous tetramer is particularly unreactive, whereas *tert*-butyllithium and isopropyllithium show nearly equal reactivities toward proton abstraction when they are in mixed aggregates (presumably tetramers).

It must be concluded that simple correlations of alkyllithium reactivities with the MSAD or other scale of inherent basicities cannot be expected when the alkyllithiums react in aggregated form. Indeed the data comprising the MSAD scale could themselves be biased by steric effects within the aggregates, as we have earlier pointed out.[10]

In spite of the difficulty of quantitative interpretation of data that has been demonstrated above, measurements have been made of relative reactivities of a number of alkyllithiums (equilibrated mixtures) with indene and fluorene in pentane, benzene, or ether–pentane, and crude linear correlations with MSAD[1] or K_ϕ[10] basicity scales have been obtained. The data are recorded elsewhere.[11]

Experimental Section

Materials.—Commercial indene was repeatedly crystallized from pentane at Dry Ice temperature until it was better than 99% pure by glpc analysis on an FFAP column. It was then vacuum distilled through a 127-cm tantalum-wire column and stored in a freezer until used.

Bulk pentane was washed several times with concentrated sulfuric acid and then with water, dried ($MgSO_4$), distilled from calcium hydride, and stored over Dri-Na (sodium–lead alloy).

tert-Butyllithium in pentane was obtained from Alfa Inorganics, Inc. Isopropyllithium was prepared by the general method of Gilman[12] from 2-chloropropane (>99% pure by glpc) and high-sodium lithium metal from Lithium Corp. of America. The alkyllithium solutions were analyzed by the Gilman double-titration method with allyl bromide or 1,2-dibromoethane,[13] and in general contained less than 2% of base other than alkyllithium. All volumetric measurements of alkyllithium compounds were made with pipets inside an argon atmosphere glove box from which traces of oxygen and water were removed by continuous circulation of the atmosphere through columns packed with molecular sieves and MnO. All solutions were flushed with argon before transfer to the glove box or before addition to alkyllithium compounds.

Competitive Reactions with Indene.—Quantitives of i-PrLi and t-BuLi in pentane were pipetted into a reaction flask to give solutions *ca.* 0.3 M in total alkyllithium and were allowed to stand for a measured time. The solvent was removed under vacuum and replaced with *ca.* 50 ml of pentane.

The flask, which was equipped with a stopcock and also with a septum, was removed from the glove box. Two dewar traps, one above the other, were flushed with argon, attached above the stopcock of the flask, and cooled with Dry Ice. The stopcock on the reaction flask was opened, and a positive pressure of argon was maintained in the system throughout the reaction. Enough indene (generally 11–20 mmol) in *ca.* 50 ml of pentane was added through the septum to leave convenient amounts of i-PrLi and t-BuLi unreacted after *ca.* 60–90% of the indene reacted. The reaction mixture was stirred magnetically at room temperature for 2 hr for freshly mixed solutions and for 1 hr for equilibrated solutions, during which time a white precipitate presumed to be indenyllithium formed. In order to analyze for unreacted alkyllithium, the reaction flask was cooled with an ice bath, and 6 ml of D_2O was carefully added through the septum to the rapidly stirred mixture. The precipitate dissolved within a few minutes of the D_2O addition, indicating that the precipitate was indenyllithium rather than an indene polymer. The lower dewar trap was warmed to 0° and a collecting flask at the top of the lower dewar trap was cooled with Dry Ice. The reaction solution was distilled and the fraction with a boiling point less than 0° was collected. The isobutane and propane in this concentrated sample were purified to greater than 99% purity by preparative glpc using a 20-ft 20% diisodecyl phthalate on Chromosorb P column at room temperature. Only traces of products with retention times identical with those of propene and isobutene were observed in addition to the expected peaks of propane, isobutane, and solvent on both diisodecylphthalate and Porapak Q columns. The purified hydrocarbons were transferred to a vacuum line and transferred through a Dry Ice cooled trap to remove any nonvolatile impurities. Fixed amounts of

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hydrocarbon as determined by pressure were transferred to a 10-cm gas ir cell, and the ir spectrum was determined under standard conditions. The ir spectrum of propane showed bands at 2860–3000, 1480, 1470, 1450, 1390, and 1380 cm^{-1}; the ir spectrum of 2-deuteriopropane showed bands at 2860–3000, 2170, 1480, 1470, 1390, 1380, and 1142 cm^{-1}; the ir spectrum of isobutane showed bands at 2850–3000, 1482, 1380, 1330, and 1175 cm^{-1}; and the ir spectrum of 2-deuterioisobutane showed bands at 2860–3000, 2155, 1482, 1380, 1242, and 1232 cm^{-1}. The ratio of absorbance at 2170 to that at 1480 and at 2170 to that at 1380 cm^{-1} for partially deuterated propane and the ratio of absorbance at 2155 to that at 1380 and at 1242 to that at 1482 cm^{-1} for partially deuterated isobutane were determined. Comparisons of the ratios of absorbances to the ratios of absorbances of mixtures with known mole fraction of monodeuterated hydrocarbon were made graphically, and the mole fraction of deuterated hydrocarbon was determined. The results from the two determinations for each sample were within 0.02 mole fraction units and an estimated error of ±0.02 mole fraction units from the mean was assigned as a reasonable limit of accuracy for the method. The error limits assigned in Tables I and II are based on an assumed error of ±0.02 mole fraction units in the final concentrations of the alkyllithium compounds. No fractionation of partially deuterated compound occurred during work-up, since a glpc-purified sample of propane with a known deuterium content was repurified and found to have the same deuterium content.

An alternative analytical method gave results within experimental error of those described above for equilibrated alkyllithium mixtures, and in addition was used to show that added lithium chloride, *tert*-butyl chloride, or *tert*-butyl alcohol did not change the ratio $k_{i\text{-PrLi}}/k_{t\text{-BuLi}}$, whatever effects they may have had on the absolute rates. When the reaction was complete, the solvent and volatile hydrocarbon products of the reaction were removed under vacuum with external heat. The reaction mixture was not allowed to warm above 30°. Benzene containing adamantane as an internal nmr standard was pipetted into each of the flasks. The precipitated aryllithium compound was broken up and dispersed in the liquid. The solution of unreacted alkyllithium compounds and adamantane was filtered from the precipitate using disposable pipets fitted with glass-wool plugs. The nmr resonances of the alkyllithium compounds (*t*-BuLi δ 1.00 (s); *i*-PrLi 1.36 (d)] and the resonance of adamantane (δ 1.75–1.85) were integrated five times. The ratio of the areas of the alkyllithium resonances to the area of the adamantane resonance was used to determine the concentration of the alkyllithium compounds.

Registry No.—*i*-PrLi, 1888-75-1; *t*-BuLi, 594-19-4; indene, 95-13-6; propane, 74-98-6; 2-deuteriopropane, 20717-74-2; isobutane, 78-28-5; 2-deuterioisobutane, 13183-68-1.

Acknowledgments.—This work was supported in part by National Science Foundation grants G-7403, GP-166, and GP-4681, and in part by the Petroleum Research Fund, administered by the American Chemical Society. Grateful acknowledgment is made to the National Science Foundation and to the donors of the Petroleum Research Fund.

The Knoevenagel Reaction. A Kinetic Study of the Reaction of (+)-3-Methylcyclohexanone with Malononitrile

FRANKLIN S. PROUT,* VICTOR D. BEAUCAIRE,[1a] GARY R. DYRKACZ,[1e] WILLIAM M. KOPPES,[1c,d] ROBERT E. KUZNICKI,[1b] THEODORE A. MARLEWSKI,[1b] JAMES J. PIENKOWSKI,[1a] AND JACQUELINE M. PUDA[1d]

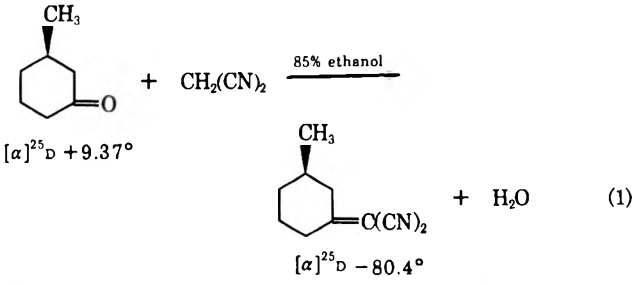
Department of Chemistry, De Paul University, Chicago, Illinois 60614

Received June 16, 1972

The condensation of malononitrile with (+)-3-methylcyclohexanone produced an 80–85% yield of (−)-3-methylcyclohexylidenemalononitrile. The reaction, followed polarimetrically in alcohol–water, is kinetically second order and efficiently catalyzed by weak bases (ω-amino acids, cyclic amino acids, NH_4OAc), furnishing solutions having an apparent pH of 7.5–8.0. With β-alanine as catalyst, the E_a was 7.6 kcal/mol compared to 11 kcal/mol uncatalyzed. Stronger bases (barbital, NaOAc, KOAc, KF, piperidine) effected more rapid condensation but poorer kinetics because of telemerization of malononitrile at the higher pHs.

Our earlier studies on the Knoevenagel condensation[2,3] have examined catalyst effectiveness in a heterogeneous system. Under these conditions efficiency of the largely insoluble dipolar ions was a function of an undetermined combination of pH and concentration.

A more desirable homogeneous system involved the reaction of (+)-3-methylcyclohexanone with malononitrile (eq 1). This reaction occurred slowly (when not catalyzed) and nearly quantitatively in an alcoholic solution at room temperature. The product can be isolated in 80–85% yield and is probably formed to an extent greater than 95%. The reverse reaction is very slow and can be neglected. With catalysts furnishing an apparent pH no higher than 8, no important side reactions seem to appear. Because the change in rotation during the course of this reaction is large and



(1)

linear with change in concentration, the progress of the reaction can be followed polarimetrically.

An extensive series of kinetic runs were made using β-alanine as catalyst (Table I). Most runs were made with a 0.400 *M* concentration of reactants and the rate calculations were based on the assumption of second-order kinetics.[4,5] It is clear in runs 11, 15, 49, 50, 52, and 53 that increasing the concentration of catalyst from 6×10^{-4} *M* to 2.5×10^{-2} *M* increased the rate of

(1) This investigation was supported by the National Science Foundation Grants for the Undergraduate Research Participation Program of the Science Education Section, Division of Scientific Personnel and Education in (a) 1962, (b) 1963, (c) 1964, (d) 1965, and (e) 1967.

(2) F. S. Prout, *J. Org. Chem.*, **18**, 928 (1953); F. S. Prout, A. A. Abdellatif, and M. R. Kamal, *J. Chem. Eng. Data*, **8**, 597 (1963).

(3) For an extensive review see G. Jones, *Org. React.*, **15**, 204–599 (1967).

(4) S. Patai and Y. Israeli, *J. Chem. Soc.*, 2025 (1960).

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Table I

Reaction of (+)-3-Methylcyclohexanone with Malononitrile Using β-Alanine Catalysis[a]

Run	[β-Alanine], mol/l.	Temp, °C	k_2,[b] l. mol^{-1} min^{-1}	k_2/[alanine]	Apparent pH[c]
65	None	25	0.0007		6.55
66	None	45	0.0022		
49, 50	6×10^{-3}	25	0.107	18	7.19
52, 53	1.2×10^{-2}	25	0.141	12	7.35
15	2.5×10^{-2}	25	0.152	6.1	7.42
51	6×10^{-3}	15	0.0643	11	
13	6×10^{-3}	35	0.151	25	
47, 48	6×10^{-3}	45	0.179	30	7.05[d]
10	6×10^{-4}	25	0.019[e]	32	
11	6×10^{-4}	25	0.036[e]	47	
16	6×10^{-3}	25	0.0973[f]	16	7.27[h]
17, 54	6×10^{-3}	25	0.0527[g]	9	7.11[h]

[a] The reaction of 2.24 g (0.0200 mol) of ketone with 1.32 g (0.0200 mol) of malononitrile in a volume of 50 ml was observed in a polarimeter and rotatory values were converted to concentrations. [b] k_2 determined graphically plotting time against $1/(a - x)$. [c] Apparent pH determined at 25 ± 5° with catalyst in 5 ml of water and 1.32 g of malononitrile, diluted up to 50 ml with 95% ethanol. [d] pH determined as in *c*, except at 48 ± 5°. [e] Run 10 performed in absolute alcohol, run 11 performed in the usual aqueous alcoholic system. [f] Reaction of 1.0 *M* ketone with 0.20 *M* malononitrile, k_2 determined graphically plotting log $a(b - x)/b(a - x)$ against time. [g] Reaction of 0.20 *M* ketone with 1.0 *M* malononitrile. k_2 determined as in *f*. [h] pH determined as in note *c*, except that in run 16 malononitrile was 0.200 *M* and in runs 17 and 54 malononitrile was 1.00 *M*.

reaction; however, the efficiency of the catalyst (k_2/C) increased as the concentration of catalyst *decreased*. The increase of efficiency must reflect a higher percentage of dissociation into the acidic (RNH_3^+) and basic ($RCOO^-$) ions at lower concentration. Second-order kinetics were apparently confirmed in runs using 1.00 *M* ketone–0.200 *M* malononitrile (run 16) and in runs using 0.200 *M* ketone–1.00 *M* malononitrile (runs 17, 54). However, the rate constant is lower with high malononitrile concentration (runs 17, 54) because the apparent pH of the reaction mixture is lower.

The plot of log k_2 against $1/T$ (runs 51, 49, 50, and 13) is linear between 15 and 35°. However, runs at 45° (47 and 48) give a point far off the line. The activation energy (E_a), calculated between 15 and 35° from the Arrhenius equation, was 7.6 kcal/mol. When no catalyst was used the E_a was 11 kcal/mol.[5]

In another series of runs (Table II) the rates were determined with several catalysts. Usually the catalyst concentrations were 6×10^{-3} *M*. The second-order rates increased as the catalyst became more basic. A plot of log k_2/C against apparent pH of the catalysts in alcohol–water (Figure 1) gave a cluster of points, suggesting that the rate is more dependent on the pH than on structural considerations.[6]

Structural features do cause aberrations; for example, the *p*-*N*,*N*-dimethylaminocyclohexanecarboxylic acids give rates which are much faster than the apparent pH would suggest. The rate calculations for the reactions when the apparent pH exceeded 8.5 were somewhat less reliable, but gave reasonable results because reaction plots were nearly linear up to 75% of reaction. (For example, with barbital, the fastest rate, the reaction was about 25% completed when the first reliable rotatory reading at 2 min was observed.)

Data for five constants are assembled in Table III and plotted in Figure 2. The runs catalyzed with β-alanine at 25° (11, 49, and 53) give straight-line plots for the 70-min time. Run 48, which was catalyzed with β-alanine at 45°, slowed markedly after 30 min. This is probably caused by the conversion of malononitrile to dimer and trimer.[7] The potassium fluoride run shows a positive inflection after 18–20 min. This is typical of the more basic catalysts and we do not understand this effect.

Other possible side reactions, such as hydrolysis of malononitrile to cyanoacetamide or dimerization of product,[8] are quite sluggish and do not appear to have a serious effect on the results.

The evidence we have assembled seems to indicate that the controlling rate of reaction is mainly a function of pH. The controlling reaction, following Zabicky's mechanism, would probably be eq 2.[9] The efficiency

(2)

of tertiary amine and nonamine catalysts seems to eliminate the imine intermediate for the reaction under these reaction conditions.[10]

Experimental Section

All melting points and boiling points were uncorrected. Fractional distillations were carried out in a 60-cm, heated Vigreux column with no head. Gas chromatographic analyses were performed on a column with silicone gum rubber (SE-30) as liquid phase in an F & M Model 720 or a Wilkins Aerograph 600C. Optical rotations were observed on a Rudolph high-precision polarimeter, Model 80. Constant temperatures were maintained to a precision of ±0.1° with a Haake Model E water circulator. The accuracy of the thermometer was ±0.2° against an NBS-calibrated thermometer. Dissociation constants were determined with a Beckman Model 76 pH meter. Infrared spectra were determined on a Perkin-Elmer Model 22 spectrophotometer.

Pulegone was obtained from Givaudan-Delawanna, Inc., $\alpha^{30}D$ +23.33 ± 0.02°. *dl*-3-Methylcyclohexanone was obtained from Distillation Products Industries. The amino acids came from Distillation Products Industries (glycine, β-alanine, γ-aminobutyric acid, and *N*,*N*-dimethylglycine hydrochloride) and Nutritional Biochemicals Corp. (ε-aminocaproic acid). The aminophenols were crystallized commercial products previously reported.[2] Malononitrile, obtained from Kay-Fries, Inc., was distilled prior to use, bp 95–99° (2 mm), fp 32°, homogeneous when gas chromatographed at 165°. The ethyl *cis*- and *trans*-*p*-dimethylaminocyclohexanecarboxylates were kindly given to us by Dr. Frank J. Vilani of the Schering Corp., Bloomfield, N. J.

(6) Similar plots result when log k_2/C is plotted against pI (Table II), pK_1, or pK_2. The pI values are from E. J. Cohn and J. T. Edsall, "Proteins, Amino Acids and Peptides," Reinhold, New York, N. Y., 1943, pp 84, 99, 128.

(7) A mixture of 0.66 g of malononitrile and 27 mg of β-alanine in a 50-ml ethanol–H_2O solution was allowed to stand overnight at room temperature. Crude malononitrile remaining when the solvent was removed showed development of infrared absorption at 3370, 3270, 2230, 2215, and 1660 cm^{-1}, suggesting the formation of malononitrile dimers and/or trimers. A sample of dimer, prepared inefficiently by boiling a mixture of malononitrile and β-alanine in ethanol–water, had ir absorptions at 3360, 3210, 2270, 2230, 2210, and 1660 cm^{-1}, just as reported by R. A. Carboni, D. D. Coffman, and E. G. Howard, *J. Amer. Chem. Soc.*, **80**, 2838 (1958).

(8) M. R. S. Weir and J. B. Hyne, *Can. J. Chem.*, **41**, 2905 (1963); **42**, 1440 (1964).

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(10) The Knoevenagel reaction in benzene with piperidine catalysis might well involve an enamine intermediate; *cf.* G. H. Alt and G. A. Gallegos, *J. Org. Chem.*, **36**, 1000 (1971); F. S. Prout, *ibid.*, **38**, 399 (1973).

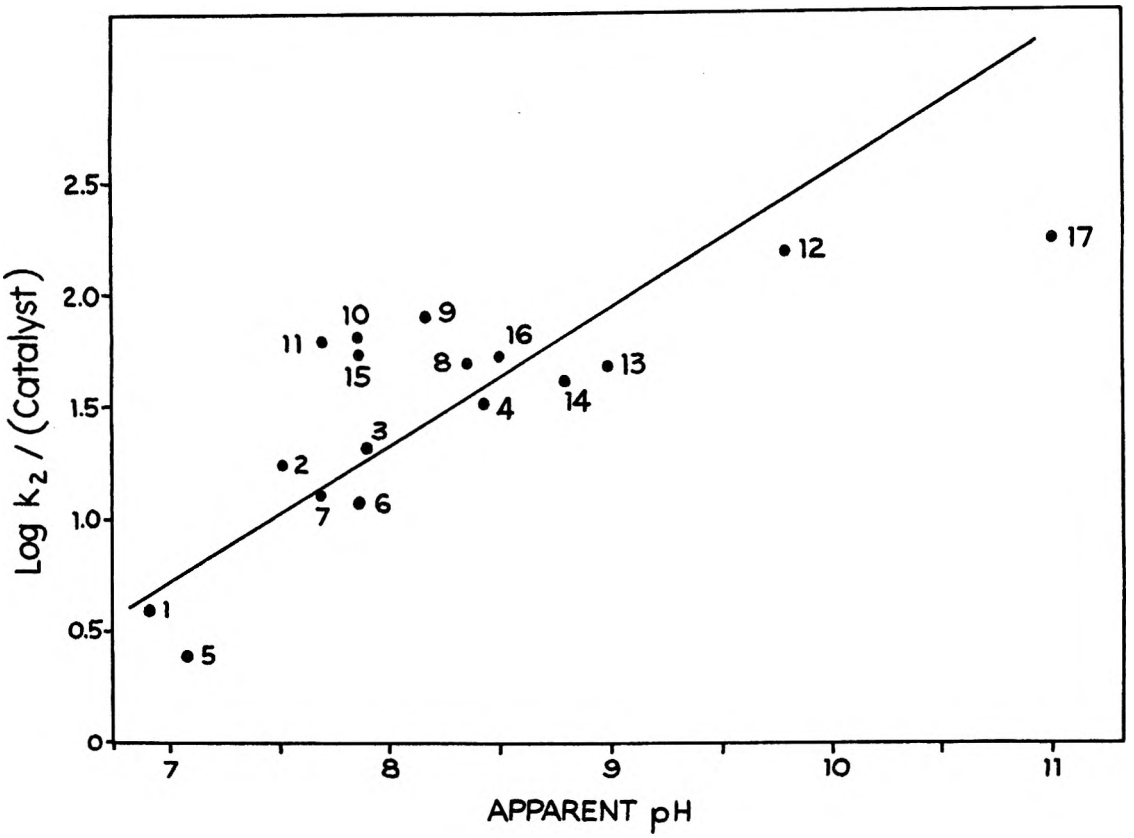

Figure 1.—Plot of log k_2/(catalyst) against apparent pH, data from Table II: 1, Glycine; 2, β-alanine; 3, γ-aminobutyric acid; 4, ε-aminocaproic acid; 5, *N*,*N*-dimethylglycine; 6, *cis*-HHAA; 7, *trans*-HHAA; 8, *cis*-*p*-ACHCA; 9, *trans*-*p*-ACHCA; 10, *cis*-*p*-DMACHCA; 11, *trans*-*p*-DMACHCA; 12, barbital buffer; 13, NaOAc; 14, KOAc; 15, NH_4OAc; 16, KF; 17, piperidine.

TABLE II

CONDENSATION OF (+)-3-METHYLCYCLOHEXANONE WITH MALONONITRILE USING SEVERAL CATALYSTS AT 25°[a]

Catalyst (C), 6×10^{-3} *M*	k_2,[b] M^{-1} min^{-1}	k_2/C	Log k_2/C	pI[c]	pH[d]
Glycine	0.024[e]	4.0	0.602	5.97	6.91
β-Alanine	0.107[e]	18	1.252	6.90	7.52
γ-Aminobutyric acid	0.12	21	1.32	7.33	7.90
ε-Aminocaproic acid	0.20	33	1.52	7.59	8.43
N,*N*-Dimethylglycine	0.015	2.5	0.399	5.87	7.07
cis-HHAA[f]	0.071[e]	12	1.08	7.02	7.86
trans-HHAA[f]	0.077[e]	13	1.11	6.72	7.69
cis-*p*-ACHCA[g,h]	0.150	50	1.70	7.49	8.36
trans-*p*-ACHCA[g,h]	0.250	81	1.91	7.37	8.17
cis-*p*-DMACHCA[h,i]	0.195[e]	65	1.81	7.46	7.86
trans-*p*-DMACHCA[h,i]	0.190[e]	63	1.80	7.28	7.70
Glycylglycine[j]	0.017	7.1	0.85	5.60	6.49
Barbital buffer[k]	0.61	153	2.18	8.00[k]	9.80
Sodium acetate	0.29	48	1.68		8.99
Potassium acetate	0.25	42	1.62		8.80
Ammonium acetate[l]	0.33	55	1.74		7.87
Potassium fluoride	0.32	53	1.73		8.50
Piperidine[h]	0.53	176	2.25		11.10
o-Aminophenol	0.027	4.5	0.65		
m-Aminophenol	0.0067	1.1	0.048		7.70
p-Aminophenol	0.056	9.3	0.97		

[a] Mixture containing 1.32 g (0.0200 mol) of malononitrile, 2.24 g (0.0200 mol) of (+)-3-methylcyclohexanone, and catalyst in 5 ml of water diluted to 50 ml with 95% ethanol. [b] K_2 determined graphically, $1/(a - x)$ *vs.* time. [c] pI determined in water, from Cohn and Edsall (ref 6), pp 84, 99, and 128, or Table IV. [d] Apparent pH of catalyst in a solution of 5 ml of water diluted to 50 ml with 95% ethanol. [e] Average of two runs. [f] HHAA is hexahydroanthranilic acid. [g] *p*-ACHCA is *p*-aminocyclohexanecarboxylic acid. [h] Catalyst concentration was 3×10^{-3} *M*. [i] *p*-DMACHCA is *p*-dimethylaminocyclohexanecarboxylic acid. [j] Catalyst concentration was 2.4×10^{-3} *M*. [k] Buffer contains 2×10^{-4} mol each of barbital and sodium barbital in 5 ml of water. Thus C is 4×10^{-3} *M*. Reported pH 8.00: R. Nasanen and T. Heikkila, *Suom. Kemistilehti B*, **32**, 163 (1959); *Chem. Abstr.*, **54**, 5215*i* (1960). [l] Ammonium acetate prepared by the action of 0.0178 mg of acetic acid with 0.0170 mg of ammonium carbonate (30% NH_3).

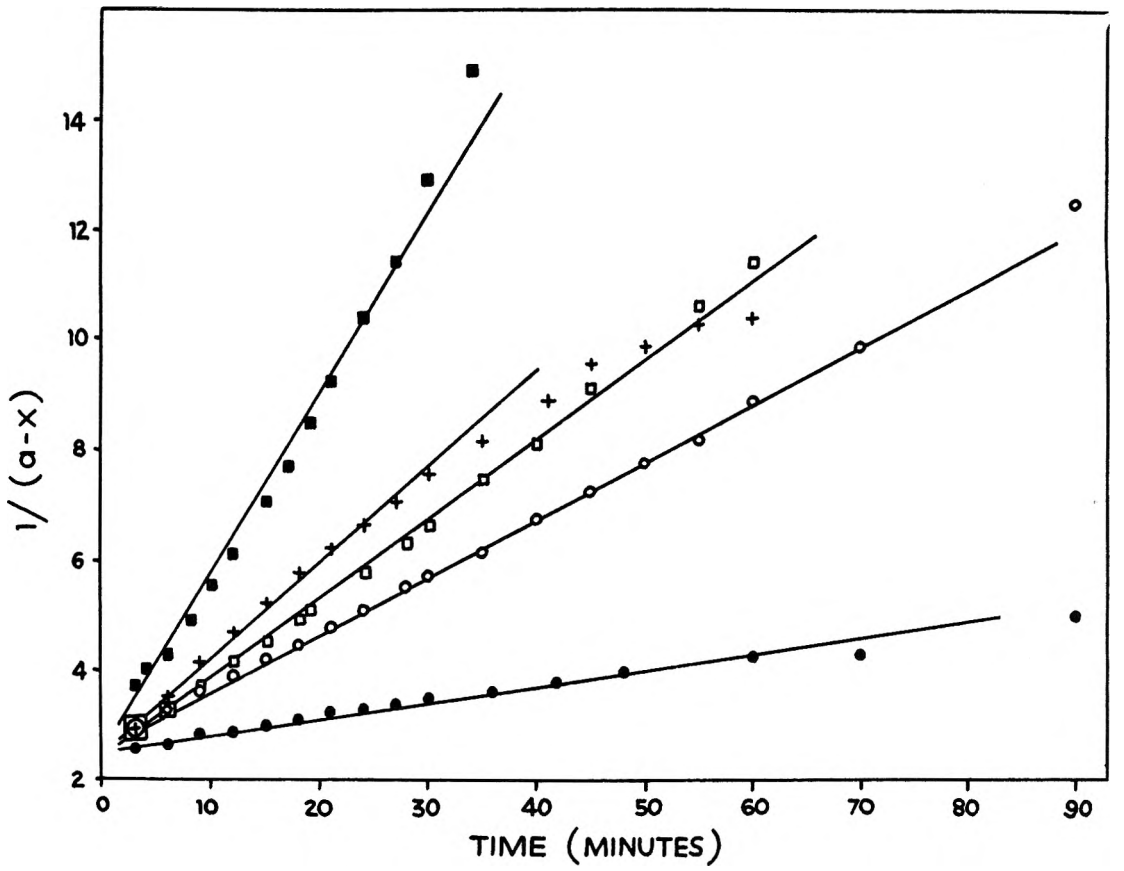

Figure 2.—Reaction of malononitrile with (+)-3-methylcyclohexanone. Plot of data in Table III: ●, run 11, 0.0006 *M* β-alanine; ○, run 49, 0.006 *M* β-alanine; ⊡, run 53, 0.012 *M* β-alanine; ■, 0.006 *M* KF all at 25°; +, run 48, 0.006 *M* β-alanine at 45°.

Amino Acids. ***cis*-Hexahydroanthranilic Acid.**—Hexahydrophthalimide[11] (42.7 g, mp 129–134°) was dissolved in a solution of 16 g of sodium in 350 ml of methanol. Dry chlorine generated from the action of 15.8 g of potassium permanganate and 200 ml of concentrated hydrochloric acid[12] was passed into the solution at 40–50°. The mixture was boiled for 15 min. After cooling the salt was removed, and the mixture was diluted with 500 ml of water and continuously extracted with ether.[13]

The crude ester–urethane (51 g) was mixed with 125 ml of concentrated hydrochloric acid and was heated under reflux for 6 hr. The brownish reaction mixture was filtered with Norit and Celite and was concentrated at reduced pressure to furnish a solid residue. This amino acid hydrochloride was dissolved in water and was placed on a 160-g column of Amberlite IR-120 (sulfonic acid resin). After the mineral acid was washed out the amino acid was eluted with 0.9 *M* ammonia. Eluates with pH 7–10 contained the amino acid and were concentrated *in vacuo*. The crude product (mp 213–218°) was crystallized from alcohol–acetone to furnish 16.5 g (41.3%) of product, mp 222–224°. The purified acid was obtained from a mixture of ethanol–methanol diluted with acetone, mp 224.5–226.5°. This acid showed no loss in weight upon heating at 80° *in vacuo*. This acid has been reported to have melting points of 230–231,[14] 235,[15] and 236°.[16]

The benzenesulfonamide as a 1:1 benzene complex was recrystallized from benzene. Drying *in vacuo* at 80° gave the pure product, mp 160–161.5°.

Anal. Calcd for $C_{13}H_{17}O_4NS$: C, 55.10; H, 6.05. Found:[17] C, 55.08; H, 6.56.

***trans*-Hexahydroanthranilic Acid.**—Forty grams of anthranilic acid was reduced by the action of 60 g of sodium in isoamyl alcohol.[18]

The combined aqueous washes containing the sodium salts from this reduction were allowed to stand with 440 g (*ca.* 1.85 equiv) of Amberlite IP-120 to remove much of the sodium ion. The aqueous washes were passed through columns of Amberlite IR-120. The amino acid was eventually collected on the resin after the sodium ion had been adsorbed. The amino acid was eluted with 0.9 *M* ammonia. The amino acid rich eluates (*ca.* 1000 ml) were concentrated to a volume of 25–35 ml and diluted with 150 ml of acetone to give the crude amino acid, 14.4 g (34.6%), mp 248–250°. Recrystallization of the amino acid from 50 ml of water and 75 ml of acetone furnished 6.40 g, mp 264–265°. The purest sample had mp 267–270°. This acid has melting points reported at 274,[18] 273,[15] 269–272,[14] and 269–271°.[16]

The benzenesulfonamide was crystallized four times from acetone–benzene, mp 188–191°. The sample showed no loss upon drying at 80° *in vacuo*.

Anal. Calcd for $C_{13}H_{17}O_4NS$: C, 55.10; H, 6.05. Found:[17] C, 55.18; H, 6.40.

***cis*- and *trans*-4-aminocyclohexanecarboxylic acids** were prepared by reduction of *p*-aminobenzoic acid over platinum.[19] The cis acid had mp 301–303°. The trans acid melts with gasing and resolidification when immersed in a block at 380–390°. However, there is no apparent transition when the acid was heated normally. Eventually charring occurred at 480–500°. The cis acid is reported to melt at 302,[19] 304–305,[20] 303–304,[21] 286,[22] and 324–325°.[23] The trans acid has been reported to melt above 340,[19] 486–488,[20] above 495,[22] and above 400°.[23]

***cis*-4-Dimethylaminocyclohexanecarboxylic Acid.**—Ethyl *cis*-4-dimethylaminocyclohexanecarboxylate[24] (5.26 g) was heated under reflux with 25 ml of concentrated hydrochloric acid for 6 hr. The mixture, after concentration to 13 ml, was placed on a column of Amberlite IR-120 (sulfonic acid resin). Elution with

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TABLE III

DATA FOR CALCULATION OF RATE CONSTANTS OR PLOTTING GRAPHS IN THE REACTION OF 3-METHYLCYCLOHEXANONE AND MALONONITRILE

$1/(a - x)$, mol^{-1} l.[a]

Time, min	β-Alanine 0.0006 M Run 11	β-Alanine 0.006 M Run 49	β-Alanine 0.012 M Run 53	β-Alanine 0.006 M Run 48[b]	KF 0.006 M
(0)	(2.50)	(2.50)	(2.50)	(2.50)	(2.50)
3	2.58	2.89	2.87	2.95	3.74
4		3.03	3.00	3.15	4.03
6	2.65	3.26	3.26	3.53	4.30
8		3.50	3.54	3.92	4.93
9	2.82	3.60	3.69	4.12	
10		3.70	3.88	4.32	5.56
12	2.94	3.92	4.11	4.66	6.10
14		4.04	4.38	4.99	
15	3.01	4.22	4.52	5.22	7.08
17		4.42	4.81	5.55	7.73
18	3.11	4.44	4.94	5.75	
19		4.61	5.08	5.90	8.50
21	3.23	4.77		6.20	9.24
24	3.31	5.10	5.82	6.60	10.24
27	3.38			7.05	11.62
28		5.53	6.34		
30	3.49	5.72	6.65	7.55	12.92
34					14.89
35		6.13	7.45	8.15	
36	3.63				
40		6.73	8.13		17.3
41				8.90	
42	3.79				
45		7.25	9.13	9.55	20.5
48	3.97				
50		7.78	9.79	9.85	23.9
54	4.13				
55		8.19	10.60	10.3	
60	4.24	8.93	11.42	10.4	29.8
70	4.51	9.90			37.9
90	5.03	12.5			54.2

[a] Calculation based on rotation of synthetic mixtures; thus at 25° $1/(a - x) = 26.5/(\alpha_D + 9.75)$. [b] Reaction at 45°, $1/(a - x) = 26.1/(\alpha_D + 9.66)$ is the equation.

0.6 *M* ammonia liberated the amino acid. Fractions containing the amino acid were concentrated to give 4.26 g of crude product, mp 161–200°. Crystallization from equal portions of alcohol and ether gave 0.63 g of acid which was largely the trans form, mp 160–215°. Dilution of the mother liquor with large amounts of ether furnished the cis acid. After many crystallizations (finally from alcohol–acetone–ether), 1.25 g of pure amino acid was obtained, mp 179–181°. The purest sample had mp 181.5–184° after drying *in vacuo* at 80°.

Anal. Calcd for $C_9H_{17}O_2N$: C, 63.12; H, 10.01. Found:[17] C, 62.82; H, 9.97.

***trans*-4-Dimethylaminocyclohexanecarboxylic Acid.**—A solution of 5.15 g of ethyl *trans*-4-dimethylaminocyclohexanecarboxylate[24] and 2.8 g of potassium hydroxide in 35 ml of 95% ethanol was heated under reflux for 1.5 hr. The mixture was diluted with water and placed on a 70-g column of IR-120. Elution with 3 *N* ammonia furnished fractions containing the amino acid. The richest 100-ml fraction was concentrated to furnish 2.63 g, mp 205–214°. Two crystallizations from alcohol–ether gave 2.66 g of amino acid apparently as the alcoholate. After drying at 80° *in vacuo*, 2.02 g of amino acid remained, mp 223–224°.

Anal. Calcd for $C_9H_{17}O_2N$: C, 63.12; H, 10.01; N, 8.18. Found:[17] C, 63.10; H, 9.96; N, 8.15.

***N,N*-Dimethylglycine.**—*N,N*-Dimethylglycine hydrochloride (9.85 g, mp 188–190°) was placed on a column of Amberlite IR-120. Elution with 0.5 *M* ammonia furnished fractions (pH 5–11) which provided 7.0 g of amino acid. Recrystallization from isopropyl alcohol[25] gave the purified *N,N*-dimethylglycine (Table IV), mp 177.5–179°. The reported melting point is 177–182°.[26]

Condensation. (+)-**3-Methylcyclohexanone**[27] was prepared by retrograde aldol reaction of pulegone in dilute hydrochloric acid. Fractionation furnished a 65.2% yield of ketone: bp 119–120° (119 mm); $n^{26}D$ 1.4438; $[\alpha]^{26}D$ +11.90 ± 0.05° (homogeneous); $[\alpha]^{26}D$ +8.96 ± 0.1° (2.299 g of ketone dissolved up to 50 ml in 95% ethanol, $\alpha^{26}D$ +0.823 ± 0.01° in a 2-dm tube). Gas chromatography at 100° indicated a purity of about 98%.

Eisenbraun and McElvain[27] have reported bp 166–168° (735 mm), $[\alpha]^{26}D$ +12.01°.

3-Methylcyclohexylidenemalononitrile. A. *dl* Form.—A mixture of 28.0 g of *dl*-3-methylcyclohexanone, 16.5 g of malononitrile, 50 ml of 95% ethanol, 5 ml of acetic acid, and 0.20 g of β-alanine was heated under reflux for 1.5 hr. Distillation gave two fractions: (1) 3.36 g, bp 120–146° (34–14 mm), $n^{26}D$ 1.4988; (2) 32.6 g (81.5%), bp 146–154° (14 mm), $n^{26}D$ 1.5028, mp *ca.* 15°, ir (neat) 2200 (conjugated nitrile), 1590 cm^{-1} (double bond), nmr ($CDCl_3$) δ 1.06 (d, 3 H, J = 6 Hz, $=CHCH_3$).

Anal. Calcd for $C_{10}H_{12}N_2$: C, 74.96; H, 7.55; N, 17.49. Found:[28] C, 74.90; H, 7.57; N, 17.51.

Preparation using benzene as solvent while removing water azeotropically gave a 78.8% yield.

B. (−) Form.—A mixture of 22.4 g, $[\alpha]^{27}D$ +11.76°, of (+)-3-methylcyclohexanone, 13.2 g of malononitrile, and 0.89 g of β-alanine was swirled with 50 ml of 95% ethanol. The mixture then stood at room temperature for 20 hr. The green solution was decanted from the undissolved β-alanine and fractionated: (1) 3.19 g, bp 97–121° (4 mm), $[\alpha]^{25}D$ −51.2 ± 0.1° (95% ethanol); (2) 9.18 g, bp 121–122° (4 mm), mp 42.2°, $[\alpha]^{27}D$ −76.7 ± 0.2° (95% ethanol); (3) 17.96 g, bp 122–122° (4 mm), mp 45.8°, $[\alpha]^{27}D$ −77.8 ± 0.2° (95% ethanol), one component by gas chromatography. Fractions 2 and 3 represent an 84.6% yield.

The infrared absorption of fraction 3 (supercooled liquid) was identical with that of the *dl* form. However, fractions 1 and 2 and the last drop of fraction 3 showed some absorption at 1690 cm^{-1}, suggestive of amide.

The recrystallization of fraction 3 from 25 ml of 95% ethanol furnished 12.12 g of pure nitrile: mp 45.8–46.6° (softens at 42°); $[\alpha]^{25}D$ −77.9 ± 0.2° (1.661 g of nitrile dissolved up to 25 ml in 95% ethanol, $\alpha^{25}D$ −10.35 ± 0.02° in a 2-dm tube).

In an earlier run in benzene the product had been obtained in an 82.8% yield as a liquid: bp 148–151° (13 mm); $n^{25}D$ 1.5030; d^{25} 0.989; $[\alpha]^{27}D$ −81.02 ± 0.08° (homogeneous, 0.5-dm tube), $[\alpha]^{30}D$ −78.2 ± 0.2° (95% ethanol). Gas chromatography at 170° revealed only one component in this product.

Kinetic Studies. Synthetic Mixtures.—Eleven mixtures of (+)-3-methylcyclohexanone, malononitrile, and (−)-3-methylcyclohexylidenemalononitrile were made up in *ca.* 80% ethanol. These mixtures (total volume 50.0 ml) represented the potential product and reactant mixtures resulting when 0.020 mol of ketone and 0.020 mol of malononitrile were mixed along with 5 ml of water and diluted to 50.0 ml with 95% ethanol. The results of a 1962 study, cited in Table V, show a linear relationship between optical activity and concentration of reactants. The equation $A = (\alpha_D + 9.75)/26.5$ can be developed from these data for the calculation of the reacting substrates (ketone or nitrile) in moles per liter in kinetic runs. (With purer product later developed, the maximum values were $[\alpha]^{25}D$ +9.37° and $[\alpha]^{25}D$ −80.4°. In the equation for A, change 9.75 to 10.31 and 26.5 to 27.5.)

For other mixtures and temperatures, the synthetic mixtures calculated for the start and for the end at 100% conversion were prepared. From the rotatory values observed the appropriate equations were developed (60% perchloric acid (0.5 ml) was added to prevent the uncatalyzed reaction).

Kinetic Runs.—For rate studies aliquot portions of malononitrile (1.32 g, 0.200 mol) and (+)-3-methylcyclohexanone (2.24 g, 0.0200 mol) in 95% ethanol were mixed in a 50-ml volumetric flask. After short equilibration in the constant-temperature bath, the catalyst in 5 ml of water was added, the mixture was diluted to precise volume with 95% ethanol, and the mixture was transferred to a 2-dm, thermostated polarimeter tube. Timing was begun when the catalyst was added to the

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(26) L. Kahovec and K. W. F. Kohlrausch, *Monatsh. Chem.*, **68**, 371 (1936).

(27) E. J. Eisenbraun and S. M. McElvain, *J. Amer. Chem. Soc.*, **77**, 3383 (1955).

(28) Analysis by Weiler and Strauss, Oxford, England.

Table IV
Apparent Dissociation Constants for Some Amino Acids in Water[a]

Registry no.	Amino acid	pK_1	pK_2	pI
1118-68-9	*N,N*-Dimethylglycine	1.74[b]	10.00	5.87
5691-20-3 (36805-33-3)[e]	*cis*-Hexahydroanthranilic acid	3.31	10.73	7.02
5691-19-0 (38605-35-5)[e]	*trans*-Hexahydroanthranilic acid	3.25[c]	10.18[c]	6.72
3685-23-2	*cis*-*p*-Aminocyclohexanecarboxylic acid	4.24[d]	10.73[d]	7.49
3685-25-4	*trans*-*p*-Aminocyclohexanecarboxylic acid	4.13	10.59	7.37
38605-38-8	*cis*-*p*-*N,N*-Dimethylaminocyclohexanecarboxylic acid	4.34	10.58	7.46
38605-39-9	*trans*-*p*-*N,N*-Dimethylaminocyclohexanecarboxylic acid	4.18	10.37	7.28

[a] pK_1 and pK_2 determined at room temperature (22–30°) by titration with standard acid and base to determine the pH at the half-equivalence point with a Beckman Model 76 pH meter. Precision was ±0.02 units. [b] pK_1 reported to be 1.85 (ref 25). [c] pK_1 of 3.4 and pK_2 of 10.1 reported by J. P. Greenstein and J. Wyman, Jr., *J. Amer. Chem. Soc.*, 60, 2341 (1938). [d] pK_1 of 4.3 and pK_2 of 10.4 reported by Greenstein and Wyman. [e] Benzenesulfonamide.

Table V
Synthetic Mixtures of (+)-3-Methylcyclohexanone (A), Malononitrile (B), and (−)-3-Methylcyclohexylidenemalononitrile (C)

Moles of reactants[a]		Observed rotation[b] $\alpha^{28}D$,
A and B	C	deg
0.020	0.000	+0.85[c]
0.018	0.002	−0.24
0.016	0.004	−1.28
0.014	0.006	−2.36
0.012	0.008	−3.35
0.010	0.010	−4.46
0.008	0.012	−5.60
0.006	0.014	−6.63
0.004	0.016	−7.66
0.002	0.018	−8.76
0.000	0.020	−9.75[d]

[a] Moles of A, B, and C mixed with 5 ml of water, diluted up to 50 ml with 95% ethanol. [b] Readings ±0.01°, average of two. [c] The specific rotation of (+)-3-methylcyclohexanone in the presence of malononitrile, $[\alpha]^{28}D$ +9.4 ± 0.1°. [d] The specific rotation is $[\alpha]^{28}D$ −76.0 ± 0.5°.

mixture. Rotatory values were determined as quickly as possible and as often as seemed indicated by the rate of reaction.

Rotatory values were converted to concentration, A, from the equation developed above. The reciprocal of the concentration, $1/A$, was calculated and a plot of $1/A$ against time was used to calculate the second-order rate constant. Straight lines were usually observed up to at least 75% conversion. Results of five runs are collected in Table III and plotted in Figure 2.

Study of the rate of uncatalyzed reaction indicated a reaction rate $k_2 = 0.0007$ mol^{-1} min^{-1} at 25° and $K_2 = 0.0022$ mol^{-1} min^{-1} at 45°. The rate of reversal could be neglected in these reactions (1.6% reaction after 4 hr uncatalyzed at 45° and 6.7% reaction after 2 hr at 30° with 2.4×10^{-2} mol/l. of ε-aminocaproic acid.)

The effects of several parameters were tested when β-alanine was used as a catalyst. These results are recorded in Table I.

The influence of various amino acids, aminophenols, lithium fluoride, and buffer at pH 8 are assembled in Table II.

Apparent pH values in Table II are pH's observed in solutions containing the solvent system but omitting the reactants (Tables I and II). In Table I the malononitrile was added too.

Registry No.—Hexahydrophthalimide, 1444-94-6; anthranilic acid, 118-92-3; ethyl *cis*-4-dimethylaminocyclohexanecarboxylate, 38615-90-6; ethyl *trans*-4-dimethylaminocyclohexanecarboxylate, 38615-91-7; (+)-3-methylcyclohexanone, 13368-65-5; malononitrile, 109-77-3; (±)-3-methylcyclohexylidenemalononitrile, 38614-92-8; (−)-3-methylcyclohexylidenemalononitrile, 38615-93-9.

π-Complexed β-Arylalkyl Derivatives. IV. The Preparation and Solvolysis of 2-[π-(Phenyl)chromium tricarbonyl]ethyl and 2-[π-(Phenyl)chromium tricarbonyl]-1-propyl Methanesulfonates and Their Noncomplexed Analogs[1a]

ROBERT S. BLY,* RICHARD A. MATEER,[1b] KUEN-KWONG TSE, AND RICHARD L. VEAZEY

Department of Chemistry, University of South Carolina, Columbia, South Carolina 29208

Received September 13, 1972

The π-(arene)chromium tricarbonyl complexed methanesulfonates 2-phenylethyl (**2**-OMs), 2-phenylethyl-*1,1*-d_2 (**4**-OMs), and 2-phenyl-1-propyl (*dl*-**6**-OMs) have been prepared and their acetolysis and formolysis rates and/or products compared with those of the noncomplexed derivatives, 1-OMs, **3**-OMs, and *dl*-**5**-OMs, respectively. At ~90° in buffered acetic acid, **2**- is ten times as reactive as 1-OMs, *dl*-**6**- about six times as reactive as *dl*-**5**-OMs; in buffered formic acid 2- is 8.5 times more reactive than 1-OMs, *dl*-6- 2.4 times more reactive than *dl*-5-OMs. The formolysis of *dl*-6-OMs yields 17% [π-(phenyl)chromium tricarbonyl]-migrated product; the formolysis of 4- and the acetolysis of 4- and *dl*-6-OMs yield unrearranged products exclusively. By comparing Fk_Δ's of the complexes with those of the corresponding noncomplexed *p*-nitro derivatives, estimates of anchimeric assistance to product formation by β-[π-(phenyl)chromium tricarbonyl] have been deduced: **2**-OMs, 10^4 (HOAc), $10^{3.6}$ (HCOOH); *dl*-6-OMs, $10^{3.2}$ (HOAc), $10^{3.1}$ (HCOOH). Steric buttressing effects are considered to be relatively unimportant and electron donation by the π-complexed phenyl moiety is suggested as the probable cause of these effects.

In previous papers of this series[2] we reported the acetolytic rates and products of a series of chromium tricarbonyl complexed 3-phenyl-2-butyl, 2-phenyl-3-pentyl, and neophyl-type methanesulfonates. After making a correction for the apparent inductive effect of the tricarbonylchromium group, we concluded that the acetolytic reactivity of the complexes was enhanced by factors of from 6.8 to 1600 times at 75°. We were able to infer that a substantial portion of the enhancement is due to an electronic effect of the metal moiety, but were unable to evaluate the magnitude of the steric effect on these reactions.[2b]

One of the techniques that has been effectively used to detect and establish the importance of neighboring group participation in solvolytic reactions is that of varying the nucleophilicity and ionizing power of the solvent.[3-12] Thus it is generally accepted that both the importance of kinetic neighboring group participation and the extent of rearrangement increase as the solvent becomes less nucleophilic and/or more ionizing, *i.e.*, in the order ethanol < acetic acid < formic acid < trifluoroacetic acid < sulfuric acid < fluorosulfonic acid. The good linear free energy correlations that have been obtained for both the assisted and the unassisted processes[2b] strongly imply that the driving force for participation is predominantly electronic rather than steric in nature.

In an effort to confirm its importance and assess the nature of tricarbonylchromium participation during the solvolysis of β-[π-(aryl)chromium tricarbonyl]alkyl derivatives, we have examined the acetolysis and formolysis rates and/or products of 2-phenylethyl (**1**-OMs), 2-[π-(phenyl)chromium tricarbonyl]ethyl (**2**-OMs), 2-phenyl-*1,1*-d_2-ethyl (**3**-OMs), 2-[π-(phenyl)-chromium tricarbonyl]-*1,1*-d_2-ethyl (**4**-OMs), 2-phenyl-1-propyl (*dl*-**5**-OMs), 2-[π-(phenyl)chromium tricarbonyl]-1-propyl (*dl*-**6**-OMs), 2-(*p*-nitrophenyl)ethyl (**7**-OMs), and 2-(*p*-nitrophenyl)-1-propyl (*dl*-**8**-OMs) methanesulfonates.

Methods and Results

The known noncomplexed alcohols, **1**-, **3**-, *dl*-**5**-, **7**-, and *dl*-**8**-OH, obtained as described in the Experimental Section, were converted to methanesulfonates in the usual manner.[2a] The chromium tricarbonyl complexes, **2**-, **4**-, and *dl*-**6**-OMs were prepared as described previously[2a] (*cf.* Chart I).

Acetolysis products, determined by combination of the direct analysis, decomplexation, and reduction techniques described previously,[2a] are summarized in Chart II.

Formolysis products, determined in a similar manner (*cf.* Experimental Section), are summarized in Chart III. As noted previously,[2] chromium tricarbonyl complexation prior to solvolysis inhibits phenyl migration; only during the formolysis of *dl*-**6**-OMs is a significant amount of rearranged product formed.

Titrimetric acetolysis and formolysis constants for the complexed and noncomplexed methanesulfonates were determined as detailed previously[2] and in the Experimental Section at concentrations similar to those

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(4) (a) D. J. Cram, *J. Amer. Chem. Soc.*, **74**, 2129 (1952); (b) J. A. Thompson and D. J. Cram, *ibid.*, **91**, 1778 (1969).

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(6) (a) H. C. Brown, K. J. Morgan, and F. J. Chloupek, *J. Amer. Chem. Soc.*, **87**, 2137 (1965); (b) C. J. Kim and H. C. Brown, *ibid.*, **91**, 4289 (1969).

(7) (a) J. E. Nordlander and W. J. Deadman, *J. Amer. Chem. Soc.*, **90**, 1590 (1968); (b) J. E. Nordlander and W. J. Kelly, *ibid.*, **91**, 996 (1969).

(8) W. G. Dauben and J. L. Chitwood, *J. Amer. Chem. Soc.*, **90**, 6876 (1968).

(9) (a) C. J. Lancelot and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **91**, 4291 (1969); (b) *ibid.*, **91**, 4296 (1969); (c) C. J. Lancelot, J. J. Harper, and P. v. R. Schleyer, *ibid.*, **91**, 4294 (1969); (d) P. v. R. Schleyer and C. J. Lancelot, *ibid.*, **91**, 4297 (1969); (e) J. M. Harris, F. L. Schadt, P. v. R. Schleyer, and C. J. Lancelot, *ibid.*, **91**, 7508 (1969).

(10) (a) P. C. Myhre and K. S. Brown, *J. Amer. Chem. Soc.*, **91**, 5639 (1969); (b) P. C. Myhre and E. Evans, *ibid.*, **91**, 5641 (1969).

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(12) (a) J. L. Coke, F. E. McFarlane, M. C. Mourning, and M. G. Jones, *J. Amer. Chem. Soc.*, **91**, 1154 (1969); (b) M. G. Jones and J. L. Coke, *ibid.*, **91**, 4284 (1969).

Chart I

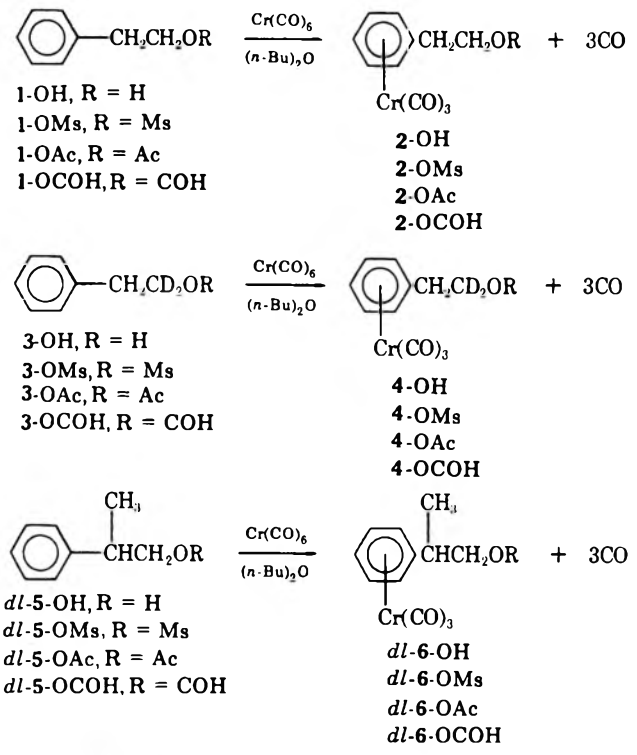
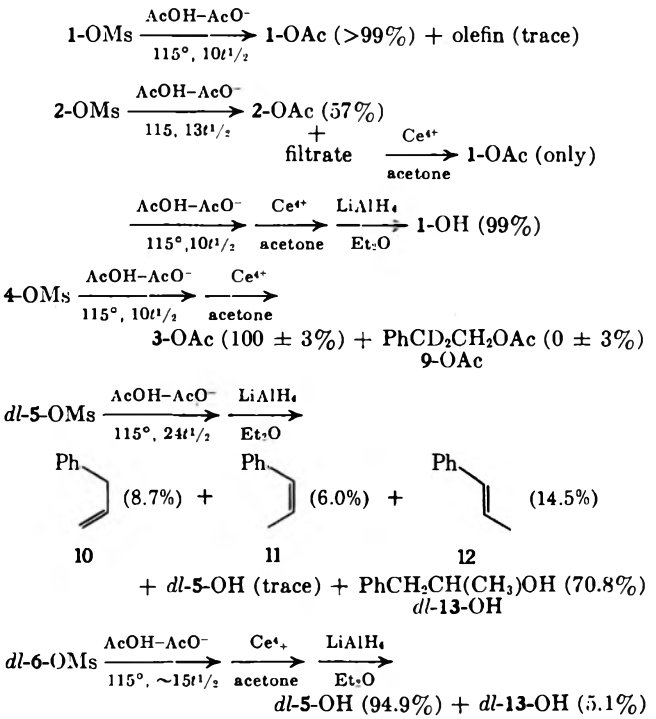


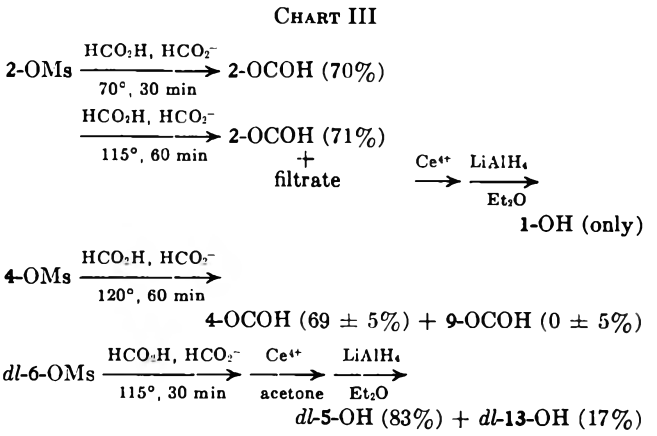
Chart II



used in the product studies. These data are summarized and compared with those of some related noncomplexed derivatives[3b,9e,13,14] in Table I. With the exception of

(13) (a) S. Winstein and R. Heck, *J. Amer. Chem. Soc.*, **78**, 4801 (1956); (b) J. W. Clayton and C. C. Lee, *Can. J. Chem.*, **39**, 1510 (1961); (c) *ibid.*, **39**, 1512 (1961).

Chart III



the acetolysis of *dl*-5-OMs, *cf.* runs 41 and 42, each of the solvolyses exhibited clean first-order kinetics through at least 75% reaction.

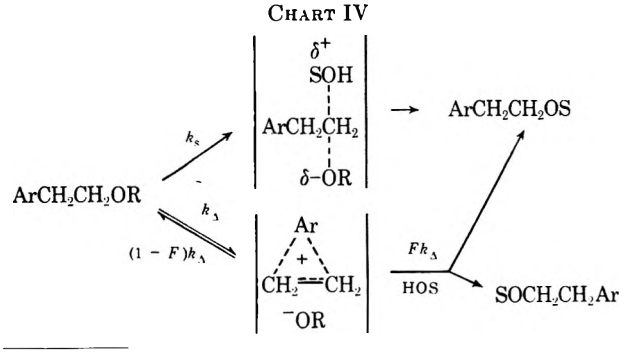
The effects of added salts on the acetolysis rates of 1-, 2-, 7-, and *dl*-8-OMs are recorded in Table II.[15]

Discussion

The fact that in both the β-arylethyl and the 2-arylpropyl series the ratios of the relative titrimetric rate constants for solvolysis of the complexed and noncomplexed methanesulfonates at 86.6° do not change markedly as the solvent is changed from acetic to formic acid, *viz.*, k_t(2-OMs)/k_t(1-OMs), 17.4/1.68 = 10.4 (HOAc), 1117/131.7 = 8.5 (HCOOH); k_t(6-OMs)/k_t(5-OMs), 47.6/7.81 ≈ 6.1 (HOAc), 2990/1270 ≈ 2.4 (HCOOH), implies at first glance that the enhanced reactivity of the former might more properly be attributed to steric than to electronic factors. However, this view is certainly oversimplified and probably incorrect, for it fails to consider the substantial electron-withdrawing inductive effect of the π-tricarbonylchromium and the extent to which the solvolyses are accompanied by nucleophilic solvent participation.

The solvolyses of noncomplexed β-arylalkyl derivatives in the absence of added base have been successfully interpreted in terms of the discrete, competing solvent- and aryl-assisted pathways represented in Chart IV,[3c-e,9e,12a,13,16] where F is the fraction of bridged ion pairs which is converted to product, Chart IV, so that $k_t = Fk_\Delta + k_s$. Thus, when comparing the relative abilities of differing aryl groups to enhance the rate of product formation through neighboring-

Chart IV



(14) S. Winstein and K. C. Schreiber, *J. Amer. Chem. Soc.*, **74**, 2171 (1952).

(15) A. H. Fainberg and S. Winstein, *J. Amer. Chem. Soc.*, **78**, 2763 (1956).

(16) (a) C. C. Lee and K. J. Noszkó, *Can. J. Chem.*, **44**, 2481 (1966); (b) *ibid.*, **44**, 2491 (1966).

TABLE I

APPARENT FIRST-ORDER SOLVOLYSIS CONSTANTS AND ACTIVATION PARAMETERS OF 2-ARYL-1-ETHYL AND -1-PROPYL DERIVATIVES[a]

Run	Compd	Solvent	Temp, °C[b]	$10^6 k_t$, sec^{-1}	ΔH^*, kcal/mol	ΔS^*, eu
1, 2	1-OMs	AcOH/AcO$^-$ [c]	85.0	1.405 ± 0.045	24.9[d]	−16.2[d]
3, 4			97.3	4.605 ± 0.015		
5, 6			115.1	23.0 ± 0.00		
7			115.2	11.9[e]		
8			115.3	19.0[f]		
9				27.4[g]		
			86.7	1.68[h]		
			90.0	2.31[h]		
	1-OTs[aa]			1.28	24.9	−17.3
10, 11	1-OMs	HCO_2H/HCO_2^- [i]	86.7	131.65 ± 0.05		
	1-OTs[j]		86.6	111		
12, 13	2-OMs	AcOH/AcO$^-$ [c]	85.0	14.5 ± 0.4	24.5[k]	−12.5[k]
14, 15			97.4	49.7 ± 0.5		
16			113.0	42.1[e]		
17				42.6[e,l]		
18, 19			115.0	227.5 ± 5.5		
20			115.2	64.9[e]		
21			115.3	227[m]		
			86.7	17.4[h]		
			90.0	24.0[h]		
			115.3	236[h]		
22–24		HCO_2H/HCO_2^- [i]	86.7	1117 ± 19		
25	4-OMs		86.7	902[n]		
26			86.8	889		
27, 28	7-OMs	AcOH/AcO$^-$ [c]	86.95	2.00 ± 0.00	22.4[o]	−22.9[o]
29, 30			113.1	18.0 ± 0.15		
31			113.15	26.3[p]		
32				32.1[q]		
33			113.2	12.9[r]		
34			113.4	6.2[s]		
			86.7	1.97[h]		
			90.0	2.64[h]		
	7-OTs[bb]			0.715	23.7	−22
35, 36	7-OMs	HCO_2H/HCO_2^- [i]	69.25	1.275 ± 0.025	21.3[g]	−23.6[g]
37, 38			86.2	6.015 ± 0.045		
39, 40			99.4	17.4 ± 0.1		
			86.7	6.16[h]		
41, 42	*dl*-5-OMs	AcOH/AcO$^-$ [c]	86.65	~7.81 ± 0.17[t]		
	dl-5-OBs[cc]		86.7[h]	35.0	25.5	−8.5
			90.0[h]	48.8		
43, 44	*dl*-5-OMs	HCO_2H/HCO_2^- [i]	86.4	1270 ± 20		
45, 46	*dl*-6-OMs	AcOH/AcO$^-$ [c]	69.3	7.165 ± 0.165	26.3[u]	−5.5[u]
47, 48			86.8	48.85 ± 0.85		
49, 50			112.45	609 ± 9		
			86.5	47.6[h]		
			90.0	68.5[h]		
51, 52		HCO_2H/HCO_2^- [i]	86.45	2990 ± 80		
53, 54	*dl*-8-OMs	AcOH/AcO$^-$ [c]	99.8	0.6115 ± 0.0115	25.6[v]	−18.8[v]
55–57			115.1	2.26 ± 0.18		
58				3.74[w]		
59				3.32[x]		
60				1.99[y]		
61				1.15[e]		
62, 63			130.0	8.875 ± 0.065		
			86.7	0.167[h]		
			90.0	0.233[h]		
64, 65		HCO_2H/HCO_2^- [i]	69.25	0.226 ± 0.000	26.6[z]	−11.6[z]
66, 67			86.2	1.51 ± 0.005		
68, 69			99.4	5.81 ± 0.06		
			86.7	1.58[h]		

[a] Contains 0.0185–0.0250 *M* ROMs unless otherwise specified. [b] Controlled to ±0.03°. [c] Contains 0.0461–0.0508 *M* sodium acetate unless otherwise specified. [d] Computed from runs 1–6. [e] Contains no sodium acetate. [f] Contains 0.0286 *M* sodium acetate. [g] Contains 0.0327 *M* lithium perchlorate. [h] Calculated from data at other temperatures. [i] Contains 0.0250–0.0350 *M* sodium formate unless otherwise specified. [j] Extrapolated from the data in ref 3b and 13c. [k] Calculated from runs 12–15, 18, and 19. [l] Contains 0.0203 *M* sodium methanesulfonate. [m] Contains 0.0286 *M* sodium acetate. [n] Contains 0.0141 *M* ROMs. [o] Calculated from runs 27–30. [p] Contains 0.0772 *M* sodium acetate. [q] Contains 0.0989 *M* sodium acetate. [r] Contains 0.0302 *M* sodium acetate. [s] Calculated from runs 35–40. [t] Since this reaction is accompanied by extensive internal return to the more reactive *dl*-13-OMs, this constant was approximated from the first 20% reaction (*cf.* ref 14). [u] Calculated from runs 45–50. [v] Calculated from runs 53–57, 62, and 63. [w] Contains 0.0950 *M* sodium acetate. [x] Contains 0.0752 *M* sodium acetate. [y] Contains 0.0326 *M* sodium acetate. [z] Calculated from runs 64–69. [aa] Reference 3b. [bb] Reference 9e. [cc] Reference 14.

Table II
Dependence of Apparent First-Order Acetolysis Constants of 2-Aryl-1-ethyl and 2-Aryl-1-propyl Type Sulfonates upon Added Salts

Compd	Temp, °C	$10^6 k_t°$,[a] sec^{-1}	Value of "b" for added NaOAc[b]
1-OMs	115.2	12.5	18[c,d]
1-OTs[i]	115	13.0	19
2-OMs	115.2	217	1.9[e,f]
7-OMs	113.2	4.35	64[g]
8-OMs	115.1	0.93	30[h]

[a] Extrapolated value at zero acetate concentration. [b] Calculated from the relation $k_t = k_t°(1 + b_1[\text{NaOAc}] + b_2[\text{salt 2}])$.[16] [c] Calculated from runs 5, 6, and 8; $(k_t°)_{\text{extrapolated}} = 1.05 (k_t°)_{\text{measured}}$. [d] $b(LiClO_4) \approx 11$ (*cf.* runs 5, 6, and 9). [e] Calculated from run 21 and an interpolated value at this temperature for 0.0401 *M* sodium acetate; $(k_t°)_{\text{extrapolated}} = 3.35 (k_t°)_{\text{measured}}$. [f] b(NaOMs) ≈ 0 (*cf.* runs 16 and 17). [g] Calculated from runs 29–33; $(k_t°)_{\text{extrapolated}} = 0.70 (k_t°)_{\text{measured}}$. [h] Calculated from runs 55–60; $(k_t°)_{\text{extrapolated}} = 0.81 (k_t°)_{\text{measured}}$. [i] Reference 3b.

group participation during solvolysis, it is apparent that Fk_Δ's rather than k_t's should be employed.[12,17]

In previous papers in this series we have taken the titrimetric rate constant of the *p*-nitro derivative as a model for that of the π-complexed derivative in the absence of participation.[2] This treatment appeared to yield reasonable estimates of π-complexed aryl participation, since in the systems considered, *viz.*, 3-aryl-2-butyl[2a,18] and neophyl,[2b,15] direct displacement by solvent is relatively unimportant. However, in the solvolyses of β-arylethyl and 2-arylpropyl derivatives direct solvent participation is frequently the dominant reaction.[3f,5a,12a,13a,14] Hence, estimates, not of titrimetric rate constants, k_t, but of the rate constants Fk_Δ, for product formation *via* the bridged ion pair are desired.[12a] These may be estimated from experimental data reported here and elsewhere as follows.

Acetolysis of β-[π-(Phenyl)chromium tricarbonyl]-ethyl Methanesulfonate (2-OMs).—Jones and Coke have demonstrated the existence of a good linear correlation between log k_t for the acetolysis of para-substituted neophyl tosylates at 75° and log k_Δ for the acetolysis of like-substituted β-arylethyl tosylates at the same temperature,[12b] *viz.*, $\log k_\Delta(\beta\text{-arylethyl}) = 1.02 \log k_t(\text{neophyl}) - 1.85$.[19a] Since, as Jones and Coke[12b] have determined from rate and product data and Schleyer, *et al.*, have derived from rate data alone, "*F* is nearly constant for all participating substrates,"[9e] a plot of log k_t(neophyl) *vs.* log k_Δ(β-arylethyl) should also be linear[19b] and have a slope of approximately unity.[19c] The plot shown in Figure 1, which is based on the acetolysis rates at 90° (Table III), confirms this expectation.

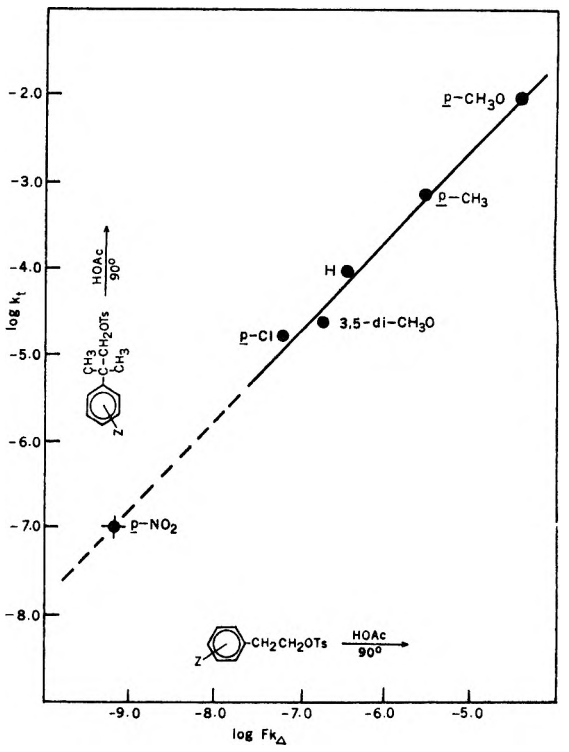


Figure 1.—Acetolysis of substituted β-arylethyl and neophyl tosylates at 90°, 0.00 *M* acetate ion.

Table III
Acetolysis Rates of Substituted β-Arylethyl and Neophyl Tosylates at 90°[a]

Substituent	β-Arylethyl Fk_Δ, sec^{-1}	Neophyl k_t, sec^{-1}
p-CH_3O	4.65×10^{-5} [b]	8.93×10^{-3} [c]
p-CH_3	3.19×10^{-6} [b]	7.25×10^{-4} [c]
H	3.75×10^{-7} [b]	9.57×10^{-5} [c]
3,5-di-CH_3O	2.15×10^{-7} [d]	2.36×10^{-5} [e]
p-Cl	6.99×10^{-8} [b]	1.87×10^{-5} [c]
p-NO_2		9.93×10^{-8} [f]

[a] At 0.00 *M* sodium acetate. [b] Reference 12b. [c] Extrapolated value from data in ref 12b. [d] Reference 16b. [e] Estimated as k_t(ROBs)/3.49, where k_t(ROBs) is calculated from the Yukawa-Tsuno relation, $\log k_t = -3.711[\sigma + 0.4828(\sigma^+ - \sigma)] - 3.478$, for the acetolysis of neophyl-type brosylates at 90° (*p*-CH_3O, *p*-CH_3, *m*-CH_3, H, *m*-CH_3O, *p*-Cl, *p*-Br, *p*-CO_2CH_3, *p*-CN, *p*-NO_2) assuming that σ(3,5-di-CH_3O) = 2σ(*m*-CH_3O) = 0.230 and σ^+(3,5-di-CH_3O) = $2\sigma^+$(*m*-CH_3O) = 0.094. [f] Estimated from k_t of the brosylate corrected for the extent of *p*-nitrophenyl migration assuming that the fraction of aryl-migrated products (0.75) is similar for the brosylate at 137° and the brosylate at 90° [20] and that k_t(ROTs) = k_t(ROBs)/3.49.

Extrapolation of the resulting double least squares regression line,[19d] $\log (Fk_\Delta°) = 0.998 \log (k_t°) - 2.327$ (which is linear over approximately three powers of ten), through the estimated k_t[19e] for *p*-nitroneophyl (another two powers of ten, Table III)[19f] yields an Fk_Δ of 4.85×10^{-10} sec^{-1} for the acetolysis of β-(*p*-nitrophenyl)ethyl *p*-toluenesulfonate (7-OTs) at 90°

(17) We emphasize that the *overall* effect of neighboring-group participation *on the rate of product formation* is given by Fk_Δ and is a composite of the effect of the neighboring group on *F*, the fraction of bridged ion pair going on to product, and on k_Δ, the rate of ionization; *cf.* ref 9d, footnote 14.

(18) (a) D. J. Cram, *J. Amer. Chem. Soc.*, **86**, 3767 (1964), and references cited therein; (b) S. Winstein and R. Baker, *ibid.*, **86**, 2071 (1964).

(19) (a) This empirical equation is a special case of the more general relation log (Fk_Δ)(neophyl) = log (Fk_Δ)(β-arylethyl) + *C*, and is valid apparently because nucleophilic solvent participation is relatively unimportant for all but the least reactive neophyl derivatives,[3f,9c,20] so that for this series $k_t = Fk_\Delta$, because the anchimeric assistance to ionization provided by the β-aryl group is proportional in the two series of compounds, *i.e.*, k_Δ(neophyl) ∝ k_Δ(β-arylethyl) (the proportionality constant is incorporated into the intercept, *C*) and because the fraction, *F*, of ion pairs going on to product in the neophyl case is constant—though not necessarily unity—over the range of substituents tested. (b) *Cf.* ref 9e, footnote 17. (c) The only significance that can properly be attributed to the unitary slope of an empirical log–log correlation such as this is that the proportionality relationships[19a] are maintained throughout the range of substituents tested. (d) All rate constants are corrected to zero acetate ion concentration. (e) Corrected for the extent of direct displacement so that the value of k_t used here and quoted in Table III is actually Fk_Δ; *cf.* ref 3f, footnote 13. (f) Note that the validity of this extrapolation is dependent not upon *F* for β-(*p*-nitrophenyl)ethyl remaining unchanged, but rather upon the ratio *F*[β-(*p*-nitrophenyl)ethyl]/*F*(*p*-nitroneophyl) remaining approximately constant.

(20) H. Tanida, T. Tsuji, H. Ishitobi, and T. Irie, *J. Org. Chem.*, **34**, 1086 (1969).

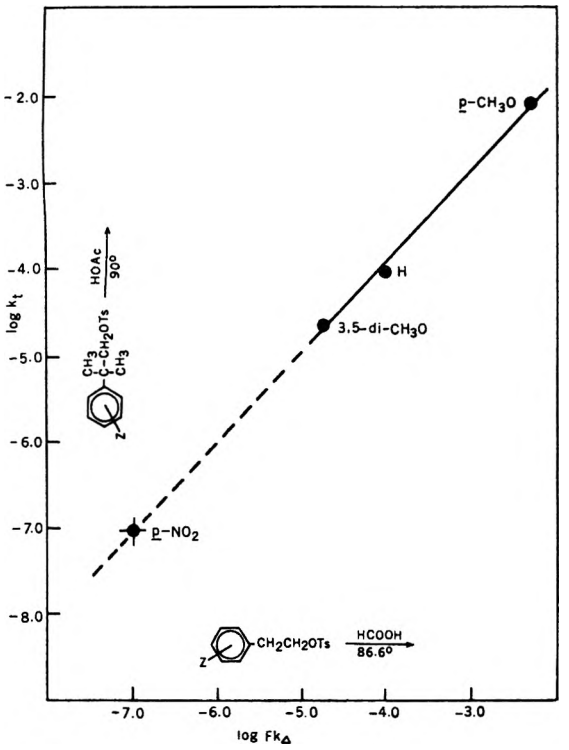


Figure 2.—Formolysis of substituted β-arylethyl tosylates at 86.6° *vs.* acetolysis of like-substituted neophyl tosylates at 90°, 0.00 *M* base.

in the absence of added sodium acetate. Since $k_s^\circ = k_t^\circ - Fk_\Delta^\circ = 7.15 \times 10^{-7} - 4.85 \times 10^{-10} = 7.15 \times 10^{-7}$ sec^{-1}, it is apparent that *p*-nitrophenyl participation is relatively unimportant under these conditions.[9e] Correction of our data (Table II) for the acetolysis of the corresponding mesylate (7-OMs) at 90° in the presence of added sodium acetate yields estimates of 8.9×10^{-7}, 8.9×10^{-7}, and 5.6×10^{-10} sec^{-1}, respectively, for k_t°, k_s°, and Fk_Δ° at zero acetate ion concentration.[21] A similar correction applied to the titrimetric acetolysis rate of β-[π-(phenyl)chromium tricarbonyl]ethyl methanesulfonate (2-OMs) (Table II) yields an estimated k_t° at 90°, zero acetate ion concentration, of 6.5×10^{-6} sec^{-1}.

The inductive effects of *p*-nitrophenyl and π-phenylchromium tricarbonyl are similar,[22] while the steric bulk of the latter is not less than that of the former; thus it follows that the solvent-assisted rate constant in the absence of base, k_s°, of 7-OMs constitutes an upper limit for k_s° (2-OMs) under comparable conditions, *i.e.*, k_s°(7-OMs) ≈ k_t°(7-OMs) ≈ 8.9×10^{-7} sec^{-1} ≥ k_s°(2-OMs). Therefore Fk_Δ° for the acetolysis of 2-OMs at 90° in the absence of added acetate must be equal to or greater than k_t°(2-OMs) − k_s°(7-OMs) ≥ $6.5 \times 10^{-6} - 8.9 \times 10^{-7} \geq 5.6 \times 10^{-6}$ sec^{-1}. Comparison of Fk_Δ°(2-OMs) and Fk_Δ°(7-OMs) provides an estimate of the relative ability of π-(phenyl)chromium tricarbonyl and *p*-nitrophenyl to enhance the rate of product formation during acetolysis at 90°; *i.e., the complexed aryl is* $5.6 \times 10^{-6}/5.6 \times 10^{-10}$ *or ~10,000 times more effective.*

The rate constant for product formation *via* the internally assisted acetolysis (Fk_Δ°) of β-phenylethyl methanesulfonate (1-OMs) at 90° and zero acetate ion concentration, estimated in a similar manner from that of the tosylate (1-OTs),[3b] is 4.4×10^{-7} sec^{-1}. Thus, the π-complexed phenyl, in spite of its large rate-retarding inductive effect, is $5.6 \times 10^{-6}/4.4 \times 10^{-7}$ or 13 times more effective than phenyl itself in promoting product formation under these conditions.

Formolysis of β-[π-(Phenyl)chromium tricarbonyl]-ethyl Methanesulfonate (2-OMs).—We are prevented by the lack of sufficient data in this solvent from utilizing an analogous method to estimate the rate enhancement which accompanies the formolysis of 2-OMs. Diaz and Winstein[3f] have, however, demonstrated the existence of a good linear correlation between log k_Δ° of *formolysis* for para-substituted 1-phenyl-2-propyl tosylates at 75° and log k_t of *acetolysis* for like-substituted neophyl tosylates under similar conditions. Thus it is reasonable to expect that a similar correlation would exist between log Fk_Δ° of formolysis for para-substituted β-phenylethyl tosylates at 86.6° and log k_t of acetolysis for like-substituted neophyl derivatives at 90°.[23] Such a plot, based on the data of Table IV, is shown in Figure 2. Extrapolation of the correlation line fitted to the data by a double least squares regression analysis, log (Fk_Δ°) = 0.944 log k_t − 0.323, through k_t for *p*-nitro (Table IV) yields an estimated Fk_Δ° of 1.2×10^{-7} sec^{-1} for the formolysis of 7-OTs at 86.6° in the absence of added base. The predicted Fk_Δ° for the corresponding mesylate (7-OMs) under these conditions would be $1.16 \times 1.2 \times 10^{-7}$ or 1.4×10^{-7} sec^{-1}. The titrimetric formolysis constant, k_t, of 7-OMs at 86.6° in the presence of 0.035 *M* sodium formate is 6.07×10^{-6} sec^{-1} (Table I). Although *b* values have not been determined in this solvent system, that of the anchimerically assisted process, Fk_Δ, can be expected to be relatively small so that $k_s \approx k_t - Fk_\Delta^\circ \approx 6.07 \times 10^{-6} - 1.4 \times 10^{-7} \approx 5.9 \times 10^{-6}$ sec^{-1} at 86.6° in the presence of 0.035 *M* formate ion. Thus under these conditions about 2% of the products are apparently formed *via* a *p*-nitrophenyl-bridged ion pair. The titrimetric formolysis constant, k_t, of 2-OMs under similar conditions is 1117×10^{-6} sec^{-1}, so that Fk_Δ for the complex equals $1117 \times 10^{-6} - k_s$(2-OMs) ≥ $1117 \times 10^{-6} - k_s$(7-OMs) ≈ $1117 \times 10^{-6} - 5.9 \times$

TABLE IV
SOLVOLYSIS RATES OF β-ARYLALKYL-TYPE TOSYLATES

Substituent	β-Arylethyl formolysis, 86.6°, Fk_Δ, sec^{-1}	Neophyl acetolysis, 90°, k_t, sec^{-1}
p-CH_3O	4.96×10^{-3} [a]	8.93×10^{-3} [b]
H	9.93×10^{-5} [c]	9.57×10^{-5} [b]
3,5-di-CH_3O	1.86×10^{-5} [d]	2.36×10^{-5} [e]
p-NO_2		9.93×10^{-8} [f]

[a] Extrapolated from data at other temperatures, 0.000–0.055 *M* sodium formate; *cf.* ref 3b and 3c. [b] Extrapolated from the data in ref 12b. [c] Calculated from k_t at other temperatures, 0.000–0.0291 *M* sodium formate, assuming $Fk_\Delta = k_t/0.91$, *cf.* ref 3b, 13a, and 16b, and $k_\Delta/(k_\Delta + k_s) = 0.90$, *cf.* ref 3c. [d] Estimated from data on the brosylate interpolated from other temperatures, *cf.* ref 13a and 16b, assuming k_t(OBs) = 2.50 k_t(OTs), *cf.* ref 13a, and that the fraction of products formed *via* the bridged ion in the case of the brosylate at 75°, *i.e.*, 52%, equals that from the tosylate at 86.6°, *cf.* ref 16b. [e] Table III, footnote *c*. [f] Table III, footnote *f*.

(21) In agreement with Schleyer, *et al.*,[9e] we note that the value of Fk_Δ for acetolysis of 7-OMs, though small, is not zero; *cf.* Table II, ref 9b.

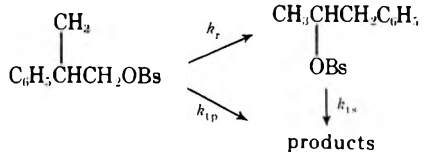
(22) B. Nicholls and M. C. Whiting, *J. Chem. Soc.*, 551 (1959).

(23) Note that because the solvents and temperatures are different, the slope of such a correlation line is no longer unity; *cf.* ref 3f, Figure 2.

$10^{-6} \geq 1111 \times 10^{-6}$ sec^{-1}. Hence π-tricarbonylchromium enhances the rate of product formation during formolysis by a factor of $1111 \times 10^{-6}/1.4 \times 10^{-7} = 7900$ times compared to *p*-nitro. Similarly (*cf.* Table IV), the complexed mesylate is enhanced by a factor of $(1111 \times 10^{-6})/(1.16 \times 9.93 \times 10^{-5}) = 9.6$ times with respect to the β-phenylethyl derivative (1-OMs).

Acetolysis of 2-[π-(Phenyl)chromium tricarbonyl]-1-propyl Methanesulfonate (*dl*-**6-OMs**).—Attempts to estimate the rate enhancement due to π complexation in this system are complicated by two factors: the occurrence of extensive internal return to the more reactive 1-phenyl-2-propyl isomer in the case of *dl*-**5**-OR[3b,f,14] and the lack of suitable kinetic data for substituted phenyl derivatives. The following approach seems best under the circumstances. Assuming that the acetolyses of both **7**- and *dl*-**8**-OTs at 90° occur predominantly *via* the solvent-assisted pathway, k_s,[9e,24] the ratio of their titrimetric rate constants, k_t, at this temperature (Table I) represents the steric effect of the β-methyl group upon the solvent-assisted reaction. Hence k_s(*dl*-**5**-OTs) $\approx [k_t(dl\text{-}\mathbf{8}\text{-OMs})/k_t(\mathbf{7}\text{-OMs})] \cdot k_s$(1-OTs)[25] $= [(2.33 \times 10^{-7})/(2.64 \times 10^{-6})](8.92 \times 10^{-7}) = 7.87 \times 10^{-8}$ sec^{-1}. Winstein, *et al.*, have carried out a detailed kinetic analysis of the acetolysis of *dl*-**5**-OBs within the kinetic framework shown in Chart V.[14]

CHART V



Since

$$\frac{-\text{d[2-aryl-1-propyl]}}{dt} = (k_r + k_{tp})\text{[2-aryl-1-propyl]}$$

while

$$\frac{-\text{d[neophyl]}}{dt} = k_t\text{[neophyl]} = (Fk_\Delta + k_s)\text{[neophyl]}$$

it seems appropriate to equate $(k_r + k_{tp})$ for 2-aryl-1-propyl derivatives with k_t for systems whose solvolysis is not accompanied by extensive internal return to a more reactive isomer, *i.e.*, $k_r + k_{tp} = k_t = Fk_\Delta + k_s$. Thus, at 90° Fk_Δ(*dl*-**5**-OTs) $= k_t$(*dl*-**5**-OTs) $= (k_r + k_{tp})$(*dl*-**5**-OTs) $- k_s$(*dl*-**5**-OTs) $= 1.67 \times 10^{-5}$ [26] $- 7.87 \times 10^{-8} \approx 1.67 \times 10^{-5}$ sec^{-1}.

For the aryl-assisted acetolysis of *dl*-**8**-OTs, Fk_Δ at 90° can be approximated as follows. Both β-arylethyl and 2-aryl-2-methyl-1-propyl (neophyl) tosylates give correlation lines of unit slope (*cf.* Figure 1) when values of log Fk_Δ for acetolysis at 90° are plotted against values of log k_t for like-substituted 2-aryl-2-methyl-1-propyl tosylates under similar conditions.[19c] It follows that the structurally intermediate 2-aryl-1-propyl tosylates should also be related to like-substituted 2-aryl-2-methyl-1-propyl tosylates in a similar manner, *i.e.*, that log Fk_Δ(2-aryl-1-propyl tosylate, HOAc, 90°) = 1.0 log k_t(2-aryl-2-methyl-1-propyl tosylate, HOAc, 90°) + C. This being true, the constant C can be computed from the value of Fk_Δ(*dl*-**5**-OTs) estimated previously and the measured k_t of neophyl tosylate (Table III), *viz.*, for acetolysis at 90° log $(1.67 \times 10^{-5}) = 1.0$ log $(9.57 \times 10^{-5}) + C$, or $C = -0.7582$, so that the equation for the expected correlation becomes log Fk_Δ(2-aryl-1-propyl tosylate, HOAc, 90°) = log k_t(2-aryl-2-methyl-1-propyl tosylate, HOAc, 90°) − 0.7582.

Using this equation and the estimated acetolysis constant, k_t, for *p*-nitroneophyl tosylate at 90° (Table III), a value for Fk_Δ(*dl*-**8**-OTs) under these conditions can be predicted, *viz.*, log Fk_Δ(*dl*-**8**-OTs) = log $(9.93 \times 10^{-8}) - 0.7582$ or Fk_Δ (*dl*-**8**-OTs, HOAc, 90°) $= 1.7 \times 10^{-8}$ sec^{-1}.

Schleyer[9e] has demonstrated that the solvent-assisted rate constant, k_s, for the acetolysis of a β-arylethyl tosylate at 90° can be computed from the Hammett relation log $k_s = -0.115\sigma +$ log k_s^H. It follows from this and our previous arguments that under similar conditions, *e.g.*, for acetolysis at 90°, k_s(*dl*-**5**-OTs) > k_s(*dl*-**8**-OTs) ≥ k_s(*dl*-**6**-OTs), so that Fk_Δ(*dl*-**6**-OTs) ≥ k_t(*dl*-**6**-OTs) − k_s(*dl*-**5**-OTs) or Fk_Δ(*dl*-**6**-OTs) ≥ $(6.85 \times 10^{-5}/1.26)$[27] $- 7.87 \times 10^{-8} \geq 5.4 \times 10^{-5}$ sec^{-1}. Thus, π-phenylchromium tricarbonyl is $5.4 \times 10^{-5}/1.7 \times 10^{-8}$ or 3200 times more effective than *p*-nitrophenyl in promoting product formation during the acetolysis of 2-aryl-1-propyl derivatives at 90°. It is $5.4 \times 10^{-5}/1.67 \times 10^{-5}$ or 3.2 times more effective than phenyl itself.

Formolysis of 2-[π-(Phenyl)chromium tricarbonyl]-1-propyl Methanesulfonate (*dl*-**6-OMs**).—Since there are essentially no kinetic data available for the formolysis of either 2-aryl-2-methyl-1-propyl or 2-aryl-1-propyl derivatives other than those reported here in the latter case, and since the assumption that the *p*-nitro derivatives solvolyze preponderantly *via* the solvent-assisted path may not be valid in formic acid, it seems best to estimate the effect of π complexation by direct comparison of the titrimetric rate constants at 86.6° (Table I). Thus, Fk_Δ(*dl*-**6**-OMs)/Fk_Δ(*dl*-**8**-OMs) ≈ k_t(*dl*-**6**-OMs)/k_t(*dl*-**8**-OMs) $= 3000 \times 10^{-6}/1.6 \times 10^{-6}$ or 1900 times; Fk_Δ(*dl*-**6**-OMs)/Fk_Δ(*dl*-**5**-OMs) ≈ k_t(*dl*-**6**-OMs)/k_t(*dl*-**5**-OMs) $= 3000 \times 10^{-6}/1270 \times 10^{-6}$ or 2.4 times.

The rate enhancements of solvolytic product formation induced by the prior chromium tricarbonyl complexation of primary β-arylethyl derivatives, estimated as the ratios of Fk_Δ(π complex)/Fk_Δ(*p*-nitro), are summarized in Table V.

In considering the possible implications of these data several questions come to mind. First and foremost: could these enhancements be due predominantly to steric effects? We think not. Chromium tricarbonyl complexation increases the absolute acetolytic reactivity at 85–90° by 10 times in the β-phenylethyl case, 6.1 times in the 2-phenyl-1-propyl derivative, and 1.6 times in the neophyl methanesulfonate. Thus the absolute rate enhancement is greatest in the least sterically congested β-phenylalkyl derivative and least in the most congested system. This is in spite of the fact that π complexation must certainly inhibit the

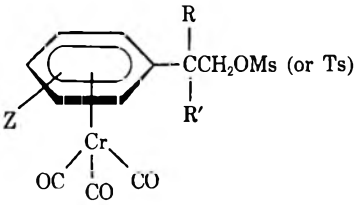
(24) *Cf.* acetate "*b*" values for the corresponding mesylates, Table II.

(25) Calculated from the data in ref 12b.

(26) Calculated by extrapolating the data in ref 14 (*cf.* Table I) and assuming that the measured acetolysis rate ratio, $(k_r + k_{tp})$(*dl*-**5**-OBs)/$(k_r + k_{tp})$(*dl*-**5**-OTs) = 2.92 at 75°,[3f] is maintained at 90°.

(27) Assuming that k_t(*dl*-**6**-OMs) = 1.26 k_t(*dl*-**6**-OTs); *cf.* Table I.

TABLE V
ESTIMATED SOLVOLYTIC RATE ENHANCEMENT DUE TO CHROMIUM TRICARBONYL COMPLEXATION



Z	R	R'	Solvent	Temp, °C	Enhancement[a]
H	H	H	HOAc	90	10,000[b]
			HCOOH	86.6	7,900[b]
H	CH_3	H	HOAc	90	3,200[b]
			HCOOH	86.6	1,900[b]
H	CH_3	CH_3	HOAc	75	1,600[c]
m-CH_3					800[c]
p-CH_3					400[c]
p-CH_3O					80[c]

[a] After correction for the rate-retarding inductive effect of the tricarbonylchromium; *vide supra*. [b] This work. [c] Reference 2b.

solvent-assisted process, k_s, to a greater extent in the less crowded β-phenylethyl methanesulfonate. Since the change in reactivity upon complexation is exactly opposite from that which would have been anticipated had steric butressing effects been dominant, we conclude that the rate factors which we have estimated in Table V are consonant with the idea of a relatively unimportant steric effect due to π complexation[28] coupled with some sort of electron-donating effect by the β-[π-(aryl)chromium tricarbonyl] group. We cannot on the basis of our data distinguish between the alternate possibilities of σ–π type homoconjugation or the direct chromium bridging suggested previously[2] as the manner in which this electronic effect is transmitted. We see no paradox in the fact that the estimated anchimeric effects of the π-(phenyl)chromium tricarbonyl during solvolysis are manifest in the absence of rearrangement, for in this sense the two primary π-complexed derivatives reported here resemble the secondary 1-aryl-2-propyl arenesulfonates studied by Winstein[3f] and by Schleyer.[9a-d] In each case the rate-limiting step of the reaction appears to be the formation of a nonsymmetric bridged cation–anion pair which reacts with the solvent to yield unrearranged products predominantly or exclusively.

A second question which these data raise concerns the relative extent of apparent participation by π-(phenyl)chromium tricarbonyl in acetic and in formic acid: it is slightly greater in the former than in the latter (Table V). Why? Our estimates of the magnitude of neighboring-group participation have involved numerous assumptions, some of which may at best be unwarranted and at worst be incorrect. Paramount among these is the idea that the inductive effect of π-(phenyl)chromium tricarbonyl may be approximated by that of *p*-nitrophenyl. This suggestion is not original with us but stems from the observation that [π-(phenyl)chromium tricarbonyl]acetic and *p*-nitrophenylacetic acids have experimentally identical ionization constants in 50% ethanol at 25°.[22] However, the geometries of these two aryl groups are obviously quite different and the individual bond moments in each must clearly be oriented in different directions with respect to the remainder of the molecule. Hence, it is the time-averaged net moment of all possible conformations which must be similar in 50% ethanol. The relative population of the various conformers of a polar molecule is known to be solvent dependent,[29] so that the *p*-nitrophenyl may not be a good model for the conformationally averaged net inductive effect of the π-complexed phenyl in other solvents, especially when their dipole moments differ as much as those of acetic (D = 6) and formic acids (D = 58). While we recognize the possible pitfalls of the assumption, in the absence of something better we see no recourse but to continue to use it.

Another possibility may be that the ability of the tricarbonylchromium to act as a source of electrons is diminished by protonation in the more acidic formic acid (pK_a = 3.75). Both Wilkinson, *et al.*,[30] and Sahatjian[31] have demonstrated by nmr that π-arenechromium tricarbonyl complexes are extensively protonated on chromium in trifluoroacetic acid. Clearly to the extent that such protonation occurs during solvolysis, the effective concentration of the more reactive unprotonated starting material will be reduced. Although we have been unable to detect any high-field resonance in the 60-MHz nmr spectrum of a solution of 2-OAc in unbuffered formic acid, we cannot completely discount metal protonation as a possible source of the reduced participation observed in this solvent.

While it is possible that the slightly reduced apparent participation by π-phenylchromium tricarbonyl in formolysis relative to acetolysis may be an artifact of our interpretation, other β-arylalkyl groups *do* exhibit the same phenomena in systems such as β-arylethyl and neophyl, where the leaving group is attached to a primary carbon. As the data in Table VI illustrate, the increase in solvolysis rate which accompanies a solvent change from acetic to formic acid is always greater under comparable conditions for the unsubstituted phenyl derivative than for the comparable *p*-methoxy compound. In other words, in highly solvated primary systems[32] the effectiveness of *p*-anisyl as a neighboring group is decreased relative to phenyl when the solvent itself can provide more electrophilic stabilization. As a similar reactivity pattern prevails for π-phenylchromium tricarbonyl relative to phenyl, it is perhaps not surprising that in the primary sulfonate esters examined here the apparent additional anchimeric effect re-

(28) This conclusion is corroborated by the finding, reported elsewhere [R. S. Bly and R. C. Strickland, *J. Amer. Chem. Soc.*, **92**, 7459 (1970)], that under kinetically controlled conditions the acetolysis of both *exo*-2-[π-*exo*- and -*endo*-(benzonorbornenyl)chromium tricarbonyl] methanesulfonates yields the less stable, more hindered *exo*-[π-*endo*-(benzonorbornenyl)-chromium tricarbonyl] acetate preferentially.

(29) *Cf.* E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Wiley, New York, N. Y., 1965, pp 159–160, and references cited therein.

(30) A. Davison, W. McFarlane, L. Pratt, and G. Wilkinson, *J. Chem. Soc.* 3653 (1962).

(31) R. A. Sahatjian Ph.D. dissertation, University of Massachusetts, 1969.

(32) Primary cations are far too unstable to exist in solution;[9d] *cf.* S. Winstein, E. Grunwald, and H. W. Jones, *J. Amer. Chem. Soc.*, **73**, 2700 (1951); M. Saunders and E. L. Hagen, *ibid.*, **90**, 6881 (1968). In fact it has been suggested that in such primary systems the rate-limiting step may actually be the dissociation of a tight ion pair;[2a] *cf.* R. A. Sneen and J. W. Larson, *ibid.*, **91**, 6031 (1969); V. J. Shiner, Jr., and W. Dowd, *ibid.*, **91**, 6528 (1969); J. M. Scott, *Can. J. Chem.*, **48**, 3807 (1970).

Table VI
Effect of Solvent on the Extent of Aryl Participation in Primary β-Arylalkyl Sulfonate Esters

Compd	Temp, °C	Fk_Δ, sec^{-1} HCOOH	Fk_Δ, sec^{-1} HOAc	HCOOH/HOAc
β-Phenylethyl tosylate (1-OTs)	74	2.64×10^{-5} [a]	6.88×10^{-8} [b]	384
β-*p*-Anisylethyl tosylate	74	1.61×10^{-3} [c]	8.78×10^{-6} [b]	183
β-Phenylethyl methanesulfonate (1-OMs)	90	9.93×10^{-5} [d]	4.4×10^{-7} [d]	~225
π-β-Phenylethyl methanesulfonate (2-OMs)	90	1.11×10^{-3} [d]	5.6×10^{-6} [d]	~198
2-Phenyl-1-propyl methanesulfonate (*dl*-5-OMs)	90	1.27×10^{-3} [d]	1.67×10^{-5} [d]	76
π-2-Phenyl-1-propyl methanesulfonate (*dl*-6-OMs)	90	3.00×10^{-3} [d]	5.4×10^{-5} [d]	56
2-Phenyl-2-methyl-1-propyl tosylate	25	1.16×10^{-5} [e]	3.11×10^{-8} [f]	374
2-*p*-Anisyl-2-methyl-1-propyl tosylate	25	8.31×10^{-4} [g]	6.00×10^{-6} [f]	139

[a] Reference 13c. [b] Calculated from the data in ref 12b. [c] Interpolated from the data of ref 3b and W. H. Saunders, Jr., and R. Glaser, *J. Amer. Chem. Soc.*, **82**, 3586 (1960), assuming $Fk_\Delta \approx k_t$ in this solvent. [d] This work. [e] Data of A. H. Fainberg quoted by R. Heck, J. Corse, E. Grunwald, and S. Winstein, *J. Amer. Chem. Soc.*, **79**, 3278 (1957), assuming $Fk_\Delta \approx k_t$. [f] Extrapolated from the data in ref 12b assuming $Fk_\Delta \approx k_t$. [g] S. Winstein and R. Heck, *J. Amer. Chem. Soc.*, **78**, 4801 (1956).

sulting from π complexation prior to solvolysis is less in formic than in acetic acid.[33]

Experimental Section[34]

Preparation of the Methanesulfonates (1-, 3-, *dl*-5-, 7-, and *dl*-8-OMs).—The methanesulfonates were prepared by the reaction of methanesulfonyl chloride in pyridine with the corresponding alcohols 1-OH,[35] 3-OH,[36] *dl*-5-OH,[14,37] 7-OH,[38] and *dl*-8-OH[39] as described previously.[2a] Melting points and yields are listed in Table VII.

Table VII
Melting Points and Yields of the 2-Arylethyl and 2-Arylpropyl Methanesulfonates

Compd	Mp, °C	Yield, %
1-OMs	Liquid at room temperature	61
3-OMs	Liquid at room temperature	56
dl-5-OMs	Liquid at room temperature	60
7-OMs	80–81	41
dl-8-OMs	85–86	27

2-Phenylethyl Methanesulfonate (1-OMs).—Ir analysis showed ($CHCl_3$) 3070, 3060, 3020 (CH phenyl); 2960, 2930 (CH aliphatic); 1610, 1590 (aromatic nucleus); 1350, 1165 (OSO_2); and 699 cm^{-1} (monosubstituted phenyl); nmr ($CDCl_3$) δ 7.25, singlet (C_6H_5); 4.36, triplet, J = 7.0 Hz ($-CH_2CH_2O$); 3.01, triplet, J = 7.0 Hz ($C_6H_5CH_2CH_2-$); and 2.78, singlet ($-OSO_2CH_3$).

Anal. Calcd for $C_9H_{12}O_3S$: C, 53.97; H, 6.04; O, 23.97; S, 16.01. Found: C, 54.08; H, 6.20; O, 23.91; S, 15.86.

2-Phenylethyl-*1,1-d*$_2$ Methanesulfonate (3-OMs).—Ir analysis showed ($CHCl_3$) 3030 (CH phenyl); 2940 (CH aliphatic); 2250, 2170 (CD aliphatic); 1610, 1590 (aromatic nucleus); 1370, 1178 (OSO_2); 700 cm^{-1} (monosubstituted phenyl); nmr ($CDCl_3$) δ 7.19, singlet (C_6H_5); 2.95, singlet ($C_6H_5CH_2-$); 2.75, singlet (OSO_2CH_3).

2-Phenyl-1-propyl Methanesulfonate (*dl*-5-OMs).—Ir analysis showed (CCl_4) 3080, 3060, 3025 (CH phenyl); 2960, 2935, 2895, 2875 (CH aliphatic); 1610, 1590 (aromatic nucleus); 1355, 1175 (OSO_2); 700 cm^{-1} (monosubstituted phenyl); nmr (CCl_4) δ 7.12, singlet (C_6H_5-); 4.10, doublet, J = 7.0 Hz ($>CHCH_2O-$); 3.08, multiplet [$C_6H_5CH(CH_3)CH_2-$]; 2.65, singlet (OSO_2CH_3); 1.29, doublet, J = 7.0 Hz ($>CHCH_3$).

Anal. Calcd for $C_{10}H_{14}O_3S$: C, 56.05; H, 6.59; O, 22.40; S, 14.96. Found: C, 55.91; H, 6.75; S, 15.14.

2-(*p*-Nitrophenyl)ethyl Methanesulfonate (7-OMs).—Ir analysis showed ($CHCl_3$) 3040 (CH aromatic); 2980, 2920, 2880, 2820 (CH aliphatic); 1530, 1370, 1350 (CNO_2, OSO_2), 1170 (OSO_2); 850 cm^{-1} (disubstituted phenyl); nmr ($CDCl_3$) δ 8.28, 8.13, 7.54, 7.39, AB quartet, J = 8 Hz ($-C_6H_2^AH_2^B-$); 4.54, triplet, J = 6.5 Hz ($-CH_2CH_2O-$); 3.25 ,triplet, J = 6.5 Hz ($-C_6H_4CH_2CH_2-$); 3.04, singlet ($-OSO_2CH_3$).

Anal. Calcd for $C_9H_{11}NO_5S$: C, 44.07; H, 4.52; N, 5.71; O, 32.62; S, 13.07. Found: C, 44.06; H, 4.62; N, 5.59; S, 13.13.

2-(*p*-Nitrophenyl)-1-propyl Methanesulfonate (*dl*-8-OMs).—Ir analysis showed ($CHCl_3$) 3060, 3020 (CH phenyl); 2970, 2930 (CH aliphatic); 1350, 1170 (OSO_2); 855 cm^{-1} (phenyl); nmr (acetone-d_6) δ 8.16, 8.01, 7.57, 7.42, AB quartet, J = 8 Hz ($-C_6H_2^AH_2^B-$); 4.34, doublet, J = 6.5 Hz ($>CHCH_2O-$); 3.35, multiplet ($-CHCH_3CH_2-$); 2.98, singlet ($-OSO_2CH_3$); 1.35, doublet, J = 6.5 Hz ($>CHCH_3$).

Anal. Calcd for $C_{10}H_{13}NO_5S$: C, 46.32; H, 5.05; N, 5.40; O, 30.86; S, 12.37. Found: C, 46.32; H, 5.15; N, 5.27; O, 30.91; S, 12.36.

Preparation of the π-Complexed Methanesulfonates (2-, 4-, and *dl*-6-OMs).—The methanesulfonates 2-, 4-, and *dl*-6-OMs were prepared by the reaction of chromium hexacarbonyl with the corresponding noncomplexed methanesulfonates, 1-OMs, 3-OMs, and *dl*-5-OMs, respectively, as described previously.[2a] The yields and melting points are summarized in Table VIII.

Table VIII
Melting Points and Yields of the π-Complexed 2-Phenylethyl and 2-Phenyl-1-propyl Methanesulfonates

Compd	Mp, °C	Yield, %
2-OMs	70–71	97
4-OMs	70–71	54[a]
dl-6-OMs	49.5–50.5	68

[a] The low yield is probably due to the reduced scale of this preparation.

2-[π-(Phenyl)chromium tricarbonyl]ethyl Methanesulfonate (2-OMs).—Ir analysis showed ($CHCl_3$) 3030 (CH phenyl); 2970, 2940 (CH aliphatic); 1980, 1910 (C≡O); 1380, 1170 (OSO_2); 660, 633, 530 cm^{-1} (CrC);[40] nmr ($CDCl_3$) δ 5.35, doublet (π-C_6H_5-); 4.43, triplet, J = 6.5 Hz ($-CH_2CH_2O-$); 3.03, singlet

(33) It is interesting to note that in the 1-aryl-2-propyl tosylate series, where the incipient cations are secondary and thus intrinsically more stable and less highly solvated in the transition state, these effects are reversed, *viz.*, the better neighboring group *p*-anisyl provides relatively more additional internal nucleophilic assistance than phenyl when the solvent is changed from acetic to formic acid.[9c]

(34) Melting points are uncorrected. Microanalyses were performed by Bernhardt Mikroanalitisches Laboratorium, 5251 Elbach über Engelskirchen, West Germany. Spectra were determined on a Perkin-Elmer grating infrared spectrometer, Model 337, a Model 202 ultraviolet spectrometer, and a Varian A-60A nmr spectrometer. Gas chromatographic analyses were performed on a F & M Model 500 chromatograph equipped with a 16 ft × 0.5 in. column packed with 20% Carbowax 20M on 60–80 mesh Gas-Chrom CL. Helium was used as carrier gas at flow rates of 80–100 ml/min. The potentiometric titrations were performed on a Radiometer Auto-Burette using glass and standard calomel electrodes.

(35) Eastman Organic Chemicals, List No. 45, compound 313.

(36) (a) W. H. Saunders, Jr., S. Asperger, and D. H. Edison, *J. Amer. Chem. Soc.*, **80**, 2421 (1958); (b) G. S. Hammond and K. R. Kopecky, *J. Polym. Sci.*, **60**, 54–59 (1962).

(37) K and K Laboratories Inc., Catalog No. 7, compound 7594.

(38) R. Fuchs and C. A. Vanderverf, *J. Amer. Chem. Soc.*, **76**, 1631 (1954).

(39) F. Nerdel and H. Winter, *J. Prakt. Chem.*, **12**, 110 (1960).

(40) (a) R. D. Fischer, *Chem. Ber.*, **93**, 165 (1960); (b) R. E. Humpherey, *Spectrochim. Acta*, **17**, 93 (1961); (c) G. Klopman and K. Noack, *Inorg. Chem.*, **7**, 579 (1968).

($-OSO_2CH_3$); 2.85, triplet, $J \cong 6.5$ Hz ($C_6H_5CH_2CH_2-$); uv (C_2H_5OH) 218 mμ (ε 22,000), 254 (6000), 317 (7900).[41]

Anal. Calcd for $C_{12}H_{12}O_6SCr$: C, 42.86; H, 3.60; O, 28.55; S, 9.54; Cr, 15.46. Found: C, 42.81; H, 3.67; O, 28.12; S, 9.32.

2-[π-(Phenyl)chromium tricarbonyl]ethyl-1,1-d_2 Methanesulfonate (4-OMs).—Ir analysis showed ($CHCl_3$) 3080, 3020 (CH phenyl); 2930 (CH aliphatic); 2250, 2170 (CD aliphatic); 1970, 1880 (C≡O); 1340, 1170 (OSO_2); 655, 629 cm^{-1} (CrC).

Anal. Calcd for $C_{12}H_{10}D_2O_6SCr$: C, 42.61; H, 2.98; D, 1.18; O, 28.38; S, 9.48; Cr, 15.37. Found: C, 42.75; O, 28.30; S, 9.37.

2-[π-(Phenyl)chromium tricarbonyl]-1-propyl Methanesulfonate (*dl*-6-OMs).—Ir analysis showed (CCl_4) 3030, w (CH phenyl); 2980, w (CH aliphatic); 1980, 1920 (C≡O); 1390, 1178 (OSO_2); 660, 630 cm^{-1} (CrC); nmr ($CDCl_3$) δ 5.08, singlet (π-C_6H_5–); 3.99, doublet, $J = 6$ Hz (>$CHCH_2O$–); 2.74, singlet ($-OSO_2CH_3$) superimposed on a multiplet at ~2.7 ($C_6H_5CHCH_3CH_2$–); 1.10, doublet, $J = 7.5$ Hz (>$CHCH_3$).

Anal. Calcd for $C_{13}H_{14}O_6SCr$: C, 44.57; H, 4.03; O, 27.40; S, 9.15; Cr, 14.84. Found: C, 44.68; H, 4.11; O, 27.24; S, 9.36.

Acetolysis rates were measured titrimetrically in sodium acetate buffered, deoxygenated anhydrous acetic acid[42] as described previously.[2a] The rate constants and activation parameters are recorded in Table I.

Formolysis Rates.—Anhydrous formic acid was obtained by purification of the commercial solvent (Baker and Adams CP, 98–100%) according to the procedure of Winstein.[3a] Sodium formate was dried at 120° overnight and added to the purified solvent to obtain a ~0.03 *M* solution. The buffered solution was deoxygenated as described previously for the acetic acid solvent.[2a]

The rates were measured using the ampoule technique. Enough of the methanesulfonate was dissolved in 25 ml of the buffered formic acid to obtain an ~0.02 *M* solution. Eight 3-ml samples were placed into ampoules, cooled in Dry Ice–acetone, flushed with dry nitrogen, sealed, and placed in a thermostated bath. At appropriate intervals ampoules were removed from the bath, cooled, and opened, and 2-ml aliquots were withdrawn. The measured volume was diluted with 20 ml of anhydrous acetic acid and titrated potentiometrically[34] with a standard solution of ~0.033 *M* perchloric acid in acetic acid.

Acetolysis Products of 2-Phenylethyl Methanesulfonate (1-OMs). Run A.—A 10-ml sample of a 0.02 *M* solution of 1-OMs in anhydrous acetic acid[42] buffered with 0.046 *M* sodium acetate was allowed to react at 115° for 84 hr (10 half-lives). The solution was cooled, poured over cracked ice, and extracted with three 25-ml portions of pentane. The combined extract was washed with saturated sodium bicarbonate, then washed with water and dried over anhydrous sodium sulfate. The solution was filtered and concentrated to ~2 ml by slow distillation of the pentane through a 12-in. wire spiral packed vacuum-jacketed column. Analysis by glpc at 140° showed the presence of two components whose relative retention times and (peak areas) were 4.1 (<0.1%) and 29.4 (>99.9%). No attempt was made to identify the first component. The second component was identical with the known and commercially available 2-phenylethyl acetate (1-OAc).[43]

Acetolysis Products of 2-[π-(Phenyl)chromium tricarbonyl]-ethyl Methanesulfonate (2-OMs). Run B.—A solution of 33 mg (0.099 mmol) of the methanesulfonate in 5 ml of deoxygenated acetic acid[2a] buffered with 0.046 *M* sodium acetate was heated at 115° for 8.4 hr (10 half-lives). The solution was cooled, poured over cracked ice, and extracted with three 50-ml portions of a 1:1 pentane–ether mixture. The extract was washed successively with cold saturated sodium bicarbonate and cold water. To the washed extract was added dropwise with rapid stirring a solution of ceric ammonium nitrate in acetone.[44] The resulting colorless solution was washed with cold water, dried (Na_2SO_4), and treated with an excess of lithium aluminum hydride.[2a] Analysis of the reduced product solution by glpc on the 16-ft Carbowax column revealed the presence of three components with relative retention times (peak areas) of 10.4 (<0.1%), 19.0 (<0.1%), and 22.5 (>99%). The first two components were not isolated and characterized. The third component was identical in all respects with authentic 2-phenylethanol (1-OH).[35] A duplicate run C gave identical results.

Acetolysis of 2-[π-(Phenyl)chromium tricarbonyl]ethyl-1,1-d_2 Methanesulfonate (4-OMs). Run D.—This reaction was carried out in the same manner as run B except that the lithium aluminum hydride reduction step was omitted. The acetate product(s), isolated by glpc, showed ir (CCl_4) peaks at 3090, 3070, 3040 (CH phenyl); 2950 (CH aliphatic), 2260, 2180 (CD aliphatic); 1760 (C=O ester); 1610, 1590 (phenyl nucleus); 1028 (CO ester); 721, 700 cm^{-1} (monosubstituted phenyl); nmr (CCl_4) δ 7.18, singlet (C_6H_5–); 2.87, singlet ($C_6H_5CH_2$–); 1.95, singlet ($-COCH_3$). No signals were observed at δ ~4.3 ($-CH_2O$–). We estimate that ~3% of α-hydrogen-containing material could have been detected had it been present. The acetate isolated in a duplicate run E also contained <3% of hydrogen at the α position.

π-Complexed Products from the Acetolysis of 2-[π-(Phenyl)-chromium tricarbonyl]ethyl Methanesulfonate (2-OMs). Run F.—To 50 ml of 0.0487 *M* sodium acetate in deoxygenated acetic acid[2a] was added 0.650 g (1.92 mmol) of 2-OMs. The sample was sealed under nitrogen and heated at 115° in the dark for 11 hr (13 half-lives). The solution was poured over ~200 ml of cracked ice and then extracted as described for run B. The extract was dried ($MgSO_4$) and filtered. Addition of pentane to the filtrate caused the precipitation of 0.332 g (57.4%) of yellow crystals, mp 51–52°. Ir analysis showed ($CHCl_3$) 3020 (CH phenyl), 2960 (CH aliphatic); 1970, 1880 (C≡O); 1735 (C=O ester); 660, 630, 530 cm^{-1} (CrC); nmr ($CDCl_3$) δ 5.33, singlet (π-C_6H_5–); 4.32, triplet, $J = 6$ Hz ($-CH_2CH_2O$–); 2.77, triplet, $J = 6$ Hz ($C_6H_5CH_2CH_2$–); 2.16, singlet (CH_3CO_2–).

Anal. Calcd for $C_{13}H_{12}O_5Cr$: C, 52.00; H, 4.03; O, 26.65; Cr, 17.32. Found: C, 52.11; H, 4.10; O, 26.52.

The pale yellow mother liquor was treated with ceric ammonium nitrate (see run B) and analyzed by glpc on the 16-ft Carbowax column. A single component was observed. The product, isolated by glpc, was found to be identical with authentic 1-OAc.

Acetolysis Products of 2-Phenyl-1-propyl Methanesulfonate (*dl*-5-OMs). Run G.—To 50 ml of 0.0486 *M* sodium acetate in acetic acid was added 0.43 g (2.02 mmol) of the methanesulfonate. The solution was heated at 115° for 22 hr (~24 half-lives) and the product(s) were extracted and reduced with lithium aluminum hydride as described for run B. Analysis by glpc at 155° revealed the presence of five components whose relative retention times (peak areas) were 4.0 (8.7%), 5.3 (6.0%), 7.1 (14.5%), 34.8 (70.8%), and 42.0 (trace). The first, second, third, and fourth components were found to be identical with the known and commercially available[45] compounds allylbenzene (**10**), *cis*-β-methylstyrene (**11**), *trans*-β-methylstyrene (**12**), and 1-phenyl-2-propanol (*dl*-**13**-OH), respectively. The fifth component was not present in sufficient amounts for isolation and identification.

Acetolysis Products of 2-[π-(Phenyl)chromium tricarbonyl]-1-propyl Methanesulfonate (*dl*-6-OMs). Run H.—The reaction was carried out at 115° for 4 hr (~15 half lives) as described for run B. A glpc analysis of the decomplexed and reduced product mixture showed two components in a relative abundance of 5.1 and 94.9% which were identified by spectral comparison as alcohols *dl*-**13**-OH and *dl*-**5**-OH, respectively.

Formolysis Products of 2-[π-(Phenyl)chromium tricarbonyl]-ethyl Methanesulfonate (2-OMs). Run I.—To 50 ml of a solution of 0.0491 *M* sodium formate in deoxygenated formic acid (>97%, Matheson Coleman and Bell) was added 0.686 g (2.04 mmol) of 2-OMs. The solution was heated in a sealed ampoule in the dark at 115° for 1 hr, cooled, poured over cracked ice, and extracted with three 100-ml portions of a 1:1 ether–pentane mixture. The extract was washed with sodium carbonate, then with water, and concentrated to ~40 ml. Addition of ~100 ml of pentane to the concentrate gave 0.413 g (71%) of a yellow, crystalline product (2-OCOH): mp 71–72°; ir ($CHCl_3$) 3080, 3020 (CH phenyl); 2950, 2930, 2890 (CH aliphatic); 1950, 1870 (C≡O); 1735 (C=O ester); 658, 630, and 530 cm^{-1} (CCr); nmr ($CDCl_3$) δ 8.06, singlet ($-OCOH$); 5.60, broad singlet (π-C_6H_5–); 4.41, triplet, $J = 6$ Hz ($-CH_2CH_2O$–); 2.79, triplet, $J = 6$ Hz ($C_6H_5CH_2CH_2$–).

(41) E. O. Fischer and H. P. Fritz, *Angew. Chem.*, **73**, 353 (1961).

(42) Prepared by distilling reagent grade acetic acid from acetic anhydride and adding ~1% anhydride to the distillate.

(43) K and K Laboratories, Inc., Catalog No. 7, compound 17379.

(44) G. F. Emerson, L. Watts, and R. Pettit, *J. Amer. Chem. Soc.*, **87**, 131 (1965).

(45) K and K Laboratories, Inc., Catalog No. 7, compounds 4570, 25530, 25541, and 8353, respectively.

Anal. Calcd for $C_{12}H_{10}O_3Cr$: C, 50.35; H, 3.52; O, 27.95; Cr, 18.18. Found: C, 50.51; H, 3.56; O, 27.75.

The filtrate was further concentrated to ~20 ml and treated with ceric ammonium nitrate followed by lithium aluminum hydride as described for run B. Glpc analysis showed a single product, identical with authentic 1-OH.

Run J.—Another sample (0.684 g, 2.03 mmol) of the methanesulfonate 2-OMs was treated in a similar manner with anhydrous buffered formic acid at 70° for 30 min. The product was isolated as described for run I, giving 0.405 g (70%) of 2-OCOH.

Formolysis Products of 2-[π-(Phenyl)chromium tricarbonyl]-ethyl-1,1-d_2 Methanesulfonate (4-OMs). Run K.—A solution of 0.355 g (1.05 mmol) of 4-OMs in 25 ml of deoxygenated formic acid[2a] buffered with 0.0491 *M* sodium formate was heated at 120° for 1 hr. The complexed formate 4-OCOH (0.209 g, 69%) was isolated as described in run I: mp 71–72°; ir ($CHCl_3$) 3090, 3035 (CH phenyl); 2980, 2945, 2920 (CH aliphatic); 2170 (CD aliphatic); 1980, 1890 (C≡O), 1730 (C=O ester), 1190 (CO); 660, 630 cm^{-1} (CrC); nmr ($CDCl_3$) δ 8.02, singlet (-OCOH); 5.30, broad singlet (π-C_6H_5-); 2.75, singlet ($C_6H_5CH_2$-). No signals were observed at δ ~4.4 (-CH_2O-). We estimate that ~5% of α-hydrogen-containing material could have been detected had it been present.

Anal. Calcd for $C_{12}H_8D_2O_3Cr$: C, 50.01; H, 2.80; D, 1.39; O, 27.76; Cr, 18.04. Found: C, 50.28; O, 27.70.

Formolysis Products of 2-[π-(Phenyl)chromium tricarbonyl]-1-propyl Methanesulfonate (*dl*-6-OMs). Run L.—A solution of 61.8 mg (0.176 mmol) of *dl*-6-OMs in 5 ml of deoxygenated formic acid[2a] was heated at 115° for 30 min. The reaction mixture was extracted, decomplexed with ceric ammonium nitrate, reduced with lithium aluminum hydride, and analyzed by glpc as described for run B. Two components were found to be present (relative abundance 17% and 83%) which were identified by their infrared spectra as alcohols *dl*-13-OH and *dl*-5-OH, respectively.

Registry No.—1-OMs, 20020-27-3; 2-OCOH, 38599-99-4; 2-OAc, 38600-00-9; 2-OMs, 38600-01-0; 3-OMs, 38605-70-8; 4-OMs, 38600-02-1; 4-OCOH, 38600-03-2; (±)-5-OMs, 38605-48-0; (±)-6-OMs, 38600-04-3; 7-OMs, 20020-28-4; (±)-8-OMs, 38637-45-5.

Acknowledgment.—It is a pleasure to acknowledge the financial support given this work by the Directorate of Chemical Sciences of the Air Force Office of Scientific Research, Grant No. 991-66, and by the National Science Foundation, GP-11920, as well as helpful discussions with Professor Paul E. Peterson.

Kinetics of the Acid-Catalyzed Closure of Hydantoic Acids. Effect of 2-Aryl and 2-Alkyl Substituents[1]

V. STELLA AND T. HIGUCHI*

Department of Analytical Pharmaceutical Chemistry and Pharmaceutics, University of Kansas, Lawrence, Kansas 66044

Received October 24, 1972

Ring closure of hydantoic acids to hydantoins studied under aqueous acid conditions in the pH range 0–2 at 50° shows a specific acid-catalyzed component at low pH as well as a spontaneous component at higher pH. The accelerating effect of substitution on the 2 carbon of hydantoic acids by alkyl or aryl groups is not always as large as can be expected on the basis of their bulk. The observed rates appear to be rationalizable, however, in terms of a competing acceleration–inhibition mechanism resulting from the substituents being able to interfere with the reaction center as well as assisting in the process.

Hydantoic acids are known to cyclize to their respective hydantoin under acid conditions and the effects of 2 substituents has been qualitatively observed.[2] The only data available for the attack of a ureido group at a carboxyl group are the kinetics of the acid-catalyzed closure of a para-substituted phenylthiocarbamoylleucine, but the closure resulted in a thiohydantoin.[3] More recently, Projarlieff, *et al.*,[4,5] have reported studies on the acid-catalyzed reversible cyclization of ureidopropionic acid to yield dihydrouracil which, although not a hydantoin, possesses chemical characteristics similar to hydantoins. Bruice, *et al.*, studied quantitatively the conversion of *O*-ureidobenzoic acid and its esters to 2,4-(1*H*,3*H*)-quinazolinedione, a hydantoin-like molecule, under basic conditions.[6,7] The effects of alkyl and aryl substituents in intramolecular closures has been well documented, with the results suggesting that, as the bulkiness of substituents in cyclization reactions was increased, the rates of cyclization increased.[8–20] However, exceptions to this rule do exist.[16,19]

Despite the large amount of work done on hydantoins, the kinetics of the acid-catalyzed cyclization of hydantoic acids and the effects of 2 substituents have not been quantitated. In the present study the kinetics of the cyclization and the effect of 2 substituents on the

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(20) Recent papers have given a number of excellent examples of steric catalysis in intramolecular reactions and the possible mechanism of catalysis: (a) A. J. Kirby and P. W. Lancaster, *J. Chem. Soc., Perkin Trans. 2*, 1206 (1972); (b) S. Milstien and L. A. Cohen, *J. Amer. Chem. Soc.*, **94**, 9158 (1972); (c) R. T. Borchardt and L. A. Cohen, *ibid.*, **94**, 9166 (1972); (d) R. T. Borchardt and L. A. Cohen, *ibid.*, **94**, 9175 (1972); (e) J. M. Karle and I. L. Karle, *ibid.*, **94**, 9182 (1972).

TABLE I

COMPOUNDS STUDIED WITH R^i (i = 1–3) REFERRING TO THE GROUPS IN SCHEME I

Registry no.	Full chemical name	Abbreviated name	R^1	R^2	R^3
462-60-2	Hydantoic acid	HA	H	H	H
18409-49-9[a]	2-Methylhydantoic acid	MHA	CH_3	H	H
38605-63-9	2,2-Dimethylhydantoic acid	DMHA	CH_3	CH_3	H
5616-20-6	2-Phenylhydantoic acid	PHA	C_6H_5	H	H
949-45-1[a]	2-Benzylhydantoic acid	BHA	C_7H_7	H	H
38605-65-1	2,3-Trimethylenehydantoic acid	TMHA	$-C_3H_6-$	H	H
26081-02-7[a]	2-Isopropylhydantoic acid	ISPHA	i-C_3H_7	H	H
6802-95-5	2,2-Diphenylhydantoic acid	DPHA	C_6H_5	C_6H_5	H
38605-67-3	2-Ethyl-5-methyl-2-phenylhydantoic acid	EMPHA	C_6H_5	C_2H_5	CH_3
38605-68-4	5-Methyl-2-phenylhydantoic acid	MPHA	C_6H_5	H	CH_3

[a] L isomer.

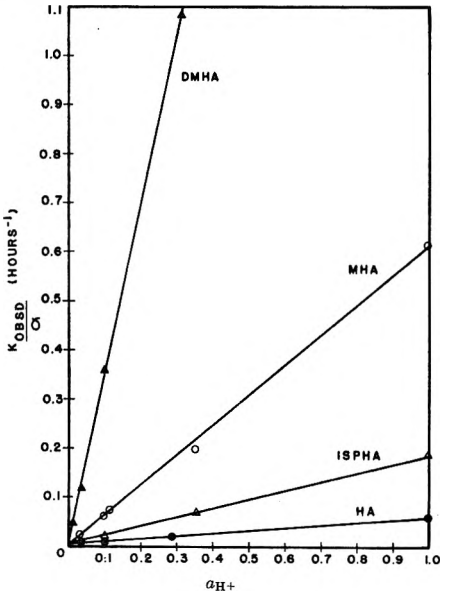
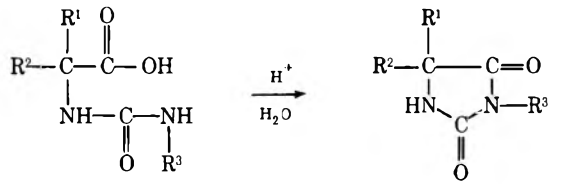


Figure 1.—Plot of k_{obsd} *vs.* a_{H^+} for the closure of HA, MHA, ISPHA, and DMHA to their respective hydantoin at 50° (μ 1.0, NaCl) from which k_1, a spontaneous rate constant, and k_2, a specific acid-catalyzed rate constant, can be determined. The intercept differences are significant and can be obtained by the use of expanded plots.

closure rate of a number of hydantoic acids were investigated in aqueous solution (μ 1.0) at 50° in the pH range 0–2. The reaction is represented as in Scheme I.

SCHEME I



R^1-R^3 = alkyl, aryl, or hydrogen substituent

Table I shows the ten acids that were studied. Included are 2,2-diphenylhydantoic acid (DPHA) and 2-ethyl-5-methyl-2-phenylhydantoic acid (EMPHA), which are the hydantoic acids of phenytoin and mephenytoin, respectively. Phenytoin and mephenytoin are two widely used anticonvulsive drugs.

Results

All the hydantoic acid closures followed first-order kinetics at constant pH and temperature. The reaction for all practical purposes appeared to be irreversible, as evidenced by spectral comparisons and by the absence of any observable reaction when the respective hydantoin was placed in the buffer.

The kinetic results obtained for the closures could be described in terms of eq 1 and 2

$$k_{obsd} = k_1\alpha + k_2\alpha a_{H^+} \quad (1)$$

$$\alpha = \frac{a_{H^+}}{K_a' + a_{H^+}} \quad (2)$$

where a_{H^+} = activity of hydrogen ions (obtained from pH measurements); α = fraction of the hydantoic acid present as the un-ionized acid; K_a' = the dissociation constant of the acid experimentally determined at 25° (μ 1.0) and corrected to 50°; k_1 = spontaneous rate constant; k_2 = specific acid catalyzed rate constant. Equation 1 predicts that a plot of k_{obsd}/α *vs.* a_{H^+} should give a straight line of slope k_2 and intercept k_1. Typical plots of k_{obsd}/α *vs.* a_{H^+} are shown in Figure 1. Actually, linear plots of k_{obsd} *vs.* $a_H{}^+$ adequately described most of the systems, since $K_a' \ll a_{H^+}$ and therefore $\alpha \cong 1$, throughout the pH range studied. However, in some of the cases, a plot of k_{obsd} *vs.* a_{H^+} showed a slight curvature as a_{H^+} approached K_a' but, more importantly, the k_1 value obtained from a linear approximate appeared too low when used to regenerate a curve to match the experimental points. The value of k_1 obtained from a plot of k_{obsd}/α *vs.* a_{H^+} was satisfactory.

Because of the low water solubility of DPHA and EMPHA, the kinetics of their closure was measured in a methanol–water mixture (1:1 v/v before mixing) with a hydrochloric acid concentration of 0.1 M. This was repeated for all the hydantoic acids. Table II gives the log $k_{2,rel}$, log $k_{pH1.0,rel}$, log $k_{pH2.0,rel}$, and log $k_{CH_3OH/H_2O,rel}$, where $k_{2,rel}$ is the relative specific acid-catalyzed rate constant in water (all rates relative to $R^1 = R^2 = R^3 = H$), $k_{pH1.0,rel}$ is the relative rate constant at pH 1.0 in water, $k_{pH2.0,rel}$ is the relative rate constant at pH 2.0 in water, and $k_{CH_3OH/H_2O,rel}$ is the relative rate constant in the methanol–water mixture. These data sets were sufficiently correlated to allow an estimation of k_2 and $k_{pH1.0}$ for DPHA and EMPHA and

TABLE II
DATA USED TO ESTIMATE k_2, $k_{pH1.0}$, AND $k_{pH2.0}$ FOR DPHA AND EMPHA

Acid	log k_{rel}[a] (k_2)	log k_{rel}[a] ($k_{pH1.0}$)	log k_{rel}[a] ($k_{pH2.0}$)	log k_{rel}[a] (k_{CH_3OH/H_2O})
HA	0.00	0.00	0.00	0.00
ISPHA	0.53	0.53	0.61	0.71
PHA	0.62	0.59	0.50	0.71
BHA	0.68	0.67	1.03	0.82
TMHA	1.04	1.03	1.05	1.22
MHA	1.05	1.02	0.97	1.21
DMHA	1.80	1.77	1.73	2.10
DPHA				1.61
EMPHA				3.23

[a] Rate data relative to where $R^1 = R^2 = R^3 = H$.

an approximate estimate of their rates of closure at pH 2.0. The results are shown in Table III. All the

TABLE III
ESTIMATED RATE CONSTANTS FOR DPHA AND EMPHA FROM METHANOL-WATER DATA

Acid	k_2, M^{-1} hr^{-1}	$k_{pH1.0}$, hr^{-1}	$k_{pH2.0}$, hr^{-1}
DPHA	1.30	1.41×10^{-1}	2.34×10^{-2}
EMPHA	32.5	3.39	4.79×10^{-1}

experimentally determined values of k_1, k_2, and pK_a' are shown in Table IV.

TABLE IV
THE VALUES OF k_1, k_2, AND pK_a' FOR THE ACIDS STUDIED

Acid	k_1, hr^{-1}	k_2, M^{-1} hr^{-1}	pK_a'
HA	3.5×10^{-4}	5.39×10^{-2}	3.52 ± 0.03
ISPHA	1.9×10^{-3}	1.81×10^{-1}	3.56 ± 0.03
PHA	1.1×10^{-3}	2.26×10^{-1}	3.04 ± 0.02
BHA	2.4×10^{-3}	2.58×10^{-1}	3.44 ± 0.02
TMHA	3.9×10^{-3}	5.99×10^{-1}	3.48 ± 0.04
MHA	2.4×10^{-3}	6.06×10^{-1}	3.55 ± 0.03
DMHA	6.5×10^{-3}	3.39	4.07 ± 0.03
MPHA		6.09×10^{-1}	
DPHA		1.30	3.01 ± 0.02
EMPHA		32.5	3.03 ± 0.03

Since the buffering species used was hydrochloric acid, the buffer concentration could not be varied without changing the pH. The effect of added acetic acid on the rate of cyclization at pH 1.0 was studied and the results are shown in Figure 2. The plot of k_{obsd} *vs.* acetic acid concentration shows that the acetic acid inhibits the rate of closure at high concentration, consistent with the findings of others on the effect of acetic acid on the rate of solvolysis of acetylsalicylic anhydride in hydrochloric acid buffer.[21,22] The inhibition was probably a solvent effect because it was not seen until the concentration of acetic acid was greater than 2% v/v.

Discussion

The results presented in the previous section can be rationalized in terms of a general mechanistic scheme for the reaction (Scheme II).

(21) E. R. Garrett, *J. Amer. Chem. Soc.*, **82**, 711 (1960).
(22) J. Koskikallio, *Acta Chem. Scand.*, **17**, 1417 (1963).

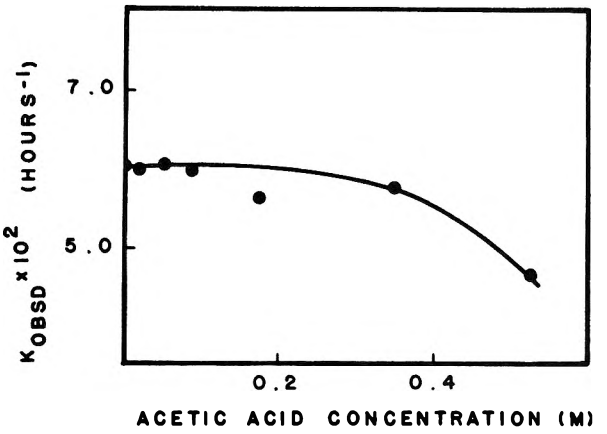
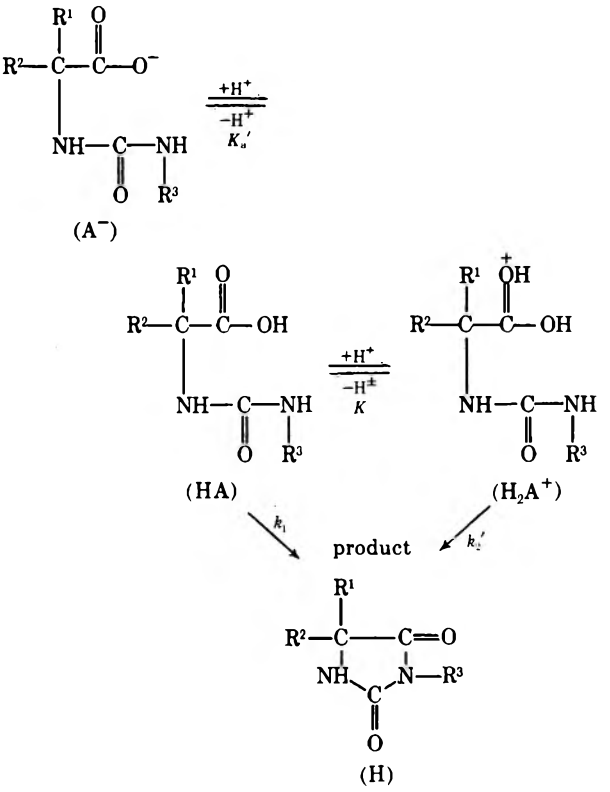


Figure 2.—Plot of k_{obsd} (pH 1.0) *vs.* acetic acid concentration (M) used to determine the effect of acetic acid on the closure rate of MHA to its hydantoin.

SCHEME II



The rate of product formation on the basis of Scheme II is

$$\frac{d[H]}{dt} = k_1[HA] + k_2'[H_2A^+] \quad (3)$$

The development of this equation leads directly to eq 1 and 2, where $k_2 = k_2'/K$. Figure 3 shows some representative plots of log k_{obsd} *vs.* pH, where, assuming Scheme II, the solid line is the path generated by the experimentally determined rate and equilibrium constants k_1, k_2, and pK_a'. As can be seen, Scheme II does appear to describe the system. k_1 corresponds to the spontaneous closure of the free hydantoic acid. However, the acid-catalyzed closure of the hydantoate anion, which is kinetically equivalent, cannot be totally discounted. It would appear, however, on a mechanistic basis that the latter route is highly unlikely.

Inhibition of the closure owing to protonation of the ureido group was not observed, probably because studies

TABLE V

COMPARISON OF LOGARITHMS OF THE EXPERIMENTAL RELATIVE RATE DATA OF VARIOUS SUBSTITUENTS USED IN THE PRESENT STUDY WITH PERTINENT LITERATURE VALUES OF OTHER INTRAMOLECULAR CLOSURES WHERE STERIC EFFECTS WERE ALSO STUDIED

R^1, R^2	2-Substituted hydantoic acid (present study)	3-Substituted mono-*p*-bromophenylglutarates[b]	2-Substituted 4-bromobutyl amines[c]	3-Substituted phthalides[d]	3-Substituted dinitroanthranilic acid[e]
H, H	0.00	0.00	0.00		0.00
CH_3, H	1.05	0.68	1.10[a]		
C_2H_5, H	0.73[a]	1.13	1.39[a]		0.57
C_6H_5, H	0.63	1.21[a]	1.86[a]		
CH_3, CH_3	1.80 (0.42)	1.36	2.20	(0.47)	1.38
i-C_3H_7, H	0.53	1.52	1.98[a]		
C_2H_5, C_6H_5	1.35[a]	2.33	3.25[a]		
C_6H_5, C_6H_5	1.38 (0.0)	2.43	3.72	(0.0)	

[a] Data obtained assuming additivity, *e.g.*, for 2-ethylhydantoic acid, log k_{rel} (R^1 = C_2H_5, R^2 = R^3 = H) = log k_{rel} (R^1 = C_2H_5, R^2 = C_6H_5, R^3 = CH_3) − log k_{rel} (R^1 = H, R^2 = C_6H_5, R^3 = CH_3). [b] Reference 12. [c] Reference 8. [d] Reference 16. [e] Reference 11.

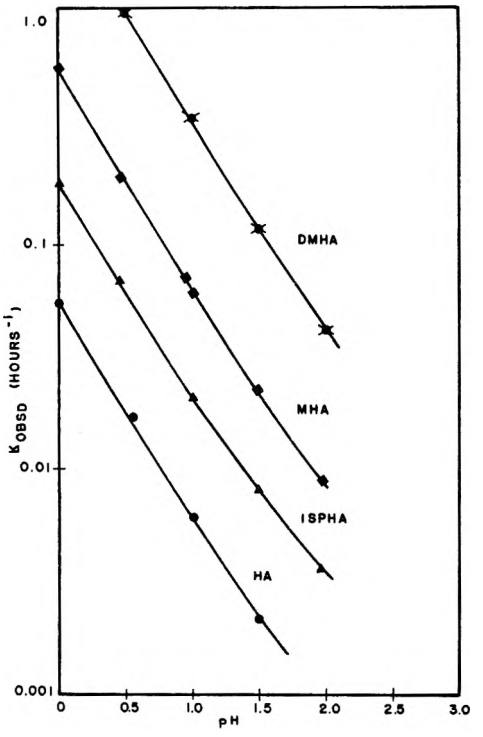
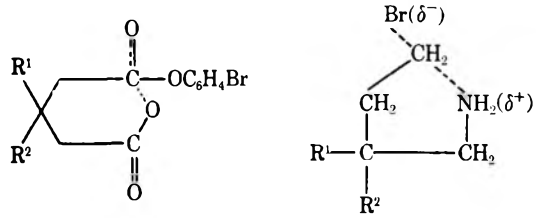


Figure 3.—pH–log k_{obsd} profile for the cyclization of HA, MHA, ISPHA, and DMHA to their respective hydantoin at 50° (μ 1.0, NaCl).

were not carried out in highly acidic systems. The protonation would have resulted in the loss of nucleophilicity by the ureido group.[4,5]

Steric Effects.—The study of steric effects of 2 substituents on the rate of intramolecular closure of hydantoic acids led to some unexpected results. The effect of steric substituents in other intramolecular closures[8-20] had generally shown that, as the bulkiness of the substituents in cyclization reactions was increased, the rate of reaction increased. It was predicted therefore that compounds like DPHA and EMPHA should close at very rapid rates. The experimental results of the present study, however, revealed that such was not the case. Substitution on the 2 carbon of hydantoic acid did increase the rate of the specific acid catalyzed and spontaneous closures, but only in partial agreement with data reported in the literature. Table V gives some pertinent literature comparisons.

Inspection of Table V shows that the effect of substitution appeared to be related to the size of the group. Bruice, *et al.*, investigated 3-substituted mono-*p*-bromophenylglutarate closures, while Brown, *et al.*, looked at 2-substituted 4-bromobutylamines. Their results were consistent with the hypothesis that substituent effects are directly related to their relative size, *i.e.*, isopropyl > phenyl > ethyl > methyl > hydrogen. A look at the possible transition states for their reactions shows that the R^1, R^2 groups are well separated from the reaction center and are unable to interfere with the reaction center in the transition state.



The rationale for the increased rates of cyclization with increased bulkiness of substituent presently has a number of schools of thought. First, the increase in bulk of R^1 and R^2 should decrease the volume in which the reactive ends of the molecule can exist. An increase in the size of R therefore should increase the rate of nucleophilic attack. That is the bulkiness cuts down the number of unprofitable rotamers.[12] Another approach attempts a quantitative analysis of the problem and discusses the rate increase in terms of gauche interactions, which are lessened in going from the ground state to the transition state. This quantitative approach, however, is limited to simple substituents but would predict *a priori* that the larger the group the faster the rate of reaction.[18] More recently Storm and Koshland,[19,23] as well as Bunnett and Hauser,[9] have suggested that the effect of the substituents may be due to orientational effects, where the substituent through interaction with the reaction center will favor certain orientations over others. The new orientation may be a favorable or an unfavorable one, so explaining the fact that substituents may occasionally lead to catalysis while at other times to inhibition. Cohen, *et al.*,[20b-d] have introduced the terms stereo population control and trimethyl lock to describe their findings on substituted *o*-hydroxycinnamic acids and their derivatives.

In the present study all the substituents cause a rate acceleration over the unsubstituted acid but the larger substituents have a smaller effect than their size

(23) D. R. Storm and D. E. Koshland, Jr., *J. Amer. Chem. Soc.*, **94**, 5805 (1972).

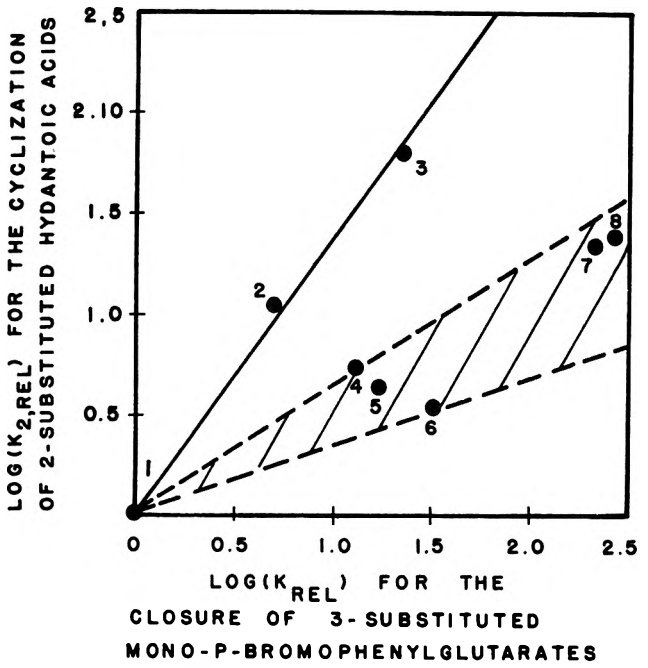
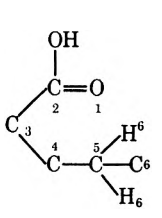


Figure 4.—Logarithms of the relative specific acid-catalyzed rate constants for the cyclization of 2-substituted hydantoic acids (present study) against the logarithms of the relative rates of closure of 3-substituted mono-*p*-bromophenylglutarates.[12] Rates are relative to $R_1 = R_2 = H$ for both the hydantoic acids and the glutarates. Key: 1 = H, H; 2 = CH_3, H; 3 = CH_3, CH_3; 4 = C_2H_5, H; 5 = C_6H_5, H; 6 = *i*-C_3H_7, H; 7 = C_2H_5, C_6H_5; 8 = C_6H_5, C_6H_5.

would predict. A plot of the logarithms of relative rate data from this study against that of 3-substituted mono-*p*-bromophenyl glutarate closure[12] is shown in Figure 4. The division into two groups is readily seen. The substituents which fall into the slower group—*i.e.*, isopropyl, phenyl, etc.—have a common property which is not shared with the methyl, dimethyl substituents. They are better able to interfere with the reaction center.

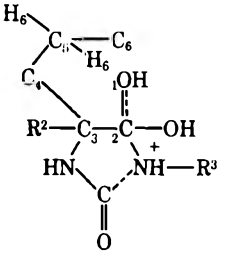
Newman[24] proposed an empirical rule called "The Rule of Six." This rule was for reactions where substituents can form a six-membered ring with some atom involved in the ground or transition state. For example, if the rates of esterification of a series of carboxylic acids are observed, there is little difference between acetic acid and propionic acid, but in going to butyric acid there is a significant drop in the rate. If the atoms in the acid are numbered, it can be seen that butyric acid and higher homologs have atoms in the six position.



This effect could be due to the blocking of the addition reaction and steric retardation owing to the increased spatial requirements in going from the ground state to the partial tetrahedral intermediate transition state.[24] The effect could also be due to solvation interference or an effect on K, the prereaction equilibrium protonation constant. Ingold has discussed steric effects in bimolecular reactions in a similar fashion but from a more energetic approach.[25]

The steric requirements discussed by Newman and Ingold, which are probably playing a role in the present work, have also been qualitatively noted by others in intramolecular reactions. In the case of 3-substituted mono-*p*-bromophenylglutarate closure,[12] moving the substituents to the 2 position[13] greatly decreased the effect of the substituent. Similarly, in the case of 2-substituted 4-bromobutylamine closures,[8] placing the substituent at the 1 or 3 position decreased the *gem*-dialkyl effect by moving the groups nearer the reaction center. With the 4-bromobutylamine closures, "substitution on the third carbon decreases the rate which is only about $^1/_6$ as fast as the parent. However, the bromine occupies a neopentyl position in this case and the observed rate represents a marked acceleration to such a hindered displacement reaction."[8]

In the present study, the transition state is probably very similar to that of the acid-catalyzed esterification of carboxylic acids. Below is a possible transition state which is susceptible to steric effects[24,26] for the acid-catalyzed closure of hydantoic acids.



A possible rate-determining transition state is the attack of the ureido group at the protonated carboxyl group with possibly some concerted leaving of a water molecule. Depending on R^1 and R^2, the coiled structure proposed by Newman as possibly causing inhibition can be superimposed on this system.

When the logarithms of the relative rate constants for the present study were plotted against those of Bruice, *et al.* (refer to Figure 4), HA, MHA, and DMHA may be assumed to be displaying relatively ideal behavior; *i.e.*, there is little steric inhibition by the substituents. The vertical distance between the line drawn through these three points (R^1, R^2; H, H; CH_3, H; CH_3, CH_3) and the experimental points for the other substituents may be taken as a measure of the inhibition by the other substituents. This distance in reality is a rough measure of the relative free energy of inhibition for the reaction assuming ideal behavior by the methyl, dimethyl substituents. Unfortunately, no effort was made to separate the catalytic and inhibitive effects into enthalpic and entropic contributions. These differences were then compared to the number of atoms in the 6 position (see Table VI). The order of inhibition was C_6H_5, C_6H_5 > C_2H_5, C_6H_5 > *i*-C_3H_7 > C_6H_5 > C_2H_5, and this order was qualitatively

(24) M. S. Newman, "Steric Effects in Organic Chemistry," Wiley, New York, N. Y., 1956, pp 203–213.

(25) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed, Cornell University Press, Ithaca, N. Y., 1969, pp 544–557, 1155–1160.

(26) K. L. Loening, A. B. Ganett, and M. S. Newman, *J. Amer. Chem. Soc.*, **74**, 3929 (1952).

TABLE VI

COMPARISON OF THE INHIBITING EFFECTS OF THE LARGE ALKYL AND ARYL SUBSTITUENTS TO THE NUMBER OF ATOMS IN THE 6 POSITION IN THE ACID-CATALYZED CLOSURE OF 2-SUBSTITUTED HYDANTOIC ACIDS

R^1, R^2	log (k_{rel})[a] I	log (k_{rel}) (exptl) II	Inhibiting[b] effect I − II	Number of atoms at 6 position
C_2H_5, H	1.56	0.73	0.83	3
C_6H_5, H	1.71	0.63	1.08	4
i-C_3H_7, H	2.10	0.53	1.57	6
C_2H_5, C_6H_5	3.21	1.35	1.86	7
C_6H_5, C_6H_5	3.36	1.38	1.98	8

[a] Obtained from Figure 4, where the individual groups would have fallen on the HA, MHA, DMHA line, *i.e.*, assuming that the HA, MHA, DMHA line represents relatively ideal behavior. [b] The difference (I − II) is really just the vertical distance from the HA, MHA, DMHA line to the experimental points, again referring to Figure 4.

identical with the number of atoms in the 6 position. If the assumption is made that the inhibition of the larger groups in the cyclization of hydantoic acids is identical with those seen in the intermolecular esterification mechanism of carboxylic acids, an inhibition factor, *IF*, can be defined

$$IF = \log \frac{k^{40°}_{CH_3CH_2COOH}}{k^{40°}_{RCOOH}}$$

where $k^{40°}_{CH_3CH_2COOH}$ is the specific acid catalyzed rate of esterification of the acid CH_3CH_2COOH;[24] $k^{40°}_{RCOOH}$ is the specific acid catalyzed rate of esterification of the acid RCOOH;[24] CH_3CH_2COOH is taken as the acid representative of hydantoic acid rather than CH_3COOH, because the terminal methyl replaces the ureido group. This means that, if HA is represented by CH_3CH_2COOH, MHA is represented by $(CH_3)_2CHCOOH$, DMHA by $(CH_3)_3CCOOH$, EHA by $CH_3CH_2CH(CH_3)COOH$, and ISPHA by $(CH_3)_2CHCH(CH_3)COOH$. Table VII gives the *IF* for the acids used. If the rates of the acid-catalyzed intramolecular cyclizations of hydantoic acids are now corrected by the respective *IF* and again compared to the works of Bruice, *et al.*, and Brown, *et al.*, the correction eliminated some of the inconsistencies in the experimental results (see Table VIII). Further data to allow the correction for all the acids was not available.

TABLE VII

LOGARITHMS OF THE RELATIVE INHIBITION EFFECTS OF 2-ALKYL GROUPS ON THE ACID-CATALYZED ESTERFICATION OF CARBOXYLIC ACIDS

Carboxylic acid (RCOOH)	$k^{40°}_{CH_3CH_2COOH}/k^{40°}_{RCOOH}$	log $k^{40°}_{CH_3CH_2COOH}/k^{40°}_{RCOOH}$ (*IF*)
CH_3CH_2COOH	1.00	0.00
$(CH_3)_2CHCOOH$	2.52	0.40
$(CH_3)_3CCOOH$	22.5	1.35
$CH_3CH_2CH(CH_3)COOH$	8.49	0.93
$(CH_3)_2CHCH(CH_3)COOH$	106	2.03[a]

[a] Obtained by extrapolation from log $k_{CH_3CH_2COOH}/k_{RCOOH}$ *vs* the number of atoms in the 6 position. For R = CH_3CH_2COOH, $CH_3CH_2CH(CH_3)COOH$, $(CH_3)_3CCH(CH_3)COOH$ gives excellent correlation, allowing the estimation of $k_{(CH_3)_2CHCH(CH_3)COOH}$.

In summary these results show that the small steric acceleration effect seen with the large groups in the present study is probably due to competing acceleration–inhibition effects resulting from the groups being able to interfere with the reaction center as well as assisting in the process. The actual mechanism of the catalysis is difficult to interpret because, as stated by Thornton,[27] the use of substituents results in changes in the electronic energy surfaces of substituted *vs.* unsubstituted molecules, giving rise to different molecular geometries as well as force constants. This means that the effect of the substituents can be broken down into the effect of the substituent on the rest of the molecule including the reaction center, but we cannot forget about the effect of the rest of the molecule on the energetics of the substituent.

TABLE VIII

COMPARISON OF CORRECTED LOGARITHMS OF RELATIVE RATE DATA FOR THE PRESENT WORK WITH PERTINENT LITERATURE VALUES

R^1, R^2	2-Substituted hydantoic acids (corrected)	Brown, *et al.* 2-Substituted 4-bromobutyl amines[a]	Bruice, *et al.* 3-Substituted mono-*p*-bromophenyl glutarates[b]
H, H	0.00	0.00	0.00
CH_3, H	1.45	1.10	0.68
C_2H_5, H	1.56	1.39	1.13
CH_3, CH_3	3.15	2.20	1.35
i-C_3H_7, H	2.56	1.98	1.52

[a] Reference 8. [b] Reference 12.

The steric effect of the benzyl group, not discussed so far because no comparison data was available, appears to fall in line with other groups studied. The steric effect of the 2,3-trimethylene substitution has a log k_{rel} of 1.05, which is identical with that of a methyl group. At first this does not appear inconsistent because the cyclopentyl group is directed away from the reaction center in the transition state and so in reality acts as a methyl group. An anomaly arises, however, in that the cyclopentyl group has frozen rotation about the 2–3 bond and such an effect in intramolecular reaction usually results in rate increases in the order of 160-fold,[28] whereas here an increase of 11.5-fold is seen. Eliel[29] explains that the most important factors to be considered in ring closures are the ease of having the ends of the acylic structure meet and a strain factor. The closure of 2,3-trimethylenehydantoic acid results in two adjacent five-membered rings with a common bond. The situation is similar to the case of succinic compared to maleic acid in the rate of cyclization of their phenyl esters,[28] where the rate increase is only 43-fold because of strain introduced into the system by a double bond. If 2,3-trimethylenehydantoic acid is corrected in a similar manner to the other substituents (refer to Tables VII and VIII) by the data of Newman,[24] the corrected rate increase over hydantoic acid is 11.5 × 3.4 or 39-fold. The apparent small increase in rate with the freezing of the 2,3 bond is due to strain imposed on the system by the added cyclopentyl group. The terminal methyl group (5-methyl) gives a log k_{rel} of 1.43, identical with that of a corrected methyl group at the 2 position. However, the mecha-

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(28) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, pp 8–15.
(29) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 198.

TABLE IX

CALCULATED VALUES, ASSUMING ADDITIVITY, COMPARED TO THE EXPERIMENTALLY DETERMINED VALUES FOR THE EFFECT OF 2 SUBSTITUENTS ON THE CLOSURE OF HYDANTOIC ACIDS

R^1	R^2	R^3	log k_{rel} exptl	log k_{rel} calcd
CH_3	CH_3	H	1.80	2.10
C_6H_5	C_6H_5	H	1.38	1.26
C_6H_5	C_2H_5	CH_3	2.78	2.73[a]
CH_3	CH_3	H	3.15[b]	2.90[b]

[a] Assuming that the effect of benzyl is approximately the same as that of ethyl. The assumption was made considering the fact that their Taft steric parameters are identical, *i.e.*, when considered as $C_6H_5CH_2CH_2$ *vs.* $C_2H_5CH_2$. [b] Using the corrected values of Table VIII.

nisms for the rate increases are probably not the same. The 5-methyl group can, by induction, increase the nucleophilicity of the ureido group and stabilize any positive charge built up on the terminal nitrogen in the transition state. The acceleration could also be due to the greater relief of the gauche carboxyl–methyl amido ($-CONHCH_3$) interaction compared to carboxyl–amido ($-CONH_2$) interaction.[18]

Additivity of the Steric Effects.—The trend toward additivity among the logarithms of the relative rates of closure is interesting. This phenomenon was also observed by Bruice, *et al.*[12] The calculation of log (k_{rel}) for $R^1 = C_2H_5$, $R^2 = R^3 = H$ and $R^1 = C_2H_5$, $R^2 = C_6H_5$, $R^3 = H$ used in the discussion so far have asssumed additivity; and, as could be observed from those results, the values obtained did seem to be in the right order of magnitude. Table IX gives the calculated values compared to the experimentally determined values for some substituents where the additivity phenomenon could be checked.

Experimental Section

Equipment.—A Cary 14 recording spectrophotometer was used for all spectroscopic measurements. The pH measurements were carried out using a Corning Model 12 research pH meter standardized with potassium tetraoxoalate standard buffer (pH 1.679, 12.61 g/l.). Infrared spectra were measured on a Perkin-Elmer 70 infrared spectrometer.

Materials.—All chemicals used were of analytical or reagent grade. Mephenytoin was supplied by Sandoz Drug Co. Buffers were made from triply distilled water and analytical grade concentrated hydrochloric acid with the ionic strength adjusted to 1.0 with sodium chloride.

The hydantoic acids were prepared from their amino acids by treatment with potassium cyanate or methyl isocyanate, or by the hydrolysis of the corresponding hydantoin.[2] The amino acids for the formation of the hydantoic acids were commercially available or, in the case of 2,2-diphenylglycine, were prepared from the hydrolysis of the corresponding hydantoin (hydrolysis of the hydantoin in this case did not allow the isolation of the hydantoic acid). Analysis of the compounds prepared, method of synthesis, infrared data, and melting points (reported melting points)[30-37] are shown in Table X. Examples of the various synthetic procedures used are listed below.

Method I. 2,2-Diphenylglycine (DPG).—To 300 ml of 20% sodium hydroxide was added 5,5-diphenylhydantoin (17 g, 0.07 mol). The solution was placed in a plunging autoclave under nitrogen at 180° for 30 hr. This was then charcoal filtered, diluted to 800 ml with water, and neutralized with acetic acid. Product was collected, washed with successive portions (100 ml) of water, ethanol, and ether, and dried in a vacuum hot air oven. DPG gave mp 258° dec (yield 10.7 g).

TABLE X

ANALYSIS,[a] METHOD OF SYNTHESIS, INFRARED DATA, AND MELTING POINTS OF COMPOUNDS STUDIED

Compd	Method of synthesis	Wavenumber for C=O stretch, cm^{-1} (NaCl cells, solvent THF)	Wavenumber for C=O stretch, cm^{-1} (KBr pellet)	Mp (dec), °C	Reported mp (dec), °C	Ref
HA	II	1680, 1720		178–179	180	30
MHA	II	1680, 1720		182–183	185	30
DMHA	II	1680, 1730		186–187	184	31
PHA	IIa	1690, 1730		195–196	181, 196.5	30, 32
BHA	IIa	1690, 1725		192–193	188–190	33
TMHA	II	1675, 1740		200–202		
ISPHA	II	1680, 1720		200–201	187, 176	34, 35
DPHA	IIa	1680, 1730	1625, 1710	190–191		
EMPHA	III	1680, 1710		189–190	177–178	32
MPHA	IIb	1680, 1720		166–167	164–165	32
DPG	I		1630	261–263	242, 263	36, 37

[a] Satisfactory combustion analytical data (±0.3%) were provided for all new compounds. Ed.

Method II. 2-Isopropylhydantoic Acid (ISPHA).—To *dl*-valine (3 g, 0.025 mol) was added an excess of potassium cyanate (3 g, 0.037 mol) in 15 ml of water. The solution was heated in a hot water bath at 90–100° for 1.5 hr. After cooling in ice water, the solution was acidified with concentrated hydrochloric acid. The precipitate was collected, washed with ice water and then with ether, and dried. After two recrystallizations from an ethanol–water mixture, a product with mp 200–201° was obtained.

Method IIa.—If the amino acid was very water insoluble, a slight variation of method II was used. The amino acid was solubilized in basic solution by the addition of some sodium hydroxide (enough to effect solution) and then the excess potassium cyanate was added.

Method IIb.—When methyl isocyanate was used as the carbamoylating agent, the amino acid was again dissolved in slightly alkaline solution and the excess methyl isocyanate was added dropwise to the reaction mixture at room temperature, not at elevated temperatures.

Method III. 2-Ethyl-5-methyl-2-phenylhydantoic Acid (EMPHA).—To 45 ml of 1 *N* sodium hydroxide was added mephenytoin (5 g, 0.02 mol). The solution was heated at 90–100° for 0.75 hr and then cooled. After extraction with 3 × 50 ml of ether and filtering, the aqueous alkaline portion was acidified. The precipitate was collected and, after recrystallization from an ethanol–water mixture, was found to decompose at 189–190°, consistent with EMPHA.

Kinetic Measurements.—All aqueous reactions were carried out at 50.0 ± 0.1° in tightly stoppered 50-ml volumetric flasks suspended in an oil bath. Samples (5 ml) were withdrawn at

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(31) C. J. West, *J. Biol. Chem.*, **34**, 187 (1918).
(32) H. Aspelund, *Acta Acad. Aboenisis, Math. Phys.*, **23**, 1 (1962).
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(36) H. C. Carrington, C. H. Vasey, and W. S. Waring, *J. Chem. Soc.*, **49**, 3105 (1953).
(37) R. Duschinsky (to Hoffmann-La Roche Inc.), U. S. Patent 2,593,860 (1952).

appropriate times, placed in screw-capped vials, quickly cooled in ice water, and then stored in a freezer (−15°). Analysis of the samples was carried out at 230 nm for hydantoic acids without aryl substitution, and at 242.5 nm for the acids with aryl substitution. The extinction coefficients of the hydantoic acids are about one-third those of the respective hydantoin. The rate constants were obtained by plotting log $(A_\infty - A_t)$ *vs.* time, where A_∞ and A_t are the absorbance readings at infinity and at time t, respectively. Reactions carried out at 50.0 ± 0.1° in the methanol–water mixture were done in ampoules to prevent evaporation problems. The reverse of the ring-closure reactions was studied under identical conditions, but no visible reactions were noted, suggesting that the reactions were for all practical purposes irreversible under the conditions employed. Similarly, the spectrum of the reaction product for the ring-closure reactions was identical with that of an equimolar solution of the respective hydantoin.

pK_a Measurements.—pK_a's were measured in a water-jacketed cell maintained at 25° under nitrogen. The apparatus and method of determination, with slight modification, was that described by Albert and Sargent[38] for carboxylic acids with low water solubility. The hydantoic acids (~0.001 mol) were dissolved in 100 ml of standard sodium hydroxide solution (0.01909 *M*, μ 1.0 with NaCl) and then back-titrated with standard hydrochloric acid solution (0.1090 *M*, μ 1.0 with NaCl). The first end point gave the concentration of the dissolved acid and the remaining points were used to calculate the pK_a, correcting for the concentration of hydrogen ions. The reactions studied were carried out at 50°, but the pK_a's were determined at 25°. King[39] has determined the thermodynamic pK_a's of some hydantoic acids at 25 and 50°, and the average variation in the pK_a's in going from 25 to 50° was 0.02. Estimation of the pK_a' values at 50° was accomplished by the addition of 0.02 to each pK_a value determined at 25°.

Acknowledgment.—This work was supported by the Institute of Pharmaceutical Chemistry. The authors also wish to thank Drs. I. H. Pitman, R. L. Schowen, and T. C. Bruice for helpful discussions.

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3-Substituted Propionaldehyde Derivatives. A Study of the Chemistry of 2-Hydroxymethylglyceraldehyde Acetonide[1]

GEORGE JUST* AND PHILLIP ROSSY[2]

Department of Chemistry, McGill University, Montreal 101, Quebec, Canada

Received September 21, 1972

The reaction of glyceraldehyde acetonide with formaldehyde gave the 4-hydroxy-1,3-dioxolane II. Distillation of II gave hydroxymethylglyceraldehyde acetonide VI, characterized as its dimethylhydrazone V, dimethylacetal VII, and *N*-methyloxazolidine derivative X. The latter compound proved to be stable to acetylation and mesylation, and the protecting group could be removed under very mild acidic conditions, allowing the synthesis of aldehydomesylate IX and aldehydothioacetate XIIa.

The replacement of the alcohol function of a β-hydroxyaldehyde is a difficult undertaking because of the ease of polymerization of such compounds. We would like to report on the synthesis and some reactions of 2-hydroxymethylglyceraldehyde acetonide, and its transformation to the 3 mesylate and 3 thioacetate in both a protected and unprotected form. Some of these compounds were required in large quantities in connection with a cepham synthesis.

Glyceraldehyde acetonide I[3] was treated with formaldehyde in aqueous methanolic potassium carbonate. Crystallization of the reaction mixture gave II in 70% yield. Its structure was determined from its reactions and from analytical and spectroscopic data. Also, 4-hydroxy-1,3-dioxanes are known to arise from the reaction of aldehydes with aldols.[4]

The acetate IIa was prepared, but was difficult to obtain in crystalline form. This was due to the fact that two isomers were present in the reaction mixture, as evidenced by the nmr spectrum, which showed two singlets for the anomeric proton at 5.65 and 5.85 ppm in a ratio of 3:1. A method was devised to achieve selective hydrolysis of the acetonide function of the acetate mixture IIa, and the diol mixture IIIa was obtained in very good yield. The method consisted of treatment of the acetonide IIa with 90% aqueous trifluoroacetic acid for 2 min. The resulting diol acetate IIIa was converted to an oily mesylate IVa, but no further work was done on it, since it could not be obtained crystalline.

However, the mixture of epimeric *p*-nitrobenzoates IIb was easily prepared in crystalline form, even though two isomers were obtained (two singlets for the anomeric proton at 6.3 and 6.5 ppm, ratio 3:1). It is evident from the nmr spectrum that the isomer in which the *p*-nitrobenzoate is equatorial is favored.[5] Compound IIb could be converted to a crystalline mixture of epimeric diols IIIb and a crystalline mixture of epimeric mesylates IVb. Attempts to displace the mesylate with potassium thioacetate or with sodium hydrogen sulfide, and to extrude formaldehyde in order to regenerate a hydroxyaldehyde, failed.

While carrying out these reactions, we noticed that high-temperature distillation of compound II gave the aldehyde VI, which we had wanted in the first place. The ir spectrum indicated the presence of an aldehyde (1730 cm^{-1}) and a hydroxyl group (3400 cm^{-1}). The nmr spectrum was consistent with the proposed structure. Upon standing at room temperature for a few hours, the hydroxyaldehyde became very viscous and the carbonyl absorption in the ir decreased considerably. Aldols are known[4] to polymerize or dimerize on standing. It was thus necessary to protect the alde-

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(2) Abstracted from part of the Ph.D. thesis of Phillip Rossy.

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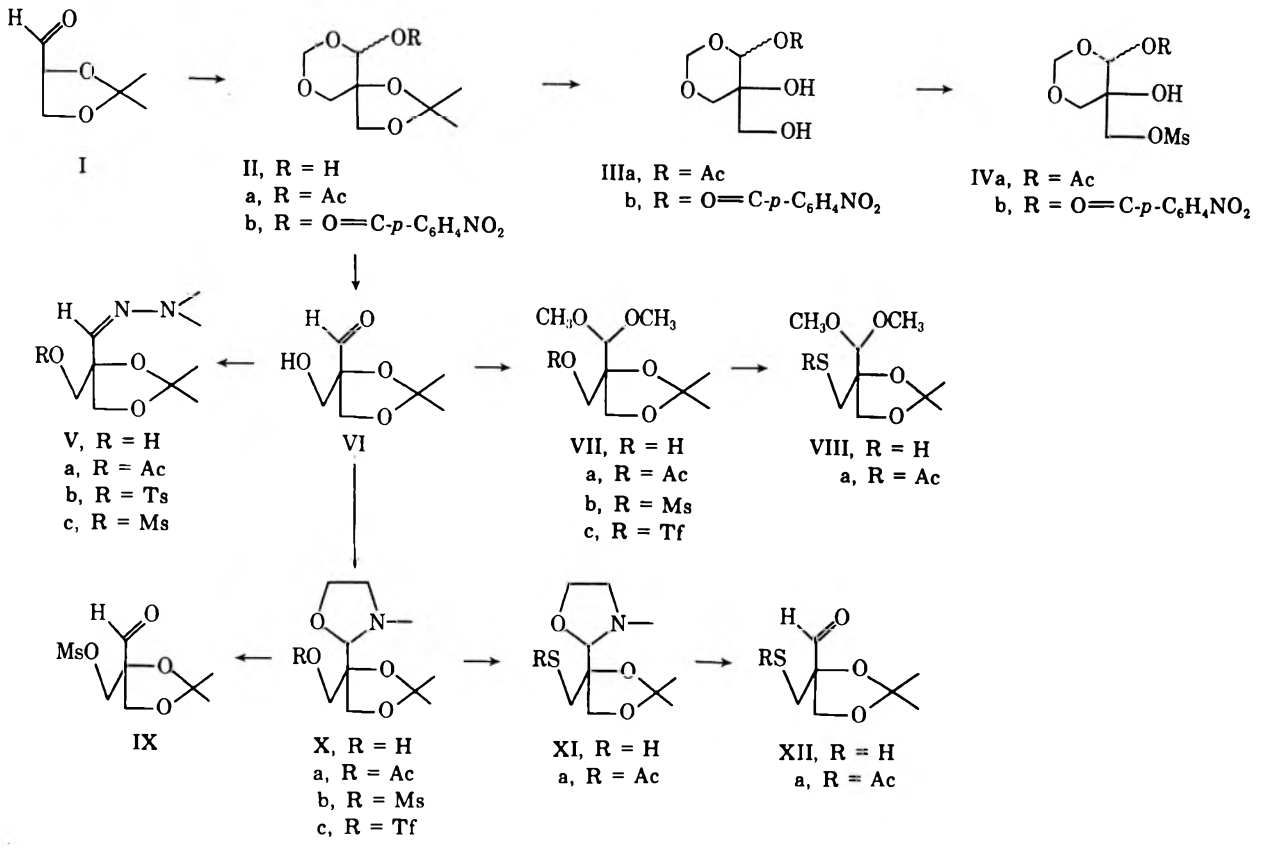

hyde function, before attempting to convert the hydroxy function to a good leaving group. The first derivative to be considered was a *N*,*N*-dimethylhydrazone. They are known to be hydrolyzed[6] rapidly by treatment with 95% ethanol, after quaternization with methyl iodide. The aldol VI was treated with dimethylhydrazine in ethanol and a 75% yield of V was obtained. It was easily converted to its acetate Va, tosylate Vb, and mesylate Vc. However, attempted displacement of the mesylate group with potassium thioacetate or sodium hydrogen sulfide gave intractable materials, presumably because of intramolecular cyclization. It was shown by an nmr study that the tosylate Vb decomposed on standing in methanol for a few hours. No attempts were made to isolate the products of the deterioration of this compound.

Next, the aldehyde was protected as its dimethyl acetal VII, which was obtained using carefully defined conditions in 60–65% yield. Compound VII was converted easily to its acetate VIIa, mesylate VIIb, and trifluoromethanesulfonate[7] VIIc. Displacement of the mesylate was accomplished by refluxing for several days with potassium thioacetate or sodium hydrogen sulfide in acetone or methanol. Displacement of the triflate group in VIIc could be carried out in a few hours, giving the pure thioacetate VIIIa. The thiol VIII could be obtained directly from the triflate VIIc by reaction with sodium hydrogen sulfide or by hydrolysis of the thioacetate VIIIa using sodium methoxide in methanol.

Further work on this approach was discontinued when it was realized that attempts to selectively hydrolyze the acetal function of VIII or VIIIa using the usual hydrolytic methods (80% acetic acid, 10% hydrochloric acid, 2% sulfuric acid, and 10% aqueous oxalic acid at room temperature) led to hydrolysis of both the acetonide and acetal groups. No selectivity was evident, and all the above-mentioned conditions led to polymerization products.

Transketalization is a very effective method in removal of ketals. However, only the starting material was recovered when VIIa was treated at room temperature with acetone and a trace of *p*-toluenesulfonic acid for prolonged periods of time. The reaction was followed by nmr using acetone-d_6 as solvent. Exchange of the acetonide function by a deuterioacetonide group was observed, but there was no change in the methoxy absorption.

Sjöberg[8] brought to our attention the possibility of using oxazolidines[9] as protecting groups for aldehydes. Treatment of the hydroxyaldehyde VI with *N*-methylethanolamine in diethyl ether afforded the oxazolidine X. Examination of the product using vpc analysis showed the existence of one major component and an impurity of approximately 10%. Distillation did not remove the impurity. Attempted purification on a silica column led to hydrolysis of the protecting group, but filtration through alumina, using benzene as eluent, afforded pure X in an overall yield of 55%. It could be converted to acetate Xa in quantitative yield. A study was made to determine the ease of hydrolysis of the oxazolidine. The hydrolysis of Xa was followed by nmr spectroscopy in 50% deuterium oxide and acetic acid-d_4. The reaction was complete in 15 min, as evidenced by the shift of the *N*-methyl absorption from 2.5 to 2.9 ppm. Xa could also be hydrolyzed in a two-

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phase system. The oxazolidine was dissolved in chloroform-*d* and to this solution was added a 50% solution of acetic acid-d_4 in D_2O. Following the disappearance of the *N*-methyl absorption in the nmr (owing to the solubility of *N*-methylethanolamine in the upper heavy-water phase), it was shown that the hydrolysis was complete in 1 hr at room temperature.

Alcohol X could be converted to its crystalline mesylate Xb in 80% yield, using methanesulfonyl chloride and triethylamine. Hydrolysis of the oxazolidine mesylate Xb gave the aldehyde mesylate IX.

Attempts to carry out a nucleophilic displacement on the mesylate IX with thiolate anions gave addition products onto the aldehyde, rather than displacement of the mesylate function. In order to increase the reactivity of the leaving group an attempt was made to prepare the triflate of alcohol X. When the reaction was carried out using trifluoromethanesulfonic anhydride in pyridine, a sulfonamide was obtained which was not further characterized. When an excess of triethylamine was used, triflate Xc could be obtained. It was, however, contaminated by sulfonamide, and since triflates are quite unstable no attempt was made to purify it.

Since all attempts to form a pure trifluoromethanesulfonate in the presence of an oxazolidine ring failed, work was continued using the mesylate Xb. It was converted to the thioacetate XIa by displacement using potassium thioacetate in refluxing acetone for 2–3 days. The aldehyde thioacetate XIIa was easily prepared by aqueous acetic acid hydrolysis.

An effort to hydrolyze XIIa to the thiol aldehyde XII using ammonia in methanol or a trace of sodium methoxide in methanol gave intractable mixtures from which no products could be isolated.

From this result, and the fact that aldehyde mesylate IX reacted with thiolate anions at the aldehyde function, it would appear that the thiol aldehyde XII cannot be isolated using normal laboratory procedures.

However, other compounds of type XII, where R is alkyl or vinyl, could be prepared. They will form the subject of another publication.

Experimental Section

Melting points were determined on a Gallenkamp block and are uncorrected. Mass spectra were obtained on an AE1-MS-902 mass spectrometer at 70 eV using a direct-insertion probe. Nmr spectra were recorded on a Varian T-60 spectrometer with tetramethylsilane as the internal standard. The multiplets and quartets in the nmr spectral data were recorded as the center of the peaks. Ir spectra were obtained on a Unicam SP1000 and a Perkin-Elmer 257 infrared spectrophotometer. Ultraviolet spectra were determined with a Unicam SP-800 spectrophotometer. Optical rotations were measured with a Perkin-Elmer 141 polarimeter.

Thin layer chromatography was performed on silica gel coated plates (Eastman). Woelm aluminum oxide (neutral) and silica gel were used for column chromatography. Microanalyses were carried out by A. Bernhardt, Mikroanalytisches Laboratorium, Elbach uber Engelskirchen, C. Daessle, Montreal, and F. Pascher, Bonn, West Germany.

Formaldehyde Adduct II.—Freshly distilled glyceraldehyde acetonide (18 g) was added to a stirred solution of 18 g (2 equiv) of anhydrous potassium carbonate, 50 ml of a 40% aqueous formaldehyde solution, 100 ml of distilled water, and 200 ml of methanol. The clear solution was stirred at room temperature overnight. The solution was concentrated *in vacuo* (bath temperature <40°). The crystalline mass (product and potassium carbonate) was extracted three times with 60-ml portions of methylene chloride. The solvent was dried with sodium sulfate, filtered, and evaporated to a clear oil which crystallized spontaneously when the last traces of solvent were removed under high vacuum. The colorless, crystalline compound was recrystallized from ether–methylene chloride mixtures. An analytical sample was prepared by sublimation [90° (0.2 mm)]: yield 20.8 g (80%); mp 89.5–91°; ir (KBr) 3400 (OH str), 1380, 1220, 1160, 1090, 1080, 1050, 1000 cm^{-1}; nmr ($CDCl_3$) δ 1.5 (s, 6), 3.9 [AB q, 2, J = 10 Hz, $CH_2OC(CH_3)_2$], 4.2 (AB q, 2, J = 10 Hz), 5.0 (AB q, 2, J = 7 Hz, $COCH_2O$), 5.1 (s, 1), 4.0–6.0 ppm (broad, 1, OH); mass spectrum (70 eV) *m/e* 190 (m^+).

Anal. Calcd for $C_8H_{14}O_5$: C, 50.52; H, 7.42. Found: C, 50.57; H, 7.52.

Acetate IIa.—The hydroxydioxane II was acetylated using pyridine and acetic anhydride: yield 89%; mp 30–31.5° (ether–carbon tetrachloride); ir (NaCl film) 1750 (C=O str), 1380, 1170–1280 (C–O str), 1120, 1080, 1010, 930 cm^{-1}; nmr (CCl_4) δ 1.3 (s, 6), 2.1 (s, 3, CH_3CO–), 3.7 (AB q, 2, J = 10 Hz), 3.9 (AB q, 2, J = 10 Hz), 4.8 (AB q, 2, J = 7 Hz), 5.65, 5.85 (double singlets, 1, CHOAc, two isomers); mass spectrum (70 eV) *m/e* 232 (M^+), 173 ($M^+ - OCOCH_3$).

Anal. Calcd for $C_{10}H_{16}O_6$: C, 51.72; H, 6.94. Found: C, 51.51; H, 6.98.

Hydrolysis of Acetonide Acetate IIa to Diol IIIa.—The acetate IIa (2.3 g, 10 mmol) was dissolved in 250 ml of 80% aqueous acetic acid and heated at 60° for 15 hr. The acetic acid was evaporated under high vacuum to half of the original volume, diluted with 125 ml of water, and extracted with three 100-ml portions of methylene chloride. The solvent was dried over sodium sulfate, filtered, and evaporated to yield 1.5 g of a light yellow oil. The oil crystallized only with difficulty (methanol–ether): yield 79%; mp 109–110.5°; ir (NaCl film) 3300–3500 (OH str), 1740 (C=O str), 1390, 1260, 1050 cm^{-1}; nmr (pyridine-d_5) δ 2.0 (s, 3), 4.2 (AB q, 2, J = 10 Hz), 4.3 (s, 2, CH_2OH), 4.8 (AB q, 2, J = 7 Hz), 5.6 ppm (double s, CHOAc, two isomers).

Anal. Calcd for $C_7H_{12}O_6$: C, 43.75; H, 6.29. Found: C, 43.97; H, 6.09.

Another method was used to hydrolyze the acetonide: 100 mg of the acetate IIa was dissolved in 1 ml of 90% aqueous trifluoroacetic acid and stirred at room temperature for 2 min. Flash evaporation under high vacuum and evaporation several times with methanol and toluene removed the last traces of acid. The resulting oil crystallized from a methanol and ether mixture, yield 66 mg (80%).

Preparation of *p*-Nitrobenzoate IIb.—The alcohol II (4.75 g) was dissolved in 25 ml of dry pyridine, and 5.2 g of recrystallized *p*-nitrobenzoyl chloride (from CCl_4) was added at once. The reaction mixture was stirred at 0° for 2 hr and at 25° for 12 hr. The precipitated mass was stored at −20° for 24 hr. Saturated sodium bicarbonate solution (30 ml) was added while the mixture was being ice cooled. Stirring was continued for 15 min and then the mixture was poured into 300 ml of ice-cold water. Rapid stirring was continued for 1 hr and then the precipitate was filtered, air dried, and recrystallized from chloroform: yield 7.0 g (82.5%); mp 228–229.5°; ir (KBr) 1740, 1610, 1540, 1360, 1270, 1100, 1060 cm^{-1}; nmr ($CDCl_3$) δ 1.6 (d, 6), 3.85 (AB q, 2, J = 10 Hz), 4.1 (s, 2), 5.1 (AB q, 2, J = 7 Hz, OCH_2O–), 6.3, 6.55 (double s, 1), 8.5 ppm (s, 4); mass spectrum (70 eV) *m/e* 339 (M^+). It was apparent from the nmr spectrum that the two epimers were in a ratio of 3:1.

Anal. Calcd for $C_{15}H_{17}NO_8$: C, 53.10; H, 5.05; N, 4.13. Found: C, 52.92; H, 4.01; N, 4.25.

Hydrolysis of Acetonide IIb to Diol IIIb.—The procedure for the hydrolysis of acetonide IIa using trifluoroacetic acid was used. From 300 mg of IIb and 2 ml of 90% aqueous trifluoroacetic acid, 227 mg (84%) of IIIb was obtained. It was crystallized from methanol: mp 122–124° (softens 115°); ir (NaCl film) 3400–3300, 1740, 1610, 1530, 1350, 1270, 1170, 1100, 1090, 1050, 880, 720 cm^{-1}; nmr (DMSO-d_6) δ 3.8 (s, 2, CH_2OH), 3.8–4.0 (broad singlet, 2, OH), 4.0 (AB q, 2, J = 10 Hz), 5.0 (AB q, 2, J = 7 Hz, OCH_2O), 6.1, 6.4 ppm (double singlet, 1, epimeric hydrogen α to *p*-NBz), 8.7 ppm (s, 4).

Anal. Calcd for $C_{12}H_{13}NO_8$: C, 43.75; H, 6.29; N, 4.68. Found: C, 43.97; H, 6.09; N, 4.79.

Preparation of the Mesylate IVb.—Mesylate IVb was prepared by treating IIIb with mesyl chloride in pyridine at 0°: yield from 2.99 g, 3.1 g (80%); mp 146–148° (methanol); ir (KBr) 3500, 1740, 1610, 1540, 1340 (SO_2 str), 1260, 1250, 1180, 1170, 830,

720 cm^{-1}; nmr (acetone-d_6) δ 3.13 (s, 3, OMs), 4.0 (AB q, 2, J = 10 Hz, OCH_2C), 4.5 (s, 2, CH_2OMs), 5.0 (AB q, 2, J = 7 Hz), 4.8–5.2 (broad, 1, OH), 6.2 ppm (s, 1, CHOBzN-p), 8.4 ppm (s, 4); mass spectrum (70 eV) m/e 281 ($M^+ - HOSO_2CH_3$).

Preparation of Hydroxyaldehyde VI.—The formaldehyde adduct II (16 g) was placed in a 35-ml round-bottom flask, and immersed in an oil bath at 140°. The crystalline material melted and a strong odor of formaldehyde was detected. Partial vacuum was applied, while the temperature of the bath was raised to 160°. An odorless, colorless oil distilled at 101–104° (0.7 mm), yield 10.4 g (77%). Runs of 20–25 g are recommended, as the product is unstable to heat and a rapid distillation is necessary, otherwise the yield of polymerized materials increases. The nmr showed the following peaks: δ 1.7 (s, 6, acetonide), 4.0 (AB q, 2, J = 8 Hz, CH_2OH), 3.9 (s, 1, OH), 4.25 (AB q, J = 10 Hz), and 10.4 ppm (s, 1, aldehyde). The ir (NaCl film) had a strong absorption at 3300–3500 cm^{-1} (hydroxyl) and a strong aldehyde absorption at 1735 cm^{-1}.

Upon standing for a few hours, the hydroxyaldehyde polymerized; thus reactions involving this intermediate must be carried out immediately.

***N,N*-Dimethylhydrazone V.**—Into a 50-ml, two-necked flask equipped with a reflux condenser, drying tube, and rubber septum was added 2–3 g of barium oxide and a solution of 2.1 ml (1.5 equiv) of 1,1-dimethylhydrazine (distilled twice over barium oxide) in 20 ml of absolute ethanol. To the cooled solution was added dropwise 2.9 g of aldehyde V dissolved in 10 ml of absolute ethanol. The addition was made over a period of 30 min. After the initial exothermic reaction had subsided the reaction mixture was refluxed for 1 hr. The cooled solution was filtered and evaporated to yield a light yellow oil. Yield after distillation was 2.7 g (75%); bp 98–99° (0.7 mm); ir (NaCl film) 3600–3300 (OH str), 2830, 2820, 2800 [$N(CH_3)_2$], 1600, 1480, 1460, 1370, 1260, 1220, 1070, 1050, 1030 cm^{-1}; nmr ($CDCl_3$) δ 1.5 (s, 6), 2.9 [s, 6, $N(CH_3)_2$], 3.5 (s, 1, OH), 3.7 (s, 2, CH_2OH), 4.1 ppm [s, 2, $CH_2OC(CH_3)_2$], 6.6 ppm (s, 1, HC=N); mass spectrum (70 eV) m/e 202 (M^+).

Anal. Calcd for $C_9H_{15}N_2O_3$: C, 53.44; H, 8.97; N, 13.85. Found: C, 53.63; H, 8.79; N, 13.34.

Preparation of the Acetate Va.—The acetate was prepared in the usual manner using acetic anhydride and pyridine. The yield of crude product was quantitative: ir (NaCl film) 2830, 2816, 2790 [$N(CH_3)_2$], 1740 (C=O str), 1600, 1460, 1450, 1380, 1370, 1250, 1050 cm^{-1}; nmr ($CDCl_3$) δ 1.45 (s, 6), 2.1 (s, 3), 2.8 (s, 6), 4.15 (AB q, 2, J = 9 Hz, CH_2OAc), 4.3 (s, 2), 6.6 ppm (s, 1).

Anal. Calcd for $C_{11}H_{20}N_2O_4$: C, 54.09; H, 8.14; N, 11.47. Found: C, 53.98; H, 8.01; N, 11.34.

Preparation of Dimethyl Acetal VII.—To 100 ml of absolute methanol (distilled over magnesium turnings) and 10 mg of p-toluenesulfonic acid was added 10 g of molecular sieves 3A and 1.6 g (10 mmol) of the aldehyde. The mixture was stirred (with exclusion of moisture) for 12–15 hr at room temperature. After neutralization of the acid with ion exchange resin [Rexyn 203 (OH)], filtration, evaporation and distillation, pure acetal was obtained in 60% yield (1.24 g): bp 100–102° (0.5 mm); ir (NaCl film) 3600–3300 (OH str), 1470, 1410, 1390, 1270, 1230, 1120, 1100, 1080 cm^{-1}; nmr ($CDCl_3$) δ 1.55 (s, 6), 3.4 (s, 1, OH), 3.65 [s, 6, $(OCH_3)_2$], 3.8 (s, 2, CH_2OH), 4.1 (AB q, 2, J = 6 Hz, CH_2OC), 4.5 [s, 1, $HC(OCH_3)_2$].

Anal. Calcd for $C_9H_{18}O_5$: C, 52.41; H, 8.80. Found: C, 52.31; H, 8.68.

Acetate VIIa.—The compound was prepared in a 95% yield from the alcohol, by means of pyridine and acetic anhydride. Evaporation of the reagents afforded analytically pure acetate: ir (NaCl film) 1745, 1460, 1390, 1380, 1250 (C–O str), 1120, 1090, 1060 cm^{-1}; nmr ($CDCl_3$) δ 1.7 (s, 6), 2.4 (s, 3), 3.85 (d, 6), 4.2 (AB q, 2, J = 8 Hz, CH_2OC), 4.5 (AB q, 2, J = 8 Hz, CH_2OAc), 4.55 ppm [s, 1, CH $(OCH_3)_2$].

Anal. Calcd for $C_{11}H_{20}O_6$: C, 53.21; H, 8.12. Found: C, 53.30; H, 7.94.

Mesylate VIIb.—This compound was prepared by the usual method with methanesulfonyl chloride and pyridine at 0°. After ether extraction, 85% yield of light yellow foam was obtained after the usual work-up procedure: nmr ($CDCl_3$) δ 1.45 (s, 6), 3.1 (s, 3, OMs), 3.6 (s, 6), 4.0 (AB q, 2, J = 10 Hz, CH_2OC), 4.3 [s, 1, HC $(OCH_3)_2$], 4.35 ppm (AB q, 2, J = 9 Hz, CH_2OMs).

Anal. Calcd for $C_{10}H_{20}O_7S$: C, 42.25; H, 7.04; S, 11.26. Found: C, 42.01; H, 7.15; S, 11.12.

Triflate VIIc.—The alcohol V (200 mg, 1 mmol) was dissolved in 3 ml of absolutely dry pyridine and the solution was cooled to −5° and protected from moisture by the use of a calcium chloride drying tube. Freshly prepared trifluoromethanesulfonic anhydride (850 mg, 5 equiv) (prepared[6] by flame distillation of the acid over phosphorus pentoxide, bp 85°) was added slowly to the cooled mixture. A color change from colorless to green to red was observed. The red solution was stirred for 5 min and immediately evaporated to dryness on a rotatory evaporator connected to a high vacuum pump (bath temperature must not exceed 35°). The deep red oil was dissolved in methylene chloride and washed with three portions of ice-cold water. The solvent was dried and evaporated to afford an orange-red oil (yield 85.5%, 290 mg). Because of the instability of the product no attempts were made at its purification. The ir spectrum showed no hydroxyl absorption and a large absorption band at 1420 and 1390 cm^{-1} (SO_2 str); nmr ($CDCl_3$) δ 1.5 (s, 6), 3.6 (s, 6) 4.1 [AB q, 2, J = 10 Hz, $CH_2OC(CH_3)_2$], 4.45 [s, 1, $CHC(OCH_3)_2$], 4.65 ppm (AB q, 2, J = 1 Hz, CH_2OTf).

Protection of Aldol VI using *N*-Methylethanolamine.—Anhydrous sodium carbonate (5 g) was suspended in an ice-cold solution of 1 g (1.1 equiv) of N-methylethanolamine in 30 ml of dry ether; 1.95 g of freshly prepared aldol, dissolved in 10 ml of anhydrous ether, was added dropwise over a period of 30 min. The mixture was stirred for an additional 30 min at 0° and then for 1 hr at room temperature. The filtered solution was evaporated and distilled [105–108° (0.75 mm)]. Crude yield was 2.1 g (80%). Vpc analysis (0.125 in. × 6 ft column of 3% OV-25 on 80–100 mesh Chromosorb W at 150° using a Hewlett-Packard Model 5750 B gas chromatograph) showed one major component (90%) and one minor component (10%). Filtration on an alumina (activity I) column using benzene as eluent afforded pure material (3 g of alumina for 1 g crude product). After purification a yield of 1.8 g of X (overall 55%) was obtained: ir (NaCl film) 3600–3300 (OH str), 2810 (NCH_3), 1470, 1380, 1260, 1225, 1150, 1080, 1070, 1050 cm^{-1}; nmr ($CDCl_3$) δ 1.45 (s, 6), 2.55, 2.60 (d, 3, NCH_3), 2.7 (m, 1, part of AA'BB' system of NCH_2-CH_2O), 3.3 (m, 1, NCH_2CH_2O), 4.0 ppm (m, 8, part of AA'BB' system, NCHO, two AB systems for CH_2OH and CH_2OC–, and OH); mass spectrum (70 eV) m/e 217 (M^+).

Anal. Calcd for $C_{10}H_{19}NO_4$: C, 55.28; H, 8.82; N, 6.45. Found: C, 55.16; H, 8.72; N, 6.25.

Acetate Xa.—The usual procedure was used to prepare the acetate in quantitative yield. The sample was analytically pure after evaporation of the reagents: ir (NaCl film) 2810 (NCH_3), 1745 (C=O str), 1460, 1380, 1270–1210 (C–O str), 1110, 1080, 1060 (cm^{-1}); nmr ($CDCl_3$) δ 1.5 (s, 6), 2.25 (s, 3, OAc), 2.55 (s, 3, NCH_3), 2.8 (m, 1), 3.3 (m, 1), 4.2 ppm (m, 7).

Anal. Calcd for $C_{12}H_{21}NO_5$: C, 56.02; H, 7.44; N, 5.44. Found: C, 56.28; H, 7.39; N, 5.24.

Mesylate Oxazolidine Xb.—To a solution of 217 mg (1 mmol) of the alcohol in 10 ml of methylene chloride containing 220 μl (1.5 mmol) of triethylamine at −10 to 0° was added 84 μl (1.1 mmol) of methanesulfonyl chloride over a period of 30 min. Anhydrous reaction conditions were maintained. Stirring from an additional 15–30 min completed the reaction. The mixture was transferred to a separatory funnel with the aid of more methylene chloride. The mixture was washed with ice water. Drying of the organic phase followed by solvent removal gave an oil. The oil was crystallized from methylene chloride–ether: yield 242 mg (82%); mp 79.5–81°; tlc R_f 0.6 (ether, SiO_2); ir (CCl_4 solution) 2810 (N-CH_3 str), 1470, 1380 (OMs), 1220, 1180, 1080, 1010 cm^{-1}; nmr ($CDCl_3$) δ 1.5 (s, 6), 2.6 (s, 3, NCH_3), 2.7 (m, 1), 3.2 (s, 3, OMs), 3.3 (m, 1), 3.8–4.6 ppm (m, 7).

Anal. Calcd for $C_{11}H_{21}NO_6S$: C, 44.75; H, 7.12; N, 4.75; S, 10.85. Found: C, 44.63; H, 7.18; N, 4.66; S, 10.63.

Displacement of Mesylate Xb using Potassium Thioacetate.—To a solution of 295 mg (1 mmol) of the mesylate in 20 ml of dry acetone was suspended 171 mg (1.5 mmol) of recrystallized potassium thioacetate. The mixture was refluxed, under a nitrogen atmosphere, for 3 days. Filtration of the cooled solution and evaporation of the acetone gave a pale yellow oil. The oil was dissolved in methylene chloride and washed with ice water. Drying of the organic layer and evaporation afforded 264 mg (96% of theory) of a pale yellow semicrystalline oil (XIa). The sample was analytically pure: nmr ($CDCl_3$) δ 1.5 (double singlet, 6), 2.4 (s, 3, SAc), 2.55 (s, 3, NCH_3), 2.7 (m, 1), 3.2 (m, 1), 3.35 (s, 2, CH_2SAc), 4.0 [AB q, 2, J = 10 Hz, $CH_2OC(CH_3)_2$], 4.0 ppm (s, 1).

Anal. Calcd for $C_{12}H_{21}NO_4S$: C, 52.36; H, 7.64; N, 5.09; S, 11.64. Found: C, 52.11; H, 7.53; N, 4.95; S, 11.22.

Hydrolysis of Thioacetate Oxazolidine XIa to Thioacetate XIIa.—The compound (57 mg) was treated with 10 ml of a 1:1 mixture of acetic acid and water for 15–30 min at room temperature. The aqueous solution was extracted with three portions of methylene chloride and the combined extracts were dried and evaporated first on a rotatory evaporator (water aspirator) and then on a high vacuum line, to remove the last traces of acetic acid. In this way, 41 mg (91% yield) of analytically pure XIIa was obtained: nmr ($CDCl_3$) δ 1.45, 1.5 (double singlet, 6), 2.45 (s, 3, SAc), 3.3 (s, 2, CH_2SAc), 4.1 (AB q, 2, J = 10 Hz, CH_2OC), 10 ppm (s, 1, CHO).

Anal. Calcd for $C_9H_{14}O_4S$: C, 49.54; H, 6.42; S, 14.68. Found: C, 49.41; H, 6.34; S, 14.48.

Registry No.—I, 5736-03-8; II, 38615-71-3; IIa, 38615-72-4; IIb, 38615-73-5; IIIa, 38615-74-6; IIIb, 38615-75-7; IVb, 38615-76-8; V, 38615-77-9; Va, 38615-78-0; VI, 38615-79-1; VII, 38615-80-4; VIIa, 38615-81-5; VIIb, 38615-82-6; VIIc, 38615-83-7; X, 38615-84-8; Xa, 38615-85-9; Xb, 38615-86-0; XIa, 38615-87-1; XIIa, 38615-88-2; 1,1-dimethylhydrazine, 57-14-7; trifluoromethanesulfonic anhydride 358-23-6; *N*-methylethanolamine, 109-83-1.

Relative Reactivities of Nucleophilic Centers in Some Monopeptides

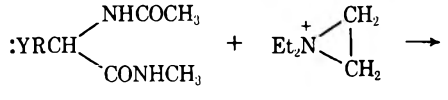
CHARLES C. PRICE,* HIROSHI AKIMOTO,[1] AND RICHARD HO[1]

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104

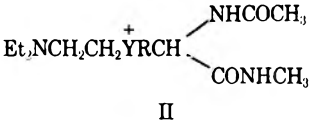
Received October 10, 1972

The "monopeptide" derivatives of a number of amino acids with nucleophilic centers have been prepared and their reactivity in water to diethylaziridinium ion, iodoacetic acid, and iodoacetamide determined. The reactivity of the imidazole ring of histidine, the mercaptan group of cysteine, the phenolate ion in tyrosine, and the sulfide group in methionine are all very nearly the same as that of these groups in model compounds. The sulfide group shows unexpectedly high reactivity when measured by iodoacetic acid or iodoacetamide.

As a sequel to studies of the effect of structure and conformation of nucleic acids on the reactivity of nucleophilic centers to alkylation,[2] we have now undertaken a similar investigation for proteins. As a prelude to study of the reactivity of nucleophilic centers in polypeptides, we have examined the nucleophilicity of some of the more significant nucleophilic centers in model "monopeptides," the *N*-acetylmethylamide derivatives of several amino acids. The alkylating agent used most generally has been the one utilized most extensively in the earlier nucleic acid studies, *N*,*N*-diethylaziridinium ion.



I



II

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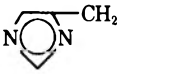
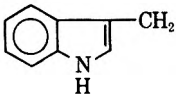
b, :YR = $HSCH_2$

c, :YR = $CH_3SCH_2CH_2$



d, :YR =



e, :YR =

f, :YR = $HSCH_2CH_2$

Experimental Section

Materials.—*N*,*N*-Diethyl-2-chloroethylamine hydrochloride (Aldrich) was recrystallized from acetonitrile.

The monopeptides Ia, Ic, Id, and Ie were prepared from the corresponding amino acids essentially as described in the literature.[3a-c] Ib was prepared from the corresponding cystine derivative by zinc and acid reduction.[3d]

L-Homocysteine monopeptide (If) was prepared in much the same way as Ib. After addition of 1.56 g of thionyl chloride dropwise with stirring to a chilled suspension of 3.20 g of L-homocystine in 30 ml of absolute methanol, the reaction mixture was heated under reflux for 2 hr. After cooling, the solvent was removed *in vacuo* to give 4.4 g (theoretical yield) of colorless solid, L-homocystine dimethyl ester hydrochloride, which was used directly in the next step. This material and 5.35 g of triethylamine in 50 ml of $CHCl_3$ was chilled and 2.12 g of acetyl chloride was added dropwise with stirring. The reaction mixture was allowed to stand for 1 hr at room temperature and then washed and dried. After removal of the solvent, the crude product was recrystallized from ethyl acetate to give 4.3 g (94%) of *N*,*N*′-diacetyl-L-homocystine dimethyl ester as colorless needles, mp 105–106°, ir (Nujol) ν_{NH} 3800, ν_{CO} 1770, 1670 cm^{-1}.

Anal. Calcd for $C_{14}H_{24}O_6N_2S_2$: C, 44.19; H, 6.36; N, 7.36; S, 16.85. Found: C, 44.07; H, 6.48; N, 7.39; S, 16.58.

After 3 days at room temperature, a solution of 3.8 g of this dimethyl ester in 40 ml of 40% aqueous methylamine was concentrated to dryness *in vacuo* to afford the desired compound in theoretical yield. The crude product was recrystallized from methanol to give 3.2 g (85%) of pure *N*,*N*′-diacetyl-L-homocystinmethylamide as colorless prisms, mp 188–189°, ir (Nujol) ν_{NH} 3350, ν_{CO} 1645, 1560, 1545 cm^{-1}.

Anal. Calcd for $C_{14}H_{26}O_4N_4S_2$: C, 44.42; H, 6.92; N, 14.80; S, 16.94. Found: C, 44.31; H, 6.86; N, 14.91; S, 16.76.

After 400 mg of zinc dust was added to 757 mg of this disulfide dissolved in 30 ml of 2 *N* aqueous acetic acid, 300 mg of concentrated sulfuric acid was dropped slowly into the stirred mixture over 15 min under nitrogen. The exothermic reaction raised the temperature to 35–40°. After this reaction mixture was warmed at 45–50° for 2 hr, it was concentrated to dryness *in vacuo*. The residue was extracted with three 25-ml portions of warm isopropyl ether, and the combined extract was evaporated *in vacuo* to give 670 mg (88%) of crude product. It was recrystallized from isopropyl ether under nitrogen atmosphere to yield 625 mg of *N*-acetyl-L-homocysteinmethylamide (If) as colorless prisms, mp 192–195°, ir (Nujol) ν_{NH} 3350, ν_{SH} 2600, ν_{CO} 1650 (sh), 1645, 1565, 1545 cm^{-1}.

Anal. Calcd for $C_7H_{14}O_2N_2S$: C, 44.19; H, 7.42; N, 14.72; S, 16.85. Found: C, 44.33; H, 7.71; N, 14.64; S, 16.81.

(1) Supported in part by NIH Grant No. NIGMS 19593.

(2) (a) C. C. Price, G. M. Gaucher, P. Koneru, R. Shibakawa, J. R. Sowa, and M. Yamaguchi, *Biochim. Biophys. Acta*, **166**, 327 (1968); (b) C. C. Price and M. T. L. Yip, in press; (c) Mei-Tak Lam Yip, "The Nitrogen Mustard Alkylation of Polynucleotides and Ribonucleic Acids," Ph.D. Dissertation, University of Pennsylvania, 1972.

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Alkylated *N*-Acetyl-L-homocysteinmethylamide (IIf).—A solution of 475 mg of If in 25 ml of distilled water was added to the cyclic imonium ion solution prepared from 645 mg of *N,N*-diethyl-2-chloroethylamine hydrochloride in 25 ml of distilled water as described below in the method of alkylation. The reaction mixture was maintained at pH 7.0 and 37° for 24 hr under nitrogen and concentrated to dryness on a warm bath under reduced pressure. The residue was extracted with three 30-ml portions of methanol and, after evaporation of the solvent, the resulting residue was chromatographed on both silica gel and alumina successively, using chloroform–methanol as an eluent. The white solid obtained was recrystallized from ether–*n*-hexane to give 452 mg (63%) of cotton-like, colorless needles: mp 91–92°; ir (Nujol) ν_{NH} 3410, ν_{CO} 1650, 1575, 1550 cm^{-1}; nmr ($CDCl_3$) τ 2.70 (broad, 1 H), 2.82 (broad, 1 H), 5.34 (q, 1 H), 7.35 (s, 3 H), 7.00–7.60 (m, 10 H), 7.90 (t, 2 H), 8.00 (s, 3 H), 8.98 (t, 6 H).

Anal. Calcd for $C_{13}H_{29}O_2N_3S$: C, 53.95; H, 9.40; N, 14.52; S, 11.08. Found: C, 53.77; H, 9.55; N, 14.32; S, 10.83.

Alkylated L-homocysteine was obtained from 289 mg of IIf by dissolving in 5 ml of 6 *N* aqueous hydrochloric acid and heating on an oil bath (110–120°) for 15 hr. After evaporation of solvent *in vacuo*, the resulting residue was redissolved in a minimum amount of distilled water and chromatographed on an ion-exchange resin (25 ml of Dowex 50W-*X*8), using distilled water and 2.5% aqueous ammonium hydroxide as eluents, successively, to eliminate chloride ion. The ninhydrin-positive fractions, eluted by 2.5% aqueous ammonium hydroxide, were collected and evaporated to dryness *in vacuo* to yield a pale yellow solid, which was triturated with ether to give 165 mg (71%) of the desired amino acid: mp 210–215° dec; ir (Nujol) $\nu_{NH_3^+}$ 3000, ~2100, $\nu_{CO_2^-}$ 1640 (sh), 1590, 1550 cm^{-1}; nmr (D_2O) τ 6.50 (broad t, 1 H), 6.95 (q, 4 H), 6.75–7.40 (m, 8 H), 8.60 (t, 6 H).

Anal. Calcd for $C_{10}H_{22}O_2N_2S$: C, 51.25; H, 9.46; N, 11.95; S, 13.68. Found: C, 51.35; H, 9.24; N, 11.57; S, 13.39.

Alkylated *N*-Acetyl-L-histidinmethylamide (IId).—A solution of 1.056 g of *N*-acetyl-L-histidinmethylamide (Id) in 100 ml of distilled water was added to the aziridinium solution prepared from 0.860 g of *N,N*-diethyl-2-chloroethylamine hydrochloride in 20 ml of distilled water as described below. The reaction mixture was maintained at pH 7.0 and at 37° for 48 hr, concentrated to dryness on a warm bath under reduced pressure, and extracted with three 50-ml portions of methanol. After evaporation *in vacuo* to dryness, the resulting residue was chromatographed on silical gel, using 15% methanol in chloroform as an eluent, to give 708 mg (46%) of colorless, oily semisolid, which was recrystallized from benzene–*n*-hexane–ether to yield colorless needles having mp 128–129°. Our data do not indicate unequivocally whether the product is 1- or 3-alkylated *N*-acetyl-L-histidinmethylamide (IId): ir (Nujol) ν_{NH} 3400, ν_{CO} 1645, 1650 (sh), 1575, 1555 cm^{-1} (sh); nmr ($CDCl_3$) τ 2.60 (s, 1 H), 3.22 (s, 1 H), 5.42 (m, 1 H), 5.99 (d, 2 H), 6.12 (t, 2 H), 7.02 (d, 2 H), 7.29 (d, 3 H), 7.50 (q, 4 H), 7.50 (t, 2 H), 8.01 (s or d, 3 H), 9.40 (t, 6 H).

Anal. Calcd for $C_{15}H_{27}O_2N_5$: C, 58.23; H, 8.80; N, 22.63. Found: C, 57.77; H, 8.50; N, 22.59.

Alkylated *N*-Acetyl-L-tyrosinmethylamide (IIa).—A solution of 2.36 g of *N*-acetyl-L-tyrosinmethylamide (Ia) in 236 ml of distilled water was added to the aziridinium solution prepared from 8.61 g of *N,N*-diethyl-β-chloroethylamine hydrochloride in 150 ml of distilled water as described previously. After incubation at pH 7.0 and at 37° for 48 hr, the reaction mixture was concentrated to one-third volume on a warm bath under reduced pressure, acidified with concentrated hydrochloric acid, and then extracted with five 50-ml portions of ethyl acetate. The extracts were washed, dried, and evaporated *in vacuo* to dryness to give 1.05 g (45%) of the starting material. The aqueous layer was made alkaline with concentrated aqueous NaOH and extracted with five 50-ml portions of ethyl acetate. The combined extract was washed with 5% aqueous NaOH and saturated NaCl, dried over magnesium sulfate, and then evaporated *in vacuo* to dryness to afford 1.45 g of oily product, which rapidly solidified on trituration with *n*-hexane. The solid (630 mg) so obtained was collected and washed with *n*-hexane, then chromatographed on silica gel, using 20% methanol in chloroform as an eluent, to give the desired alkylated tyrosine monopeptide in a yield of 9.3% (320 mg), accompanied by a small amount of starting material and *N,N*-diethylethanolamine. The crude product was recrystallized from benzene–*n*-hexane–ether to give colorless needles: mp 140–141°; ir (Nujol) $\nu_{NH,OH}$ 3400, ν_{CO} 1655, 1550, 1525 cm^{-1}; nmr ($CDCl_3$) τ 2.98 (d, 2 H), 3.20 (d, 2 H), 5.34 (m, 1 H), 6.00 (t, 2 H), 7.02 (d, 2 H), 7.14 (t, 2 H), 7.32 (s, 3 H), 7.34 (q, 4 H), 8.04 (s, 3 H), 8.90 (t, 6 H).

Anal. Calcd for $C_{18}H_{29}O_3N_3$: C, 64.45; H, 8.71; N, 12.53. Found: C, 64.17; H, 8.92; N, 12.52.

Alkylated *N*-Acetyl-L-cysteinmethylamide (IIb).—A solution of 352 mg of *N*-acetyl-L-cysteinmethylamide (Ib) in 20 ml of distilled water was added to the aziridinium solution prepared from 516 mg of *N,N*-diethyl-2-chloroethylamine hydrochloride in 20 ml of distilled water as described previously. The reaction mixture was maintained at pH 7.0 and 37° for 24 hr under nitrogen, and concentrated to dryness on a warm bath under reduced pressure. The resulting residue was extracted with three 25-ml portions of methanol, and, after evaporation of the combined extracts, the residue was chromatographed on both silica gel and alumina, successively, using chloroform–methanol (9:1) as an eluent, to afford 486 mg (88%) of white solid, which was recrystallized from a mixture of benzene–*n*-hexane–ether to give colorless needles: mp 124–126°; ir (Nujol) ν_{NH} 3360, ν_{CO} 1645, 1570, 1545 cm^{-1}; nmr ($CDCl_3$) τ 2.50 (broad d, 1 H), 3.02 (broad, 1 H), 5.50 (m, 1 H), 7.00–7.50 (m, 6 H), 7.34 (s, 3 H), 7.43 (q, 4 H), 8.00 (s, 3 H), 8.99 (t, 6 H).

Anal. Calcd for $C_{12}H_{23}O_2N_3S$: C, 52.32; H, 9.17; N, 15.26; S, 11.64. Found: C, 52.30; H, 9.15; N, 15.13; S, 11.81.

Alkylation Rates.—A 0.1 *M* solution of *N,N*-diethyl-2-chloroethylamine hydrochloride in distilled water was adjusted to pH 10.0, allowed to stand at 0° for 30 min, and then returned to pH 7.0. A 10.0-ml aliquot of this approximately 0.1 *M* aziridinium solution was added to 20.0 ml of 0.01 *M* monopeptide in distilled water. The reaction mixture was maintained at pH 7.0 and 37° usually for 48 hr. The extent of reaction was measured by selective colorimetry appropriate for each monopeptide, as described below.

Estimation of the cyclic imonium ion was carried out on 10.0 ml of *ca.* 0.1 *M* aziridinium solution added to 20.0 ml of distilled water and maintained at pH 7.0 and 37° for 48 hr. Then 10.0 ml of 0.1 *M* sodium thiosulfate was added to a 6.0-ml aliquot of this solution. After standing at room temperature for 3 hr, the excess thiosulfate was titrated by 0.1 *M* iodine solution using a starch indicator; the amount of the remaining aziridinium ion was 70.2% based on *N,N*-diethyl-2-chloroethylamine hydrochloride used, while at zero time, 88.8% of the original hydrochloride was found to be converted to aziridinium ion. From these data, the second-order rate constant for hydrolysis (k_w) is estimated as $k_w^{37} = 2.45 \times 10^{-8}$ l. mol^{-1} sec^{-1}. This is in good agreement with the value of $k_w^{45} = 3.0 \times 10^{-8}$ l. mol^{-1} sec^{-1} reported earlier.[1a]

Competition Factor for Histidine Monopeptide (Id).—Aliquots (1.0 ml) of the reaction mixture, prepared from 0.1 *M* cyclic imonium ion solution and 0.01 *M* histidine monopeptide solution, were taken at specified intervals and measured up to 100 ml by addition of distilled water. To 20.0 ml of this diluted reaction mixture was added 10.0 ml of 10% aqueous sodium carbonate and 5.0 ml of freshly prepared diazotized reagent, which was made from the same volumes of 0.5% sulfanilic acid in 3.5% aqueous hydrochloric acid and 5.0% aqueous sodium nitrite solution.[4] After 10 min at room temperature, the absorbancies of the solution and the control were measured at 490 mμ against a reagent blank. The results are summarized in Table I. From these

TABLE I
REACTION OF 0.0067 *M* HISTIDINE MONOPEPTIDE WITH 0.0295 *M* DIETHYLAZIRIDINIUM ION AT 37°, pH 7

t, min	240	550	1000	1350	1900	2880
% Alkylation	8.8	17.0	27.5	34.5	42.0	52.3

data, the second-order rate constant, k_a, for alkylation is estimated to be 2.35×10^{-4} l. mol^{-1} sec^{-1} and the competition factor k_a/k_w to be 9.6×10^3.

Competition Factor for Tyrosine Monopeptide (Ia).—After 48 hr, 5.0-ml aliquots of the reaction mixture, prepared from 0.1 *M* cyclic imonium ion solution and 0.01 *M* tyrosine monopeptide, were diluted to 100 ml by addition of 0.05 *N* aqueous sodium hydroxide solution. The optical densities of this solution and the control solution were measured at 295 mμ to be 0.678 and 0.710, respectively. From these values, the percentage of the alkylated tyrosine monopeptide was calculated to be 4.4%, giving

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a value for k_a of 1.0×10^{-5} l. mol^{-1} sec^{-1} and for the competition factor k_a/k_w of 400.

Competition Factor for Ionized Tyrosine Monopeptide.—The alkylations of the tyrosine monopeptide at pH 8.0 and 9.0 were carried out in the same way as described above. The rate constants for aziridinium ion hydrolysis (k_w) at both pH 8.0 and 9.0 were determined by the sodium thiosulfate–iodine method as described previously. Furthermore, using the value of the dissociation constant for tyrosine itself ($K = 4.0 \times 10^{-11}$),[5] the second-order rate constant for the phenolate ion was calculated from the data at pH 9 to be $k_a = 2.2 \times 10^{-3}$ l. mol^{-1} sec^{-1}, giving the competition factor $k_a/k_w = 7 \times 10^4$ (Table II).

TABLE II

REACTION OF 0.0067 *M* TYROSINE MONOPEPTIDE WITH 0.0295 *M* DIETHYLAZIRIDINIUM ION (37°, 48 HR)

	pH 7.0	pH 8.0	pH 9.0
% Alkylation	4.4	5.5	57.7
Rate constant k_w ($\times 10^8$)	2.45	2.76	3.15
Apparent k_a ($\times 10^5$)	1.0	1.15	9.5
Apparent competition factor	400	420	3200

Competition Factor for Cysteine Monopeptide (Ib).—A 1.0-ml aliquot of the reaction mixture prepared from aziridinium ion and cysteine monopeptide as described previously was taken periodically and diluted with distilled water up to 100 ml. A 1.0-ml aliquot of this diluted reaction mixture, and 0.02 ml of 5,5′-dithiobis(2-nitrobenzoic acid) solution, which was prepared from 19.8 mg of 5,5′-dithiobis(2-nitrobenzoic acid) and 5.0 ml of pH 7.0, 0.1 *M* phosphate buffer, were added to 2.0 ml of pH 8.0, 0.05 *M* phosphate buffer solution in a photometer cell.[6] After rapid color development, the adsorbancy at 412 mμ was measured against a reagent blank at each time. The data are summarized in Table III.

TABLE III

REACTION OF 0.0067 *M* CYSTEINE MONOPEPTIDE WITH 0.0295 *M* DIETHYLAZIRIDINIUM ION AT 37°, pH 7.0

t, min	50	150	330	645	1230	1890	2880
% Alkylation	8.0	19.9	30.0	38.5	56.9	70.2	81.5

From these data, the rate constant is estimated as $k_a = 1.0 \times 10^{-3}$ l. mol^{-1} sec^{-1} and the competition factor as $k_a/k_w = 4.2 \times 10^4$.

Competition Factor for Methionine Monopeptide (Ic).—A 5.0-ml aliquot of the reaction mixture, prepared from aziridinium solution and methionine monopeptide solution as described previously, was added after 24 hr to a mixture of 10.0 ml of distilled water and 20.0 ml of 0.2% aqueous pentacyanoaminoferrate ammonium disodium salt.[7] After 1 min at room temperature, 2.0 ml of glacial acetic acid and then 1.0 ml of 10% aqueous sodium nitrite were added to the above mixture. The optical densities of the reaction mixture and the control, read at 515 mμ against a reagent blank within 30 min, were 0.305 and 0.395, respectively. From these values, the percentage of the alkylated methionine monopeptide was calculated to be 23%, the second-order rate constant k_a to be 5.9×10^{-5} l. mol^{-1} sec^{-1}, and the competition factor to be $k_a/k_w = 2400$.

Analysis of Methionine Monopeptide Alkylation by Amino Acid Analyzer.—As the direct isolation of the alkylated methionine monopeptide was very difficult, the hydrolyzed products of the alkylated methionine monopeptide were measured and identified by amino acid analyzer, as proposed by Gundlach.[8a] A 1.0-ml aliquot of the above reaction mixture was oxidized with performic acid and, after lyophilization, hydrolyzed with 5.0 ml of 6 *N* aqueous hydrochloric acid by heating on an oil bath at 115–120° for 24 hr. After evaporation of hydrochloric acid *in vacuo*, and suitable dilution for amino acid analyzer with distilled water, the sample solution was analyzed and determined to contain 9.8% of methionine sulfoxide, 78.1% of methionine sulfone, 7.6% of homoserine, 1.2% of homoserine lactone, 2.3% of methionine, and 1.2% of the alkylated homocysteine (IIc).[8b] The peaks were identified by comparison with authentic samples. The formation of methione sulfoxide must arise from the alkylated methione monopeptide, since only methionine sulfone and *no* sulfoxide was observed when methione monopeptide was treated in the same way.

Alkylations of Cystine and Tryptophan Monopeptides.—Although the alkylations of both cystine monopeptide (IIa) and tryptophan monopeptide (IId) were undertaken in exactly the same procedure as described above, no detectable alkylation of either monopeptide was observed. The fluorescein–mercuric acetate method was used[9] for cystine monopeptide and the *p*-dimethylaminobenzaldehyde method[10] for tryptophan monopeptide. Furthermore, no alkylated monopeptides were isolated from the reaction mixtures, and only starting materials were recovered in almost theoretical yields (*ca.* 99%).

Alkylation of Histidine Monopeptide and Methionine Monopeptide with Iodoacetic Acid.—The alkylations of the monopeptides with iodoacetic acid were carried out in exactly the same way as for the aziridinium ion. The extent of reaction was estimated at each period by colorimetric methods, the sulfanilic acid method for the histidine monopeptide and the pentacyanoaminoferrate method for the methionine monopeptide. The data obtained are summarized in Table IV.

Alkylations of pyridine, imidazole, and diethyl sulfide (0.0067 *M*) by aziridinium ion (0.0295 *M*) were measured at pH 7.0 and 37° by determining unreacted aziridinium ion by reaction with excess 0.1 *M* thiosulfate, followed by titration of unreacted thiosulfate with 0.01 *M* iodine. After 48 hr, pyridine was 55% alkylated (C. F. = 1.2×10^4), imidazole 62% (C. F. = 1.3×10^4), and diethyl sulfide 25% (C. F. = 2.6×10^3). The results are included in Table V.

Alkylations of the above three nucleophiles under the same conditions with iodoacetic acid were monitored by measurement of iodide liberated. The iodide from 5.0-ml aliquots was converted to iodine, extracted by chloroform, and diluted to 10 ml and the optical density was read at 510 mμ. Imidazole was 3.0% alkylated in 1 hr, 29% in 17 hr; pyridine 9.0% in 1 hr, 28.8% in 3 hr; diethyl sulfide 36% in 1 hr, 50.5% in 2 hr. Values for k_a and k_a/k_w calculated from these data are included in Table V.

The solvolysis rate constant, k_w, for 0.0333 *M* iodoacetamide was measured at pH 7.0 and 37°. After 48 hr, iodide liberated indicated 2.69% reaction, corresponding to $k_w = 2.9 \times 10^{-9}$ l. mol^{-1} sec^{-1}, exactly the same as for iodoacetic acid.

Alkylation by iodoacetamide was carried out as for iodoacetic acid. Imidazole was 6.6% alkylated in 4 hr, 20.8% in 17 hr; pyridine 13.1% in 3 hr, 32.2% in 12 hr; diethyl sulfide 12.1% in 1 hr, 28% in 3 hr; histidine monopeptide 2.3% in 3 hr, 14% in 24 hr; methione monopeptide 7.9% in 1 hr, 24.8% in 3 hr.

The Competition Factors for Sodium Thiosulfate with Iodoacetic Acid and Iodoacetamide.—As the reaction of sodium thiosulfate with iodoacetic acid or iodoacetamide was too fast to be measurable by the usual iodine methods described previously, the reaction was quenched by an excess amount of iodine solution and the remaining iodine was then back-titrated with standard sodium thiosulfate. Solutions of 0.1 *M* alkylating agent and 0.01 *M* sodium thiosulfate were held at pH 7.0 and 37° for 30 min. After quick addition of 2.0 ml of 0.01 *M* sodium thiosulfate solution to 1.0 ml of the alkylating agent, the mixture was allowed to react for a specified time and then quenched by quick addition of 3.0 ml of iodine solution with stirring. The remaining iodine was back-titrated by sodium thiosulfate. The thiosulfate was 66% alkylated in 1 min with iodoacetic acid, 45% with iodoacetamide. Values for k_a and k_a/k_w are included in Table V.

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(10) D. Kupfer, *Anal. Biochem.*, **8**, 75 (1964).

TABLE IV

REACTION OF 0.0067 *M* HISTIDINE AND METHIONINE MONOPEPTIDES WITH 0.0333 *M* IODOACETIC ACID AT 37°

t, min	60	120	240	360	1080	1650	2880
Histidine							
% Alkylation			4.9		19.0	28.2	44.5
C. F. ($\times 10^{-4}$)[a]			3.8		3.8	3.8	4.0
Methionine							
% Alkylation	22.2	38.8	54.2	69.0	82.4		
C. F. ($\times 10^{-5}$)[a]	7.8	8.0	6.7				

[a] The second-order rate constant for hydrolysis of iodoacetic acid was measured by iodometry to be $k_w = 2.9 \times 10^{-9}$ l. mol^{-1} sec^{-1}

TABLE V

SECOND-ORDER RATE CONSTANTS k_a (AND COMPETITION FACTORS k_a/k_w) FOR REACTION OF VARIOUS NUCLEOPHILES WITH DIETHYLAZIRIDINIUM ION, IODOACETIC ACID, AND IODOACETAMIDE AT pH 7 AND 37° IN WATER

Registry no.	Nucleophile	Az	IAcONa	Iodoacetamide
14383-50-7	$S_2O_3^{2-}$	0.13[a]	0.55	0.29
		(5.3×10^6)[b]	(1.9×10^8)	(1.0×10^8)
288-32-4	Imidazole	3.2×10^{-4}	2.5×10^{-4}	1.5×10^{-4}
		(1.3×10^4)	(8.5×10^4)	(5.0×10^4)
	Histidine monopeptide	2.4×10^{-4}	1.1×10^{-4}	5.5×10^{-5}
		(9.6×10^3)	(3.8×10^4)	(1.9×10^4)
110-86-1	Pyridine	3.0×10^{-4}	1.0×10^{-3}	3.8×10^{-4}
		(1.2×10^4)	(3.4×10^5)	(1.3×10^5)
	Methionine monopeptide	5.9×10^{-5}	2.3×10^{-3}	7.2×10^{-4}
		(2.4×10^3)	(8.0×10^5)	(2.5×10^5)
352-93-2	Diethyl sulfide	6.4×10^{-6}	4.3×10^{-3}	1.0×10^{-3}
		(2.6×10^3)	(1.5×10^6)	(3.5×10^5)
	Cysteine monopeptide	1.0×10^{-3}		
		(4.2×10^4)		
	Tyrosine monopeptide	1.0×10^{-5}		
		(400)		
38616-08-9	Anion (pH 9)	2.2×10^{-3}		
		(7.0×10^4)		
7732-18-5	Water (k_w)	2.45×10^{-8}	2.9×10^{-9}	2.9×10^{-9}

[a] Estimated graphically from the data in ref 1; k_a in l. mol^{-1} sec^{-1}. [b] The nucleophilic constant n used by others[11-13] is log (competition factor).

Discussion

There have been many efforts made to correlate relative reactivities in SN2 nucleophilic substitutions.[11-14] Most of these published data and correlations rate the nucleophilicities of various nucleophiles in the same relative order and are in general agreement with our values for diethylaziridinium ion as alkylating agent. The most extensive listing, especially with many nucleophiles analogous to those we have studied, is for methyl iodide in ethanol.[12] The authors indicate that their nucleophilic constants are 1.4 times those of Swain and Scott,[11] which are very close to those for aziridinium and sulfonium compound.[15] Our values for imidazole (n = log k_a/k_w = 4.1), pyridine (4.1), diethyl sulfide (3.4), phenolate ion (4.8), and thiosulfate (6.7) are all reasonably close to the adjusted values of Pearson,[12] 3.55, 3.7, 3.8, 4.1, and 6.4, respectively.

It was thus a considerable surprise to find that the relative order of imidazole (a "hard" base[12]) and diethyl sulfide (a "soft" base[12]) were markedly altered on going to iodoacetic acid or iodoacetamide as alkylating agent. The sulfide group of methionine changes from about fivefold lower reactivity with aziridinium ion to about 20-fold greater reactivity with the iodoacetate alkylating agents. Thus, selection for alkylation of histidine units would be favored with aziridinium-type alkylating agents, while selection for methionine would be favored by iodoacetic acid or iodoacetamide. We are currently investigating a variety of alkylating agents to explore the structural features contributing to this reversal of order. Incidentally, none of the many general equations developed for relating nucleophilicities at sp^3 carbon accommodates such a reversal.

Examination of the results summarized in Table V clearly indicates the very remarkable reactivity of thiosulfate as a nucleophile in substitution at sp^3 carbon. This is in marked contrast to its very low reactivity as a nucleophile in reactions at sp^2 carbon, such as in attack on an ester carbonyl.[16] This dramatic reversal, and the failure to observe the "α effect" so prominent in attack at sp^2 carbon[16] in substitution at sp^3 carbon,[17] clearly support markedly different factors influencing nucleophilicity in attack at sp^3 and sp^2 carbon.

Another feature of the data in Table V is that much of the difference in competition factor, and therefore the nucleophilic constant n, for the nucleophiles studied arises from the difference in the rate of reaction with

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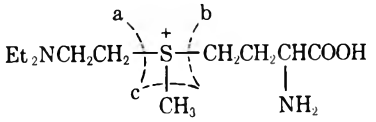
water. For example, the tenfold difference in competition factor for imidazole–aziridinium ion *vs.* imidazole–iodoacetate arises from the nearly tenfold difference in k_w for the alkylating agents. It is thus a serious question whether it is, in this case, more revealing to compare k_a's or competition factors. Since there is no compelling reason, other than convenience and custom, to pick water as the reference nucleophile, it is not the absolute magnitude of the nucleophilic constants which is significant but their relative order. Thus the significant change in relative rates for "hard" and "soft" nucleophiles with the iodoacetate alkylating agents, like the marked change in relative order for the thiosulfate ion in nucleophilic attack at sp^2 *vs.* sp^3 carbon, must signal major changes in the factors affecting the transition states involved.

The alkylation of methionine monopeptide provided a difficult problem in isolating the reaction product. The primary product is a sulfonium salt. This product can then undergo hydrolytic cleavage at each of the three C–S^+ bonds to regenerate methionine or to form homoserine (or its lactone) or alkylated homocysteine.[8,18] Our data indicate that the cleavage conditions we used favored removal of the diethylamino group (a, 12.1%) followed by the amino acid residue (b, 8.6%) and least of all the methyl group (c, 1.2%), or a:b:c 55:40:5, respectively. This ratio, which involves the assumption that the methionine sulfoxide measured by amino acid analyzer must have arisen from IIc, is supported by the fact that the sum of the



IIc

cleavage products observed (21.9%) is in good agreement with the extent of alkylation measured indirectly by colorimetry (23%).

Registry No.—Ia, 6367-14-2; Ib, 10061-65-1; Ic, 29744-03-4; Id, 6367-11-9; Ie, 6367-17-5; If, 38615-99-5; IIa, 38616-00-1; IIb, 38616-01-2; IId, 38616-02-3; IIf, 38616-03-4; L-homocystine, 626-72-2; L-homocystine dimethyl ester hydrochloride, 38616-04-5; *N,N'*-diacetyl-L-homocystine dimethyl ester, 38616-05-6; *N,N'*-diacetyl-L-homocystinmethylamide, 38616-06-7; alkylated L-homocysteine, 38616-07-8; diethylaziridinium ion, 18899-07-5; iodoacetic acid, 64-69-7; iodoacetamide, 144-48-9.

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Carbon-13 Magnetic Resonance Spectroscopy of Steroids. Estra-1,3,5(10)-trienes[1]

THOMAS A. WITTSTRUCK* AND KENNETH I. H. WILLIAMS

The Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts 01545

Received October 16, 1972

The natural abundance carbon-13 magnetic resonance spectra of estra-1,3,5(10)-triene and 17 derivatives are reported. Substituent effects upon the chemical shifts of each carbon atom are determined and discussed in terms of factors known to influence ^{13}C chemical shifts.

With the advent of instrumentation for the determination of high-resolution nuclear magnetic resonance spectra of ^{13}C in natural abundance, a number of papers have appeared describing its application to the structural elucidation of natural products. The techniques of ^{13}C magnetic resonance spectroscopy appear to promise to have as great an impact upon such studies as did the techniques of proton magnetic resonance in the last decade. Just as steroids provided model compounds from which much was learned with regard to the relationship between the observed nmr parameters (chemical shifts and spin–spin coupling constants) and molecular structure in proton spectroscopy,[2] so too this class of compounds, because of their well-defined structures, promises to aid in relating the ^{13}C magnetic resonance parameters to molecular structure.

In 1969, Reich, *et al.*, published the first extensive ^{13}C investigation of steroids, examining chiefly the spectra of cholestane derivatives.[3] These authors indicated that in general carbon resonances are far more informative than proton resonances for structural analysis of steroids.

Since we have available to us a large number of steroids of verified structure, incorporating a variety of the common functional groups, we have initiated a study of the carbon-13 magnetic resonance spectra of steroids. It is hoped that through these studies the nature of substituent effects upon ^{13}C chemical shifts may be better understood. In the present paper, the ^{13}C spectra of a number of derivatives of estra-1,3,5(10)-triene are reported, together with correlations of chemical shifts with carbon atoms of the steroids. Substituent effects upon the chemical shifts of the aromatic carbon of ring A are discussed, as well as a preliminary report of substituent effects upon the atoms of the nonaromatic portion of the molecule. A fuller discussion of these latter substituent effects will be presented in a later paper.

Experimental Section

The steroids used in this study, all known compounds, are listed in Table I. They were dissolved in dioxane, whose ^{13}C signal was used as the internal lock signal. Concentrations of steroids ranged from about 0.06 *M* to about 0.35 *M*. Three milliliters of solution was used in each case for the analysis, and was contained in a 12-mm o.d. sample tube. The tube was spun at 18 rps during the analysis, which was performed at room temperature.

Spectra were obtained at 25.1 MHz using a Varian Associates HA-100-15 spectrometer, together with a Varian Associates

(1) Supported by The Public Health Service, Research Grants No. GM16928 and AM13582.

(2) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964.

(3) H. J. Reich, M. Jautelat, M. T. Messe, F. J. Weigert, and J. D. Roberts, *J. Amer. Chem. Soc.*, **91**, 7445 (1969).

TABLE I
STEROIDS INVESTIGATED

Compd no.	Compd
I	Estra-1,3,5(10)-triene
II	3-Hydroxyestra-1,3,5(10)-triene
III	17β-Hydroxyestra-1,3,5(10)-triene
IV	Estra-1,3,5(10)-trien-17-one
V	3,17β-Dihydroxyestra-1,3,5(10)-triene
VI	3-Hydroxyestra-1,3,5(10)-trien-17-one
VII	3,17α-Dihydroxyestra-1,3,5(10)-triene
VIII	17β-Acetoxyestra-1,3,5(10)-triene
IX	3,17β-Diacetoxyestra-1,3,5(10)-triene
X	3,17α-Diacetoxyestra-1,3,5(10)-triene
XI	3-Acetoxyestra-1,3,5(10)-trien-17-one
XII	3-Iodo-17β-acetoxyestra-1,3,5(10)-triene
XIII	3-Methoxy-17β-hydroxyestra-1,3,5(10)-triene
XIV	3-Methoxyestra-1,3,5(10)-trien-17-one
XV	3-Methoxy-16β-hydroxyestra-1,3,5(10)-triene
XVI	3-Methoxyestra-1,3,5(10)-trien-16-one
XVII	3-Methoxy-16α,17α-dihydroxyestra-1,3,5(10)-triene
XVIII	3-Hydroxyestra-1,3,5(10)-trien-16,17-dione

V-3530 ^{13}C wide sweep accessory and a Varian Associates C-1024 time averaging computer. In addition, a Varian Associates V-3512 heteronuclear decoupler was used to provide both continuous wave and incoherent proton decoupled spectra.

The ^{13}C chemical shifts of steroids extend over a range of about 225 ppm. For this reason the spectra were obtained in segments. The segment occurring at lowest field contains peaks for carbonyl carbons (*ca.* 220–218 ppm downfield from TMS). The second segment contains the peaks for aromatic carbons and olefinic carbons when present, and extends from about 160 to 110 ppm.

The third segment contains peaks for carbinol carbons, in the vicinity of 80 ppm, while the fourth segment, extending from about 55 to 10 ppm, contains the peaks for the remaining nonfunctionalized carbon atoms of the steroid. The second and fourth segment were investigated for each compound, the others only when functional groups were present which indicated a need for their investigation.

Each segment was initially scanned over a range of 1500 Hz, at a sweep rate of 30 Hz/sec. The number of scans required to obtain a spectrum is primarily a function of concentration of steroid in solution, and ranged from about 100 to 1600 scans. In most cases relevant portions of each segment were then rescanned at slower sweep rates (*ca.* 10 Hz/sec) using narrower sweep widths (*e.g.*, 500 Hz). In this manner sufficient resolution was obtained for most steroids studied here to completely characterize each peak. In only a few instances did it prove impossible to resolve peaks for different carbon atoms.

The chemical shifts were measured in hertz from the lock signal (dioxane) and when feasible also from the peak for internal TMS. They are reported in parts per million downfield from TMS = 0 and are presented in Table II.

Results and Discussion

The unsubstituted estra-1,3,5(10)-triene (I) may be regarded as the parent of the steroids used in this study. Four steroids containing only one substituent each, as well as a number containing two substituents each, were available. By comparisons of the spectra of the steroids differing by only one substituent and an estimate of anticipated substituent effects, peak assignments could be made for each of the carbon atoms in a given steroid. As illustrative of the approach used in making peak assignments, the interpretation of the spectrum of I is described.

The initial assignments for the carbon atoms of the aromatic ring may be made by comparing the spectrum of I with that of 3-hydroxyestra-1,3,5(10)-triene (II). The peaks for the aromatic carbons of II are shifted relative to those of I by the influence of the

TABLE II
^{13}C CHEMICAL SHIFTS OF AROMATIC STEROIDS[a]

C	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV	XV	XVI	XVII	XVIII
1	125.96	126.88	126.12	126.31	126.90	126.90	127.17	126.19	127.02	126.91	127.07	128.51	126.69	127.32	126.95	126.53	126.81	126.91
2	126.22	113.40	126.44	126.69	113.51	113.45	113.71	126.43	119.56	119.52	119.68	135.55	112.02	112.49	112.34	112.25	112.26	113.81
3	126.22	155.59	126.44	126.69	155.64	155.76	155.73	126.43	149.78	149.76	149.90	91.63	158.26	158.92	158.70	158.71	158.44	156.06
4	129.73	115.76	129.76	129.86	115.92	115.86	116.05	129.72	122.33	122.28	122.44	138.57	114.25	114.74	114.57	114.49	114.37	115.98
5	137.40	138.42	137.50	137.49	138.43	138.20	138.66	137.35	138.46*	138.45*	138.25	140.36	138.10	138.43	138.60	138.22	138.29	138.20
6	39.48*	39.94*	39.69	39.06	39.78	39.33	40.13	39.27	39.14	39.49	38.93	38.90	39.80	39.36	39.78	39.08	39.90	38.31
7	26.87	27.25	26.98	27.33	27.10	27.41	27.05	28.21*	27.82*	28.49	27.07	27.62	27.12	27.30	27.03	27.05	28.98*	27.43
8	29.95	30.10	30.23	30.04	30.18	30.19	30.37	30.14	30.05	30.06	30.02	29.55	30.38	30.26	30.34	30.35	30.54	29.96
9	45.12	44.64	45.53	45.43	44.79	44.95	44.59	45.23	44.92	44.55	45.05	44.81	44.87	45.00	44.71	44.73	44.59	44.45
10	141.47	132.44	141.39	141.10	132.28	131.92	132.64	141.19	138.64*	138.70*	139.01	141.02	133.14	133.18	133.57	133.04	133.37	131.50
11	28.56	28.67	28.18	26.31	28.01	26.44	28.92	26.71	26.74	26.57	26.53	26.41	28.09	26.57	28.71	28.91	26.54*	26.23
12	40.89	40.96	37.88	32.56	37.61	32.51	33.14	37.71	37.70	32.64	32.48	37.57	37.57	32.43	40.98	39.08	35.94	31.64
13	41.44	41.47	44.08	48.37	43.88	48.33	46.22	43.66	43.66	45.57	48.23	43.54	43.90	48.32	39.41	39.86	46.26	48.71
14	54.19	54.05	51.25	51.26	50.77	51.11	48.39	50.64	51.66	49.96	52.02	50.54	50.90	51.10	52.22	51.34	47.10	43.20
15	25.54	25.56	23.90	22.16	23.66	22.17	24.88	23.88	23.79	24.82	22.14	23.76	23.74	22.04	37.53	39.08	17.65	36.09
16	20.88	20.90	31.25	35.93	30.99	35.86	32.36	28.09*	28.18*	30.48	35.85	28.16	31.17	35.87	71.31			204.58
17	39.24*	39.31*	81.86	218.92	81.93	219.28	79.70		82.96	82.22		83.07		219.08	53.73	56.15		204.58
18	17.56	17.64	11.61	13.92	11.47	13.92	17.53	12.46	12.35	16.77	13.84	12.37	11.55	13.76	19.27	18.27	9.72	13.73
								20.82[b]	20.78[b]	20.70[b]	20.70[b]	20.60[b]	55.13[c]	55.28[c]	55.05[c]	55.25[c]	55.20[c]	

[a] In parts per million, downfield relative to internal TMS; solvent dioxane; uncertainty ±0.05 ppm; assignments for signals marked with an asterisk are not certain; omitted values were not observed. [b] $-OCOC^*H_3$. [c] $-OCH_3$.

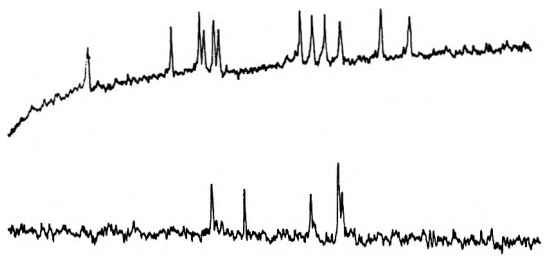


Figure 1.—Incoherent-noise decoupled spectrum of estra-1,3,5(10)-triene. Upper portion, aliphatic region (64.04–4.20 ppm downfield from TMS); lower portion, aromatic region (163.57–103.80 ppm downfield from TMS). The dip on the low-field side of the upper portion results from the proximity of the lock signal, dioxane.

phenolic hydroxyl at carbon-3. In order to estimate the substituent effect of this OH, use was made of phenolic shielding effects reported in the lieterature for a number of simpler molecules.

Comparison of the spectra of *m*- and *p*-cresol with that of toluene shows that the greatest substituent effect from the hydroxyl is observed for the carbon atom bearing this function. The signal for this carbon is shifted downfield 26.7 ppm in *m*-cresol and 27. 2 ppm in *p*-cresol from the value observed for toluene.[4-6] In both cresols the carbon atoms ortho to the OH are shielded by *ca.* 12.8 ppm, while the meta carbons are deshielded by 1–2 ppm and the para carbon is shielded by *ca.* 6.9 ppm.

The incoherent-noise decoupled spectrum of I, reproduced in Figure 1, is illustrative of the spectra obtained in this study. The aromatic segment of the spectrum consists of five peaks, one of which obviously results from the overlap of two unresolved peaks from two different carbon atoms. When the continuous wave decoupled spectrum of this region is obtained it is observed that the two lowest field peaks remain as singlets, whereas the others appear as doublets. Hence these two peaks (at 137.40 and 141.47 ppm) arise from the quaternary carbon atoms of ring A, namely, C-5 and C-10.

In similar fashion it was shown that for II the quaternary carbons give signals at 132.44 and 138.42 ppm. In II, carbon-5 is meta to the phenolic OH at carbon-3 and is expected to be deshielded in comparison to I, whereas carbon-10, which is para to the phenolic OH, is expected to be shielded relative to I. The only assignments consistent with this predicted behavior are those shown in Table II; *i.e.*, for I, δ (carbon-5) 137.40, δ (carbon-10) 141.47, and, for II, δ (carbon-5) 138.42 (deshielded 1.02 ppm), δ (carbon-10) 132.44 ppm (shielded 9.03 ppm).

The peak at 155.59 ppm in the spectrum of II must be assigned to carbon-3, since it is the only peak in this spectrum which is greatly displaced from those in the spectrum of I.

Carbon-1 of II is meta to the phenolic OH at carbon-3 and should be deshielded in comparison to I. The peak at 126.88 ppm of II is assigned to carbon-1, since it is the only unassigned peak of II which is downfield from any of the unassigned peaks of I. As a corollary to this assignment, carbon-1 of I must be assigned to either the peak at 125.96 or one of the overlapping peaks at 126.22 ppm. The peaks at 113.40 and 115.76 ppm of II must then arise from the carbon atoms ortho to the phenolic OH. Both of these carbons are symmetrically disposed with respect to carbon-9, but not with respect to carbon-6. From the data for *m*-cresol it is seen that the signal for the carbon atom between the phenolic and methyl functions occurs further downfield by about 2.4 ppm than that para to the methyl. Thus it seems reasonable to assign the peak at 115.76 ppm of II to carbon-4 and that at 113.40 ppm to carbon-2.

If a tentative assignment of the peak at 125.96 ppm of I is made for carbon-1, it is reasonable to assign one of the peaks at 126.22 ppm to carbon-2 and that at 129.73 ppm to carbon-4. The other of the unresolved peaks at 126.22 ppm of I is then assigned to carbon-3.

In order to corroborate these assignments, the spectra of 17β-hydroxyestra-1,3,5(10)-triene (III) and of 3,17β-dihydroxyestra-1,3,5(10)-triene (V) were compared, as well as those of estra-1,3,5(10)-trien-17-one (IV) and 3-hydroxyestra-1,3,5(10)-trien-17-one (VI). The aromatic segments of the spectra of III and IV are analogous to that of I, while those of V and VI are analogous to that of II, indicating that the effect of the substituent at carbon-17 is of minor importance to the chemical shifts of the aromatic ring A carbons (however, see below). The spectrum of VI has been reported by Reich, *et al.*,[3] and our assignments for VI agree with those obtained by these authors.

Assignments of peaks for the nonaromatic carbon atoms is perhaps best illustrated by reference to Figure 2, in which the appropriate spectral regions of I and III are schematically compared, followed by a comparison of I and II. The continuous wave decoupled spectrum of I shows a quartet centered at 17.56 ppm, which must arise from a methyl group, and is thus assigned to carbon-18. A similar quartet appears in the continuous wave decoupled spectrum of III, at 11.61 ppm. The peak at 41.44 ppm of I was the only peak remaining as a singlet in the continuous wave spectrum of this compound and is thus assigned to the quaternary atom, carbon-13, as, for the same reason, is the peak at 44.08 ppm in the spectrum of III.

By comparing the structures of I and III it is seen that the remaining unassigned carbon atoms may be classified into those expected to be relatively unperturbed by substitution at carbon-17, and those which might be expected to experience a greater effect from that substituent. In the former category are carbon-6, -7, and -9, and perhaps carbon-8 and -11. All other carbons are within three bonds of the substituent at carbon-17.

Using Figure 2, each unassigned peak of I is successively paired with one of the unassigned peaks of III, noting the difference in chemical shifts, $\Delta\delta$, between the pairs. These values of $\Delta\delta$ are the "substituent effects" of the 17β-OH. By this process it is seen that, at most, only six sets of peaks might possibly qualify as being relatively unperturbed by the substituent at carbon-17 of III ($\Delta\delta$ approximately 1 ppm or less). The sets, together with their values of $\Delta\delta$, are (those from III listed first) 45.53–45.12 (0.41), 39.69–39.48 (0.21), 39.69–39.24 (0.45), 30.23–29.95

(4) P. C. Lauterbur, *J. Amer. Chem. Soc.*, **83**, 1838, 1846 (1961).
(5) W. R. Woolfenden and D. M. Grant, *ibid.*, **88**, 1496 (1966).
(6) T. D. Alger, D. M. Grant, and E. G. Paul, *ibid.*, **88**, 5897 (1966).

(0.28), 28.18–28.56 (−0.38), and 26.98–26.87 (−0.11). Any other pairings result in larger values of $\Delta\delta$.

Because of the magnetic anisotropy of the aromatic ring A, it is to be expected that the signal for carbon-9 would be further downfield than that for carbon-8 or -11, while the signal for carbon-6 would be further downfield than that for carbon-7. In ethylbenzene, for instance, the methylene carbon signal occurs 13.5 ppm further downfield than the methyl carbon signal.[7] Furthermore, the secondary or tertiary nature of the carbon under consideration should influence its chemical shift. Thus, for example, the benzylic carbon signal of 2-phenylpropane occurs 5.5 ppm further downfield than the benzylic carbon signal of ethylbenzene.[7] By analogy, it would be expected that the signal from carbon-9 should occur further downfield than that from carbon-6. The signals at 45.12 ppm of I and at 45.53 of III are thus assigned to carbon-9, and the signals at 39.48 or 39.24 ppm of I and 39.69 of III are assigned to carbon-6.

Having made assignments for the benzylic carbons, tentative assignments may be made for carbon-7, -8, and -11, by analogy with ethylbenzene and 2-phenylpropane. The signal for the tertiary carbon-8 should occur further downfield than that for the secondary carbon-11. The signal at 26.87 ppm of I cannot belong to carbon-8, since it is the furthest upfield of the signals as yet unassigned. It must therefore arise from either carbon-7 or -11. The signal for the carbon atom β to the aromatic ring in ethylbenzene occurs 13.5 ppm to higher field than does the signal for the carbon α to the ring. In 2-phenylpropane these same signals are separated by 10.3 ppm.[7] Hence the signal at 26.87 ppm of I is assigned to carbon-7, since the difference between the chemical shift values for this signal and either of those to be assigned to carbon-6 is *ca.* 12.5 ppm. In contrast, had this peak been assigned to carbon-11, the difference between the signal at 26.87 ppm and that assigned to carbon-9 would be 18.25 ppm.

Assignments for carbon-8 and -11 are then made on the following basis. The signal at 29.95 ppm of I is assigned to the tertiary carbon-8, whose signal should occur at lower field than that for the secondary carbon-11, which is assigned the signal at 28.56 ppm.

Assignments for the signals of those carbon atoms of III categorized above as being most influenced by the effect of the substituent at carbon-17 were accomplished by comparing the spectrum of III with that of 19-nortestosterone, whose assignments were established by Reich, *et al.*[3] To a first approximation it may be assumed that the presence of the aromatic ring A in III will not significantly alter the chemical shifts of carbon-12, -14, -15, -16, and -17 (*i.e.*, those carbon atoms of III whose signals remain to be assigned) from the values observed in the spectrum of 19-nortestosterone. On this basis the signal at 81.86 ppm of III is assigned to carbon-17, the signal at 51.25 ppm of III to carbon-14, the signal at 37.88 ppm to carbon-12, the signal at 31.25 ppm to carbon-16, and that at 23.90 ppm to carbon-15. In general, the assumption used here appears to be valid, since the signals for carbon-12 and -16 occur at almost the same chemical shift values in III as in 19-nortestosterone. The signal for carbon-15 is shifted to slightly higher field in III, while

(7) G. B. Savitsky and K. Namikawa, *J. Phys. Chem.*, **67**, 2430 (1963).

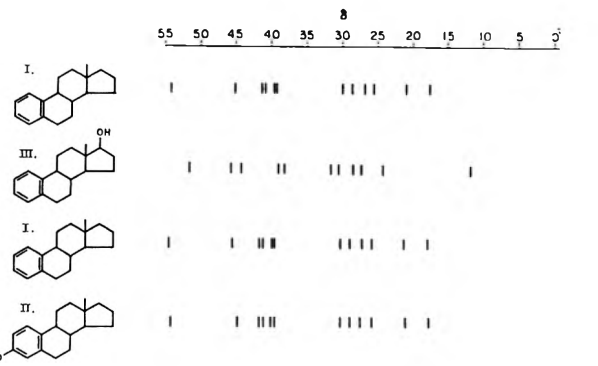


Figure 2.—Aliphatic regions of the ^{13}C spectra of compounds I, II, and III. The scale is parts per million downfield from internal TMS.

that for carbon-14 occurs about 1 ppm further downfield in III than in 19-nortestosterone.

Having made these assignments for III, the corresponding assignments for I may be attempted. This necessitates some knowledge of the effect of the 17β-hydroxy upon the chemical shifts, so that the spectra of I and III may be compared. According to Roberts, *et al.*, the effect of the hydroxyl in cyclopentanol, as compared to cyclopentane, is to shift the peak for the α carbon 48.0 ppm downfield, the peak for the β carbons 9.7 ppm downfield, and the peak for the γ carbons 1.9 ppm upfield.[8] In the present case, carbon-17 is the α carbon, carbon-13, and -16 are the β carbons, and carbon-12, -14, -15, and -18 are the γ carbons. The signals for carbon-13 and -18 have already been assigned, leaving six signals for I to be assigned. From Figure 2 it is obvious that the signal at 54.19 ppm of I must be assigned to carbon-14, and that at 25.54 ppm to carbon-15, since both of these signals should experience upfield shifts in going from I to III. This leaves four signals, at 40.89, 39.48, 39.24, and 20.28 ppm, in the spectrum of I to assign to carbons-6, -12, -16, and -17. Since carbon-16 is β to the hydroxyl at carbon-17 its signal should shift downfield in analogy with the β-carbon shift of cyclopentanol. From Figure 2 it is seen that the only assignment which will allow a downfield shift for the signal of carbon-16, once the above assignments have been made, is to assign the signal at 20.88 ppm of I to carbon-16.

Assignments of the remaining three signals (for carbon-6, -12, and -17) are tenuous, but since in general signals for carbon atoms in five-membered rings occur at higher field than those in six-membered rings, and since both carbon-12 and carbon-17 of I are methylene carbons symmetrically disposed with respect to carbon-13, the signal at 40.89 ppm of I is assigned to carbon-12. The signals for carbon-6 and -17 of I are not assigned with certainty.

Remaining assignments for II were made by comparison of its spectrum with that of I.

By a process comparable to the above, assignments were made for IV, using the comparison with the spectrum of 19-norandrostene-3,17-dione of Reich, *et al.*,[3] as well as the carbonyl substituents effects found in cyclopentanes.[9] The assignments for V and VI were made by comparing their spectra with those of III

(8) J. D. Roberts, F. J. Weigert, J. I. Kroschwitz, and H. J. Reich, *J. Amer. Chem. Soc.*, **92**, 1338 (1970).

(9) F. J. Weigert and J. D. Roberts, *ibid.*, **92**, 1347 (1970).

and IV, respectively. The spectrum of VII was assigned by comparison to those of II and V.

The spectrum of VIII was assigned by comparison with those of I and III, with the aid of the effects of the acetate function upon cyclopentyl chemical shifts reported by Christl, *et al.*[10] The spectra of IX, X, and XI were analyzed by comparison with that of VIII, and a knowledge of the acetate effect upon the chemical shifts of aromatic carbons.[11] The effect of the iodo substituent, needed for the interpretation of the spectrum of XII, was obtained from the paper of Lauterbur.[12] The interpretations of the spectra of XIII and XIV, both of which contain 3-methoxy substituents, were made in comparison with those of III and IV, using the methoxy substituent effect upon aromatic carbon chemical shifts reported by Maciel and Natterstad.[11]

Substituent Effects.—The substituent effects for carbon-13 magnetic resonance chemical shifts deduced for this study are presented in Table III. The uncertainty in these values is ±0.10 ppm. A number of these substituent effects are labeled "directly evaluated," meaning that they were obtained by subtraction of chemical shifts for compounds differing by a single substituent. For instance, the 17β-OH effects were obtained by subtracting chemical shifts for I from those for III, or of II from V. Other substituent effects listed in Table III were obtained by making use of these directly evaluated substituent effects to predict the spectrum of some compound *not* investigated here, whose values were then subtracted from those of a compound which was available. The substituent effects for 16-keto, 16β-OH, 16α,17α-di-OH, and 17α-OAc were evaluated in this manner.

In a few cases the substituent effect could be directly evaluated by subtraction of chemical shifts for I from those of a steroid bearing only the substituent of interest. For instance, the 3-OH effect can be directly evaluated from II − I. When these values are compared with those for the same substituent obtained by subtraction of chemical shifts of a monosubstituted steroid from those of a disubstituted steroid (*e.g.*, V − III, or VI − IV) it is seen that agreement is generally good, although small, but puzzling, discrepancies do occur. For example, the 3-OH effect upon the chemical shift of carbon-5 of VI appears to be 0.31 ppm less than that observed in II, which is outside the uncertainty limits of ±0.10 ppm. Similar small discrepancies are observed for the substituent effects at other carbons, and for other substituent effects. Whether this observation implies that the presence of a second, remote substituent has an influence upon the effect of the first must await the determination of substituent effects to a greater accuracy than observed here.

Ring A Substituents.—The effects of substituents upon the chemical shifts of carbon atoms in aromatic rings have been the topic of a number of investigations. The largest variations in Δδ have been found for the carbon bearing the substituent. This reflects the influence of inductive and resonance effects of the substituent on the electronic environment of this carbon, as well as purely magnetic effects of the substituent.[11]

(10) M. Christl, H. J. Reich, and J. D. Roberts, *J. Amer. Chem. Soc.*, **93**, 3463 (1971).
(11) G. E. Maciel and J. J. Natterstad, *J. Chem. Phys.*, **42**, 2427 (1965).
(12) P. C. Lauterbur, *ibid.*, **38**, 1606 (1963).

TABLE III
SUBSTITUENT EFFECTS[a]

C	3-OH[b] II–I	3-OH[b] V–III	3-OH[b] VI–IV	17β-OH[b] III–I	17β-OH[b] V–II	17α-OH[b] VII–II	16β-OH	16α,17α-diOH	17β-OAc[b] VIII–I	3-OAc[b] XI–IV	3-OAc[b] IX–VIII	17α-OAc	3-I XII–VIII	3-OMe[b] XIII–III	3-OMe[b] XIV–IV	17-Keto[b] IV–I	17-Keto[b] VI–II	16-Keto	16,17-diketo[b] XVIII–II
1	0.92	0.78	0.59	−0.16	0.02	0.29	0.10	−0.04	0.13	0.76	0.83	1.02	2.32	0.57	1.01	0.35	0.02	−0.30	0.03
2	−12.82	−12.93	−13.24	0.22	0.11	0.31	0.54	0.46	0.21	−7.01	−6.87	0.17	9.12	−14.42	−14.20	0.47	0.05	0.45	0.41
3	29.37	29.20	29.07	0.22	0.05	0.14	0.66	0.43	0.21	23.21	23.35	0.19	−34.80	31.82	32.23	0.47	0.17	0.67	0.47
4	−13.97	−13.84	−14.00	0.03	0.16	0.29	0.35	0.25	−0.01	−7.42	−7.39	−0.06	8.85	−15.51	−15.12	0.13	0.10	0.23	0.22
5	1.02	0.93	0.71	0.10	0.01	0.24	0.60	0.29	−0.05	0.76	1.11	−0.06	3.01	0.60	0.94	0.09	−0.22	0.22	−0.22
6	0.46	0.09	0.27	0.21	−0.16	0.19	0.19	0.31	−0.21	−0.13	−0.13	0.14	−0.37	0.11	−0.30	−0.42	−0.61	−0.50	−1.63
7	0.38	0.12	0.08	0.11	−0.15	−0.20	0.02	1.97	1.34	−0.26	−0.39	2.01	−0.59	0.14	−0.03	0.46	0.16	0.04	0.18
8	0.15	−0.05	0.15	0.28	0.08	0.27	0.24	0.44	0.19	−0.02	−0.09	0.20	−0.59	0.15	0.22	0.09	0.09	0.25	−0.14
9	−0.48	−0.74	−0.48	0.41	0.15	−0.05	0.25	0.12	0.11	−0.38	−0.31	−0.26	−0.42	−0.66	−0.43	0.31	0.31	0.27	−0.19
10	−9.03	−9.11	−9.18	−0.08	−0.16	−0.20	0.35	0.15	−0.28	−2.09	−2.55	−0.22	−0.17	−8.25	−7.92	−0.37	−0.52	−0.18	−0.94
11	0.11	−0.17	0.35	−0.38	−0.66	0.25	0.24	−1.93	−1.85	0.22	0.03	−2.02	−0.30	−0.09	−0.26	−2.25	−2.01	0.44	−2.44
12	0.07	−0.27	−0.05	−3.01	−3.35	−7.84	0.22	−4.84	−3.81	−0.08	0.01	−8.87	−0.14	−0.13	−0.13	−8.33	−8.45	−1.68	−9.32
13	0.03	−0.20	−0.04	2.64	2.41	4.75	−1.85	5.00	2.22	−0.14	0.00	4.13	−0.12	−0.18	−0.05	6.93	6.86	−1.40	7.24
14	−0.14	−0.48	−0.15	−2.94	−3.28	−5.66	−1.62	0.86	−3.55	0.76	1.02	−5.25	−0.10	−0.35	−0.16	−2.93	−2.94	−2.50	−10.85
15	0.02	−0.24	−0.01	−1.64	−1.90	−0.68	12.15	4.45	−1.66	−0.02	−0.09	−0.63	−0.12	−0.16	−0.12	−3.38	−3.39	13.70	10.53
16	0.02	−0.26	−0.07	10.37	10.09	11.46	50.51		7.21	−0.08	0.09	9.51	0.07	−0.08	−0.06	15.05	14.96		183.68
17	0.07	−0.03	−0.36	42.62	42.61	40.39									0.16	179.68	179.97		165.27
18	0.08	−0.14	0.00	−5.95	−6.17	−0.11	1.77	−7.78	−5.10	−0.08	−0.11	−0.68	−0.09	−0.06	−0.16	−3.64	−3.72	0.77	−3.91

[a] In parts per million; negative sign represents an upfield shift; uncertainty ±0.10 ppm. [b] Directly evaluated; see definition in text.

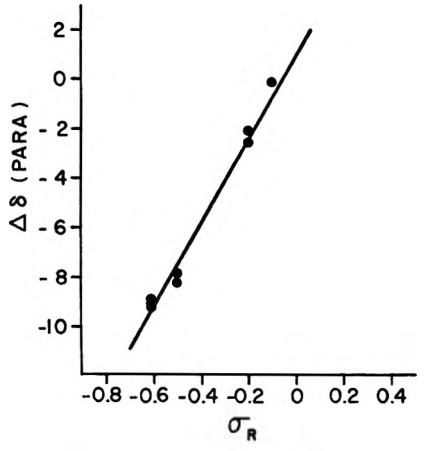


Figure 3.—Substituent effects at carbon-10 [Δδ(para)] *vs.* Taft's σ_R values. Δδ (para) = (17.94 σ_R + 1.42) ± 0.14.

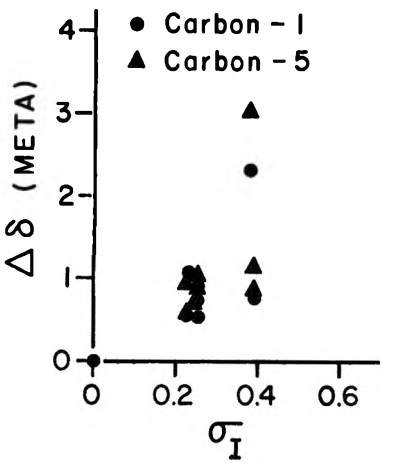


Figure 4.—Substituent effects at carbon-1 and -5 [Δδ(meta)] *vs.* Taft's δ_I values.

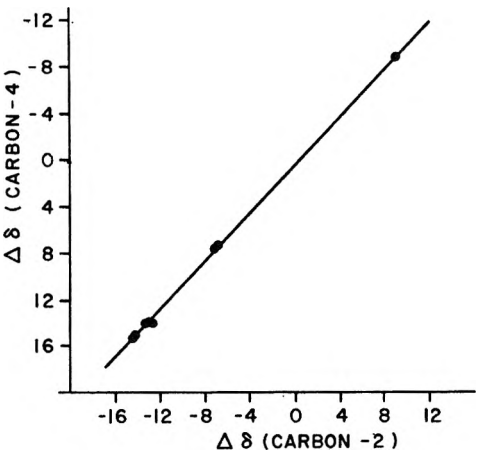


Figure 5.—Substituent effects at carbon-4 *vs.* those at carbon-2, both carbons ortho to the substituent. Δδ(C-4) = [1.03 Δδ (C-2) − 0.47] ± 0.18.

Spiesecke and Schneider pointed out that, although resonance effects, when possible, contribute substantially to the substituent effect at the ortho carbon, the magnetic field effects of the substituent appear to outweigh its inductive effects at this carbon.[13] These authors were unable to correlate the substituent effects at the meta carbon with electronegativity of the substituent, and concluded that inductive effects do not extend to these carbon atoms. Lauterbur, however, reported that Δδ of the meta carbons is inversely proportional to σ_I for certain substituents.[14] Maciel and Natterstad believed that the meta carbons are far enough away from the substituents to preclude appreciable magnetic field effects, but found no correlation between Δδ for these carbons and σ_I.[11]

There is general agreement that the changes in chemical shifts of the para carbon primarily reflect resonance effects of the substituent.

All of the ring A substituents reported in this work have been investigated as simple benzene substituents by others. Following the practice of other investigations an attempt has been made to relate the substituent effects determined here to the appropriate σ values.[15,16] Although the number of substituents available for this study was limited, the following correlations were determined. For the substituent effects at carbon-10 (*i.e.*, the para carbon) Taft's σ_R values have been used. Figure 3 shows the plot of Δδ (carbon-10) *vs.* σ_R, which indicates that in all probability resonance effects are indeed the chief contribution to substituent effects at the para position.

In the meta position carbon-1 and -5 are not equivalent owing to the presence of the rest of the steroid molecule attached to the aromatic A ring through carbon-5 and -10. The plots of Δδ (meta) for carbon-1 and -5 *vs.* Taft's σ_I values are shown in Figure 4. Although a general trend is recognizable, *i.e.*, a shift to lower field with increasing σ_I value, the correlation is not so good as that seen for carbon-10. It would appear that inductive effects are present at the meta carbon, but that in addition some other effect contributes to the observed values of Δδ(meta). This is especially obvious in the case of the iodo substituent, where the signal for carbon-5 is deshielded 0.69 ppm more than that for carbon-1 by the iodine at carbon-3.

A similar situation is observed for the ortho carbon-2 and -4, which again are not equivalent to one another. In every case the signal for carbon-4 occurs downfield from that for carbon-2, apparently as a result of deshielding effects of ring B upon carbon-4. In addition, however, upon substitution at carbon-3, carbon-4 experiences a shielding effect which is not observed at carbon-2 (or alternatively, carbon-2 experiences a deshielding effect). This is illustrated in Figure 5, in which Δδ for carbon-4 is plotted *vs.* Δδ for carbon-2. The plot is quite linear, but does *not* pass through the origin, and the slope is not unity. One explanation of such behavior is that the substituent at carbon-3 causes some other site to exert a differential shielding upon carbon-2 and -4, possibly by a resonance interaction between the substituent and this site.[17] Since presumably resonance interactions cannot occur *via* the meta carbon-5, this restricts the site to the para carbon-10 or carbon-9 which is attached to it. However, unless the aromatic ring is asymmetric (*i.e.*, not a perfect hexagon) any effect arising at either carbon-9 or carbon-10 should be equally shared at carbon-2 and -4. It therefore follows that, if the origin of this effect arises from an

(13) H. Spiesecke and W. G. Schneider, *ibid.*, **35**, 731 (1961).
(14) P. C. Lauterbur, *J. Amer. Chem. Soc.*, **83**, 1846 (1961).
(15) R. W. Taft, Jr., *ibid.*, **79**, 1045 (1957).
(16) R. W. Taft, E. Price, I. R. Fox, D. C. Levin, K. K. Andersen, and C. T. Davis, *ibid.*, **85**, 709 (1963).
(17) T. A. Wittstruck and E. N. Trachtenberg, *ibid.*, **89**, 3510 (1967).

interaction of the substituent with either carbon-9 or -10, ring A cannot be symmetric.

It should be noted here that carbon-3 substituent effects are also observed at carbon atoms outside the aromatic ring, especially at carbon-9, which is para to the substituent.

Ring D Substituents.—In studies of substituent effects upon carbon chemical shifts in cyclohexanes and cyclopentanes, previous authors have largely explained conformational differences in terms of steric effects. Roberts, *et al.*, pointed out that the major influence upon carbon-13 chemical shifts in such compounds arise from inductive, resonance, and steric effects.[8] They further point out that, in such systems as under consideration here, inductive effects may be assumed to be independent of conformation, whereas resonance, and especially steric effects, should be sensitive to conformational changes. With regards to steric effects, the role of the γ carbons and their axial hydrogens appears to be particularly important. Thus, upon introduction of an *axial* hydroxyl into cyclohexane, the interaction between the substituent and the axial γ protons presumably is responsible for the additional 5.4-ppm shielding of the α carbon when compared to the α carbon of equatorial cyclohexanols. This same steric effect in the presence of an axial substituent presumably causes an elongation of the C-β-C-α bond. This results in a shielding of the β carbon, such that the *net* substituent effect at the β carbon is smaller deshielding from an axial substituent than from an equatorial substituent.

In steroids, ring D, like other cyclopentyl rings, assumes a puckered conformation, in which the substituents are never truly axial or equatorial. Thus 1–3 steric interactions should not be expected to be as severe as in the case of cyclohexyl rings. As an example, Christl, *et al.*, interpreted the large difference in substituent effects at the α carbon (for hydroxyl and methyl substituents) between cyclohexane and cyclopentane in terms of lesser steric hindrance in the five-membered rings.[10]

The essence of the above interpretation of carbon-13 shieldings seems to be that, whatever may be the "pure" substituent effect at the α carbon, the α carbon will also experience a shielding effect from the γ carbons and their hydrogens, *which will vary* depending upon the steric relationship between the α and γ carbons. The *net* (observed) substituent effect at the α carbon will thus be different for the *same* substituent, depending upon the stereochemical relationship to other atoms in the molecule.

The same should also be true of the β and γ carbons. What is observed, then, is not just the effect of the isolated substituent (which might be assumed to be constant), but that *plus* the effects of other portions of the molecule which change upon the introduction of the substituent. For this reason, there can be no meaning to an expression such as "the hydroxyl effect," but rather each point of substitution must be considered separately.

With the above in mind, the data of Table III may be examined. The ring D substituents included here have all been previously reported in terms of their effects on cyclopentanes. In general, the substituent effects of Table III agree, at least in sign, with those reported for similarly substituted cyclopentanes.

From proton spectra, it is deduced that for 17α-OH steroids the dihedral angle between the 16α proton and the 17β proton is nearly 90° (signal for 17β proton is a doublet, $J \cong 5$ Hz). From molecular models it may be shown that the only conformation of ring D in which this may be realized is that in which the 17α OH is almost purely axial. In such a conformation, steric interactions between the 17α-hydroxyl and the axial 12α and 14α protons should be nearly maximum.

In the 17β-OH steroids, a rather broadened triplet ($J \cong 8$ Hz) is observed for the proton signal of the 17α proton, which can be interpreted as indicating that the dihedral angle between the 17α proton and the 16α proton is approximately 25°, while that between the 17α proton and the 16β proton is approximately 145°. In this conformation, the 17β OH is tilted only slightly above the plane of the D ring (quasiequatorial), and the strongest steric interactions appear to be those with the 16β proton, the 18-methyl protons, and, to a very slight extent, the 12β proton. The 17-carbon signal of 17α-OH is *less* deshielded than that of 17β-OH by 2.22 pm, which, if the steric interpretation of substituent effects is correct, means that in the 17α-OH steroids the net hydroxyl group interactions with other groups is greater than in the 17β-OH steroids. The above consideration of ring D stereochemistry from proton spectroscopy evidence seems to bear this out. Furthermore, the 17-hydroxy effects at other carbons support this theory. In the 17α-OH case, the shielding effect is much greater at carbon-12 (a secondary γ carbon) than at carbon-16 (also a secondary γ carbon), in accord with the observation that steric interactions between the 17α-OH and the axial 12α and 14α proton were maximum. Thus, from this limited data, it appears that steric effects do play a major role in controlling substituent effects in carbon-13 magnetic resonance.

Because of the relatively small amount of data as yet available, further interpretation of substituent effects upon the nonaromatic carbon chemical shifts will be postponed.

Registry No.—I, 1217-09-0; II, 53-63-4; III, 2529-64-8; IV, 53-45-2; V, 50-28-2; VI, 53-16-7; VII, 57-91-0; VIII, 2755-14-8; IX, 3434-88-6; X, 1474-52-8; XI, 901-93-9; XII, 38605-46-8; XIII, 1035-77-4; XIV, 1624-62-0; XV, 1229-33-0; XVI, 6038-22-8; XVII, 7004-98-0; XVIII, 1228-73-5.

The Preparation and Properties, Including Carbon-13 Nuclear Magnetic Resonance Spectrum, of Per-*tert*-butylcarbonic *p*-Nitrobenzoic Anhydride[1]

JAMES R. FEHLNER, D. STANLEY TARBELL,* AND DALE FULLER[2]

Department of Chemistry, Vanderbilt University, Nashville, Tennessee 37235

Received October 31, 1972

A stable percarbonic anhydride was prepared by the reaction of CO_2 with sodium *tert*-butyl hydroperoxide and subsequent reaction with *p*-nitrobenzoyl chloride. Spectra, including ^{13}C nmr, were taken. The compound was found to catalyze free-radical polymerization. In its decomposition at atmospheric pressure *p*-nitrobenzoic acid, methyl *p*-nitrobenzoate, and *p*-nitrobenzoic anhydride were found while in the sealed tube methyl *p*-nitrobenzoate and the acid predominated. Acetone and *tert*-butyl alcohol were found in both while 2,2-dimethoxypropane was found in the former and chlorotoluene in the latter. Reasons for this, including free-radical and Criegee decompositions, are discussed.

The synthesis and study of a variety of carbonic carboxylic anhydrides (1), of di- and tricarbonates, and

$$\underset{\mathbf{1}}{ROCOCR'} \longrightarrow ROCR' + CO_2$$

of carbonic anhydrides containing phosphorus and silicon moieties, have been reported.[3] The mode of decomposition of these materials is ionic, as inferred from a variety of criteria.[3d]

We have therefore prepared[4] a peroxy compound (2) as shown below, which could decompose by ionic or

$$ROOH \xrightarrow[2.\ CO_2]{1.\ NaH} ROOCOONa \xrightarrow{ArCOCl} ROOCOCAr \quad (1)$$

2, R = *t*-Bu
Ar = *p*-$O_2NC_6H_4$

free radical modes, including the Criegee reaction of the peroxide group.

Per-*tert*-butylcarbonic *p*-nitrobenzoic anhydride (PCA) was prepared as indicated and was obtained as a pure crystalline solid, mp 69–71°. An attempt was also made to prepare it from the chlorocarbonate of *tert*-butyl hydroperoxide, but the triethylamine used for the removal of HCl catalyzed the elimination of carbon dioxide to give the per ester.

In an attempt to confirm the position of the peroxide moiety, the carbon-13 nmr spectra of PCA and some related compounds were taken. The shifts are given in Table I. The assignments for the aromatic carbons were made on the basis of the size of the coupling to the aromatic hydrogens and the expected shift effects of the aromatic substituents.[5] An examination of the data shows that the peroxide group causes only minor changes in the spectra as compared to that of the carbonic anhydride and that these changes are in different directions from those observed in the two esters. Therefore, it is not possible to assign conclusively the position of the peroxide group from the carbon-13 spectra.

A test of PCA's ability to initiate the copolymerization of styrene and methyl methacrylate showed that it was much less effective than benzoyl peroxide; however, the 50:50 mixture of monomers in the polymer shows that it was a radical-induced polymerization.[6,7]

Decompositions.—The products of decomposition varied dramatically depending upon the mode of decomposition. The CO_2 given off was measured for decompositions in both the solid state and chlorobenzene solution. In the solid-state decomposition 1.03 mol of CO_2 was given off per mole of PCA, while in the chlorobenzene case 0.78 mol of CO_2 was obtained.

In the solid-state decomposition the only solid product isolated was *p*-nitrobenzoic acid. In the decompositions of PCA in chlorobenzene, either open to the atmosphere or under nitrogen, both *p*-nitrobenzoic acid and *p*-nitrobenzoic anhydride were observed as well as a small amount of methyl *p*-nitrobenzoate. Finally, the PCA was decomposed in chlorobenzene after the samples had been degassed and sealed under vacuum. In this case the solids isolated were *p*-nitrobenzoic acid and methyl *p*-nitrobenzoate, but no evidence could be found for the existence of any anhydride. After isolation of the two compounds, 47.9 mol % of the ester and 51.2 mol % of the acid were obtained.

The products derived from the *tert*-butyl end of the molecule were also investigated. In the solid-state decomposition, these products were lost owing to the rapid decomposition of the PCA. In the undegassed chlorobenzene samples, acetone, *tert*-butyl alcohol, and the dimethyl ketal of acetone were identified by gc–mass spectroscopy, but no percentages could be obtained.

In the decomposition in degassed chlorobenzene *tert*-butyl alcohol and chlorotoluene were identified by gc–mass spectroscopy, and there was also some evidence for a small amount of isobutylene in the fraction captured in liquid nitrogen. By observing the nmr of the liquid fractions from the sealed tubes, it was possible to make an estimate of the amounts of the various compounds produced. Based on the amount of PCA decomposed, there was 16.6 mol % of chlorotoluene, 32.8 mol % of acetone, and 29.8 mol % of *tert*-butyl alcohol. The calculations were made assuming that the peak for

(1) This work was aided by Grant GP-15795 from the National Science Foundation.

(2) National Science Foundation Undergraduate Research Participant, summer, 1971.

(3) Most recent papers: (a) Y. Yamamoto and D. S. Tarbell, *J. Org. Chem.*, **36**, 2954 (1971); (b) C. S. Dean and D. S. Tarbell, *ibid.*, **36**, 1180 (1971); (c) D. S. Tarbell, Y. Yamamoto, and B. M. Pope, *Proc. Nat. Acad. Sci. U. S.*, **69**, 730 (1972); for review (d) D. S. Tarbell, *Accounts Chem. Res.*, **2**, 296 (1969).

(4) *Cf.* preparation of the nonperoxy analog ROC(=O)OC(=O)Ar (R = *tert*-butyl, Ar = *p*-$O_2NC_6H_4$): C. J. Michejda and D. S. Tarbell, *J. Org. Chem.*, **29**, 1168 (1964).

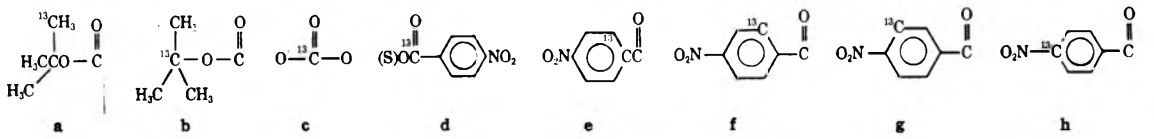
(5) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 2, Pergamon Press, Oxford, 1966, p 1004.

(6) F. M. Lewis, F. R. Mayo, and W. F. Halse, *J. Amer. Chem. Soc.*, **67**, 1701 (1945).

(7) C. Walling, E. R. Briggs, W. Cummings, and F. R. Mayo, *J. Amer. Chem. Soc.*, **72**, 48 (1950).

TABLE I

CHEMICAL SHIFTS[a]



Compd	Structure a	b	c	d	e	f	g	h
$CH_3CH(CH_3)OCOC(CH_3)_3$	167.7	107.2	45.3	32.3	61.2	61.4	69.3	41.8
$CH_3C(CH_3)_2OCOC(CH_3)_3$	165.5	106.7	46.4	32.7	60.0	61.9	69.4	41.1
$CH_3C(CH_3)_2OOC(CH_3)_3$	166.7	108.8		30.8	59.9	62.7	69.1	42.4
$CH_3CH_2OC(CH_3)_3$	164.9	111.0		29.5	55.7	62.6	69.7	42.6
$CH_3CH_2SC(CH_3)_3$	162.6	143.5		2.8	49.4	65.0	69.3	42.6

[a] In parts per million from CS_2, assuming $\delta(C_6D_6) - \delta(CS_2) = 65.0$ (ref 5, p 1003).

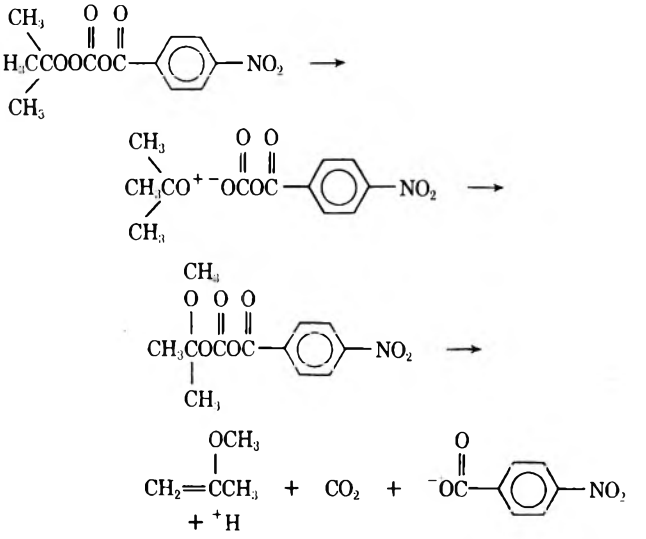
methyl *p*-nitrobenzoate represented 0.835 mmol. There was also a fairly strong unidentified peak at δ 1.11. There was a moderate amount of variation in these values in different samples, particularly in the peak at δ 1.11, which was very small in some cases. It must be remembered that a molecule of methyl *p*-nitrobenzoate or chlorotoluene and a molecule of acetone can both come from the same molecule of PCA.

Discussion

Of the products isolated from the various decompositions, chlorotoluene and *tert*-butyl alcohol must arise from a radical decomposition, while 2,2-dimethoxyethane, *p*-nitrobenzoic anhydride, and isobutylene (if it is truly present) are probably products from ionic decompositions. For the other products, carbon dioxide, *p*-nitrobenzoic acid, methyl *p*-nitrobenzoate, and acetone, it is possible to visualize both ionic and radical mechanisms for their production.

The only conceivable mechanism for the formation of the chlorotoluene would be the addition of a methyl radical to chlorobenzene,[8] since the possibility of having a methyl cation in this system is very remote. The most likely mode of formation of the *tert*-butyl alcohol is hydrogen abstraction by a *tert*-butoxy radical, probably from another *tert*-butyl group.

The formation of the 2,2-dimethoxypropane is most certainly due to the heterolytic cleavage of the peroxide bond to give the Criegee rearrangement.[9] The vinyl ether can be hydrolyzed to methanol and acetone and



subsequently the methanol can form 2,2-dimethoxypropane upon reaction with the vinyl ether. The benzoic acid anion could react with the hydrogen ion to give the acid or attack another mole of the percarbonic anhydride to give di-*p*-nitrobenzoic anhydride.

Walling suggests that both the radical decomposition

(8) C. Walling, "Free Radicals in Solution," Wiley, New York, N. Y., 1957, p 483.

(9) E. Hedaya, *et al.*, *J. Amer. Chem. Soc.*, **89**, 4875 (1967); R. Criegee and R. Kaspar, *Justus Liebigs Ann. Chem.*, **560**, 127 (1948); P. D. Bartlett and J. L. Kice, *J. Amer. Chem. Soc.*, **75**, 5591 (1953).

and the Criegee rearrangement may arise from a common radical pair–ion pair transition state.[10]

The formation of acetone, already explained in the Criegee rearrangement, could be explained in the radical decomposition by loss of a methyl radical from the *tert*-butoxy radical.

The loss of one molecule of CO_2 per mole of PCA would be expected in the ionic decomposition, while as many as 2 mol of CO_2 could be lost in the radical decomposition. In the solid-state decomposition, which is suspected to be a radical chain reaction owing to the very rapid decomposition, there is only 1 mol of CO_2 given off, while in the case of the chlorobenzene decomposition under nitrogen, where both ionic and radical mechanisms are probably involved, about 1 mol of CO_2 is evolved. Finally, in the sealed tube decomposition the most CO_2 that could be given off is 1 mol, since almost all (99%) of the *p*-nitrobenzoate group was recovered as *p*-nitrobenzoic acid or methyl *p*-nitrobenzoate.

The production of benzoic acid in the Criegee rearrangement has already been explained, while in the radical reaction it would have to arise from the hydrogen abstraction by the *p*-nitrobenzoyloxy radical.

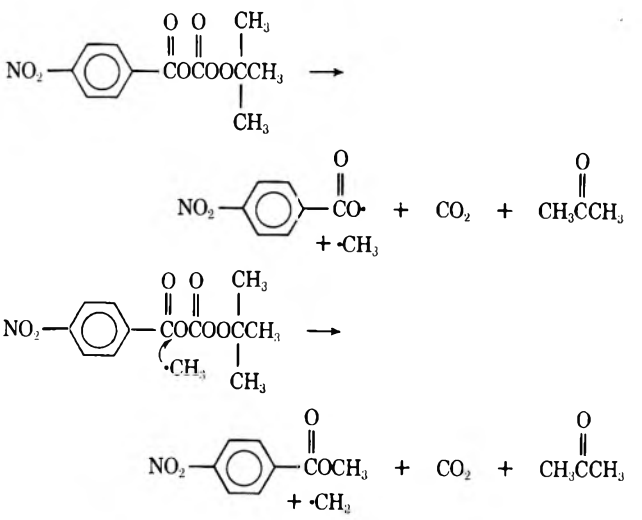
The most problematical of the compounds isolated is the methyl *p*-nitrobenzoate. One possible reaction leading to it would be the formation of methanol from the Criegee rearrangement and the attack of the methanol on PCA to give the ester. *tert*-Butyl hydroperoxide and CO_2 would probably be the other products. The hydroperoxide would go to *tert*-butyl alcohol and oxygen.[11]

The main argument against this mechanism is that no 2,2-dimethoxypropane was observed in the nmr of the products of the sealed-tube decomposition, which would be expected in the Criegee decomposition.

The second possible mechanism is a radical cage reaction where there is a homolytic scission of the O–O bond followed by loss of CO_2 and acetone and finally recombination of the methyl and *p*-nitrobenzoyloxy radical. One referee suggested that this would be unlikely, since he felt that the energy for β scission (13 kcal/mol)[12] would be substantially greater than that of the decarboxylation of the *p*-nitrobenzoyloxy radical. If the *p*-nitrobenzoyloxy radical does exist in the decomposition it certainly does not decarboxylate under these conditions, since 99% of it was recovered as *p*-nitrobenzoic acid or methyl *p*-nitrobenzoate. The formation of a moderate amount of chlorotoluene would certainly suggest that there is a strong likelihood of the presence of *p*-nitrobenzoyloxy radicals.

Cook estimates the energy of decarboxylation of the benzoyloxy radical at 18–23 kcal/mol, but this was based on only two points done over a 10° range.[13] Walling, however, is not willing to say which β scission, *tert*-butoxide or benzoyloxy, has the greater activation energy.[14] Similar data could not be found for the *p*-nitrobenzoyloxy radical; however, Ol'dekop observed that *p*-chlorobenzoyloxy radical adds to metals and salts in the cold or on heating, abstracts hydrogen from solvent, and loses CO_2 while the *p*-nitrobenzoyloxy radical adds to metals and abstracts hydrogen from solvent.[15] It was also observed that the *p*-nitrobenzoyloxy radical abstracts hydrogen from toluene at 100° to give *p*-nitrobenzoic acid.[16]

Another possible mechanism would be the radical-chain reaction in the following series of reactions.[17]



This mechanism is favored by the fact that chlorotoluene is formed, since this would suggest a proliferation of methyl radicals.

Another radical chain mechanism (2) might involve a cyclic transition state. This mechanism is less likely, though, because one would expect some attack of radical **3** on the peroxide bond to give other products, which were not observed.

The best way to distinguish between these mechanisms would be to follow the kinetics of the reaction. The rates of reaction for the ionic mechanism should vary with the polarity of the solvent while the others should not. The cage mechanism should be first order while the chain mechanism and the ionic mechanism should not.

The reason for the variation in the decomposition products in the sealed and open decompositions is not evident. One possible reason is the fact that the open decompositions were not degassed and the dissolved gases might have affected the decomposition. If the formation of the methyl *p*-nitrobenzoate is from a radical-chain reaction it might be quenched, allowing the Criegee reaction to take precedence. However, this explanation is somewhat in doubt owing to the fact that decompositions in sealed undegassed tubes gave essentially the same results as the degassed tubes.

It is not a matter of decomposition temperature or concentrations either, since variation of these factors in the open decompositions all gave at least a moderate amount of anhydride.

If Walling's proposal is correct then it might be profitable to seek a condition that would affect the separation of the radical pair–ion pair.

(10) C. Walling, H. P. Waits, J. Milovanoic, and C. G. Pappiaonnou, *J. Amer. Chem. Soc.*, **92**, 4927 (1970).

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(12) J. A. Howard in "Advances in Free-Radical Chemistry," Vol. IV, G. H. Williams, Ed., Academic Press, New York, N. Y., 1972, p 61.

(13) C. D. Cook and C. B. Depatic, *J. Org. Chem.*, **24**, 1144 (1959).

(14) C. Walling and J. C. Azar, *J. Org. Chem.*, **33**, 3885 (1968).

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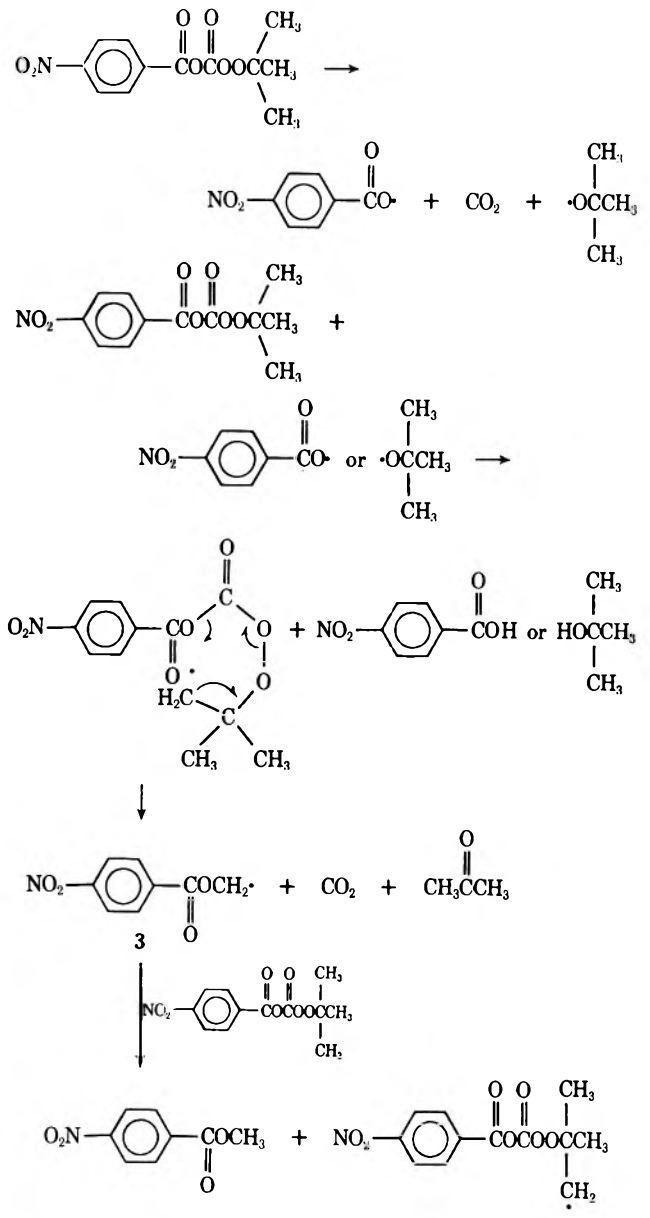
(16) R. I. Milyutinskaya, Kh. S. Bagdasaryan, and Yu. Kopytocskii, *Zh. Fiz. Khim.*, **32**, 428 (1958); *Chem. Abstr.*, **52**, 20022*d* (1958).

(17) We would like to thank Dr. D. L. Tuleen for this suggestion.



(2)

Experimental Section

Carbon-13 Nmr.—Spectra were taken on a Varian Model XL-100 nmr spectrometer. The samples were dissolved in perdeuteriobenzene and run in 12-mm tubes with heteronoise decoupling. A single scan was taken at 2500-Hz sweep width.

Preparation of PCA (I).—*tert*-Butyl hydroperoxide was purified by vacuum reflux and distillation by the procedure of Bartlett, *et al.*[18]

Sodium hydride (1.2 g of 50% in mineral oil, 0.026 mol) was washed twice with tetrahydrofuran (THF), which had been dried over $CaCl_2$ and distilled from lithium aluminum hydride. Dry THF (50 ml) was added to the sodium hydride in a 100-ml three-neck flask and *tert*-butyl hydroperoxide (2.2 g, 0.03 mol) was added dropwise to the sodium hydride suspension at room temperature. Following the evolution of H_2, carbon dioxide, bubbled through concentrated H_2SO_4, was bubbled through the suspension at −78° for 2.5 hr. A solution of 3.5 g (0.02 mol) of *p*-nitrobenzoyl chloride in 15 ml of $CHCl_3$ was added dropwise. After the temperature was increased to −10 to 0° the solution was stirred for 20 hr. The CO_2 addition was stopped 2 hr after the addition of the acid chloride.

The suspension was vacuum filtered through a fritted glass into a cooled flask and the solvents were removed from the filtrate under vacuum. The remaining solid was dissolved in a 1:1 mixture of $CHCl_3$–petroleum ether (bp 30–60°) and the solution was filtered. A large amount of petroleum ether was added and the solution was filtered again. After crystallization at −78° the precipitate was collected. After a second recrystallization 1.48 g (28%) was obtained: mp 69–71° dec; nmr δ 7.94 (narrow m, 4 H), 1.00 (s, 9 H); ir carbonyl bands at 1840 and 1763 cm^{-1}.

Anal. Calcd for $C_{12}H_{13}NO_7$: C, 50.88; H, 4.63; N, 4.95. Found: C, 50.60; H, 4.66; N, 4.68.

Titration of the Peroxide Group.—A determination of the peroxide content was done by the transesterification method of Hedaya and Winstein.[19] After correction for a blank run two titrations yielded values of 104 and 97.5% peroxide assuming 1 mol of peroxide per 283 g (1 mol) of percarbonic anhydride.

Polymerization.—Methyl methacrylate was fractionally distilled at 100° (760 mm) and styrene was fractionally distilled at 60° (40 mm). Five grams of each were mixed for each experiment and placed in a 25-ml flask. Benzoyl peroxide (0.0024 g) or 0.0028 g of PCA were added to one of the three flasks. The third was left blank. The solutions were heated at 79.5° for 4 hr. After cooling, the contents of each flask were added to 100 ml of absolute methanol with vigorous stirring. The white precipitate was filtered and washed with 15 ml of methanol. The samples were dried for 26 hr at 0.5 mm, and weighed. The yields of the polymer follow: blank, 0.0005 g; benzoyl peroxide, 1.5225 g; PCA, 0.3576 g. This is the method of Walling, *et al.*[6]

The polymers were reprecipitated from a mixture of methanol–benzene, dried under vacuum, and analyzed. The results are given in Table II.

TABLE II

Initiator	C, %	Mol % styrene[a]
Benzoyl peroxide	76.71	50.9
PCA	76.93	51.5

[a] Assuming that polystyrene requires 92.26 C and polymethyl methacrylate requires 59.98 C.

Solid-State Decomposition.—PCA (497.7 mg, 1.767 mmol) was placed in a two-neck flask. A stream of nitrogen was passed through the flask into an ice–salt bath and then through an Ascarite tube. The solid was heated in an oil bath until it melted, at which time it began to decompose. At 82° the PCA decomposed very quickly. After 3 hr, 80.1 mg (1.82 mmol) of carbon dioxide was collected in the Ascarite tube. The solid material left was recrystallized from ethanol, and *p*-nitrobenzoic acid (34.6 mg, 0.212 mmol), identified by ir, was isolated.

Decomposition in Undegassed Chlorobenzene.—PCA (1.048 g, 3.81 mmol) was dissolved in 30 ml of chlorobenzene (distilled). A stream of nitrogen was passed over the chlorobenzene through a reflux condenser in a Dean–Stark trap and then through a Dry Ice trap. After decomposition at 90° for 3 hr, the volatile materials were separated and identified by gc–mass spectroscopy. The products were separated on a 6-ft SE-30 column. No products were isolated from the Dry Ice trap. *tert*-Butyl alcohol and the dimethyl ketal of acetone were found in the Dean–Stark trap, while acetone was found in the residual chlorobenzene.

The spectrum of the acetal was identified by comparison with a known spectrum.[20]

Measurement of CO_2 in Chlorobenzene Decomposition.—PCA (0.9274 g, 3.28 mmol) was dissolved in 30 ml of chlorobenzene. A stream of nitrogen was passed over the solvent, through a condenser, an ice–salt trap, and finally an Ascarite tube. After decomposition at 90°, 0.1161 g (2.54 mmol) of CO_2 was obtained.

Decomposition in Degassed Chlorobenzene.—The sample of PCA (100 mg in 9 ml of chlorobenzene) was degassed by alternate freezing and thawing under vacuum in an apparatus similar to that described.[18] The sample was decomposed at 103° for 18 hr. It was cooled to liquid nitrogen temperature, opened under vacuum, and allowed to warm to room temperature. The material that boiled off was collected in the liquid N_2 trap. The trap was warmed and a mass spectrum was taken of the gas released. In addition to a strong CO_2 peak there were peaks suggesting the presence of isobutylene. The solvent and other volatile materials were distilled off under vacuum and were collected in a Dry Ice trap. A gc–mass spectrum showed the

(18) P. D. Bartlett and H. Minato, *J. Amer. Chem. Soc.*, **85**, 1858 (1963).

(19) E. Hedaya and S. Winstein, *J. Amer. Chem. Soc.*, **89**, 1661 (1967).

(20) E. Stenhagen, S. Abrahamsson, and J. W. McLafferty, Ed., "Atlas of Mass Spectral Data," Vol. 1, Interscience, New York, N. Y., 1969, p 307.

presence of *tert*-butyl alcohol and chlorotoluene. From the solids remaining *p*-nitrobenzoic acid and methyl *p*-nitrobenzoate were identified.

PCA (503 mg) was dissolved in 5 ml of chlorobenzene. The sample was degassed by alternated freezing and melting and was then sealed. The sample was heated at 107° for 24 hr. It was then cooled and opened, and an nmr was taken of the filtered solution. The peaks at δ 1.2 (*tert*-butyl alcohol), 1.83 (acetone), 2.09 (chlorotoluene), and 3.71 (methyl *p*-nitrobenzoate) and an unidentified peak at 1.11 were integrated. The peak at δ 1.11 was shown not to be *tert*-butyl *p*-nitrobenzoate, *tert*-butyl *p*-nitroperbenzoate, or the dimethyl ketal of acetone. This is the procedure of Hideya, *et al.*[9]

The solvents were removed and the residue was dissolved in ether and extracted with 2% NaOH solution. The ether was dried and removed under vacuum. Fairly pure (ir, mp 78–89°) methyl *p*-nitrobenzoate (148 mg) remained. The NaOH was neutralized with concentrated HCl, and the precipitate was collected. After drying the *p*-nitrobenzoic acid weighed 149.4 mg.

Decomposition in Undegassed Sealed Tubes.—Two 100-mg. samples of PCA were dissolved in 1-ml portions of chlorobenzene. The solutions were sealed in unevacuated tubes without degassing, and the samples were heated for 24 hr at 107°. (One sample turned dark while the other remained light.) The samples were opened and nmr spectra were taken as in the previous case. The spectra were similar to those of the degassed samples except that the dark sample had less *tert*-butyl alcohol and more of the material with the peak δ 1.11. The solid that crystallized out was examined and found to be *p*-nitrobenzoic acid. No evidence was obtained for the presence of *p*-nitrobenzoic anhydride.

Registry No.—2, 38401-55-7; *tert*-butyl hydroperoxide, 75-91-2; *p*-nitrobenzoyl chloride, 122-04-3; methyl *p*-nitrobenzoate, 619-50-1.

Correlation between Nuclear Magnetic Resonance and Infrared Studies of Conformational Preferences in Chloro Sulfides

GARY M. UNDERWOOD, C. T. WATTS, AND CHARLES A. KINGSBURY*

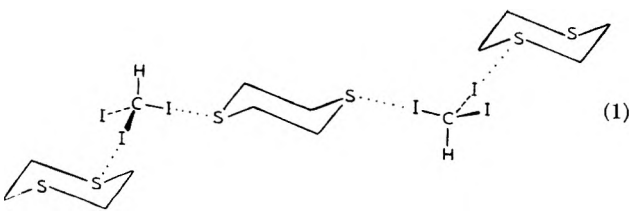
Department of Chemistry, University of Nebraska, Lincoln, Nebraska 68508

Received March 21, 1972

Nmr and ir methods of determining conformational preferences in alkyl substituted 1-chloro-2-ethyl 2,4-dinitrophenyl sulfides are in fair agreement. For *erythro*-2-chloro-3-butyl 2,4-dinitrophenyl sulfide, a preference for gauche chlorine–sulfur groups is evident. However, the study of model compounds shows that the chlorine–sulfur interaction is probably slightly repulsive. A very unusual preference for a conformer having gauche hydrogens is noted in both isomers of the above compound.

Conformational reasoning has been deeply affected by the early work on butane and on cyclohexane systems.[1,2] This work led to the idea that alkyl groups, and presumably other large groups, prefer a trans orientation in order to minimize repulsive nonbonded interactions.[3] In recent years, there has been a growing realization that many groups, some sizable, have attractive rather than repulsive interactions. In substituted propanes, $XCH_2CH_2CH_3$, the conformer having X gauche to methyl is slightly more stable or of equivalent stability to the trans conformer where X is F, Cl, Br, CN, NC, C≡CH, and OH.[4] A slight dipolar attraction is presumed to overcome steric repulsions. Notable among other interections that are considered attractive in nature are the interactions of oxygen-containing groups,[5,6] cyano–cyano groups,[7] mercury–amine,[8] sulfoxide–hydrogen,[9] and chlorine–hydrogen.[10] Halogen–halogen interactions are complex, and these may vary from compound to compound depending upon bond angle and internuclear distance.[11] However, it is noteworthy that, in a large variety of dihaloethylenes, the cis isomer is the more stable.[11c] In acyclic compounds capable of internal rotation, the gauche X–X conformer is stabilized in solvents of high dielectric constant, since the solvent effect counteracts the repulsive effects of the halogen dipoles.[6a,7,12] The list of attractive interactions is diverse enough so as to suggest that the phenomenon is widespread, though many times rather weak.

The present work is an inquiry into the possibility of an attractive interaction between sulfur and halogen. Precedent for considering this interaction as attractive exists in the work of Bjorvatten and Hassel,[13] who observed the alignment of molecules shown in



(1)

(1) by X-ray analysis. The tendency for halogens to complex with sulfides is well known,[14] though this

(1) D. H. R. Barton, *Experientia*, **23**, 316 (1950).

(2) S. Mizushima, "Structure of Molecules and Internal Rotation," Academic Press, New York, N. Y., 1954.

(3) E. L. Eliel, N. Allinger, J. Angyal, and G. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, pp 5–22.

(4) E. B. Wilson, *Chem. Soc. Rev.*, **1**, 293 (1972).

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(6) (a) A. A. Bothner-By and C. Naar-Colin, *J. Amer. Chem. Soc.*, **84**, 743 (1962); (b) F. A. L. Anet, *ibid.*, **84**, 747 (1962).

(7) (a) L. I. Peterson, *ibid.*, **89**, 2677 (1967); (b) J. P. Aycard, H. Bodot, R. Garnier, R. Lauricella, and G. Pouzard, *Org. Magn. Resonance*, **2**, 7 (1970).

(8) (a) E. F. Kiefer, W. L. Walters, and D. A. Carlson, *J. Amer. Chem. Soc.*, **90**, 5127 (1968); (b) E. F. Kiefer and W. Gericke, *ibid.*, **90**, 5131 (1968).

(9) (a) C. R. Johnson and D. McCants, Jr., *ibid.*, **87**, 110 (1965); (b) N. L. Allinger, J. Hirsch, M. Miller, and I. Tyminski, *ibid.*, **91**, 337 (1969).

(10) (a) R. J. Abraham and K. Parry, *J. Chem. Soc. B*, 539 (1970); (b) B. Hawkins, W. Bremser, S. Borcic, and J. D. Roberts, *J. Amer. Chem. Soc.*, **93**, 4472 (1971), and references cited therein.

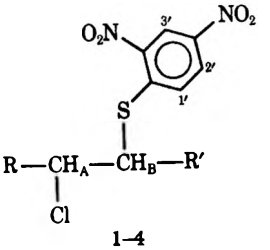
(11) (a) A. Berlin and F. Jensen, *Chem. Ind. (London)*, 998 (1960); (b) R. A. Pethrick and E. Wyn-Jones, *Quart. Rev. Chem. Soc.*, **23**, 301 (1969); (c) H. Viehe, J. Dale, and E. Franchimont, *Chem. Ber.*, **97**, 244 (1964), and many related papers.

(12) G. Hamer, W. F. Reynolds, and D. Wood, *Can. J. Chem.*, **49**, 1755 (1971).

(13) T. Bjorvatten and O. Hassel, *Acta Chem. Scand.*, **15**, 1429 (1961).

(14) (a) J. D. McCullough, G. Chao, and D. Zuccaro, *Acta Crystallogr.*, **12**, 815 (1959); (b) M. Good, A. Major, J. Nag-Chaudhuri, and S. McGlynn, *J. Amer. Chem. Soc.*, **83**, 4329 (1961).

TABLE I
NMR PARAMETERS[b] (60 MHz) OF 1–4



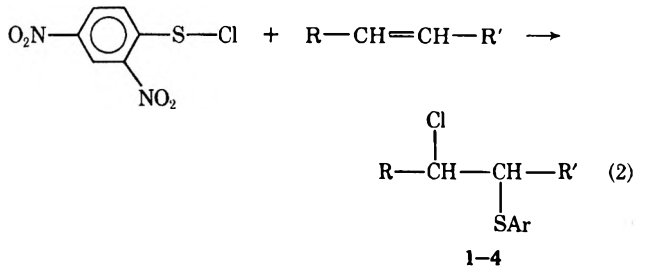
1–4

Compound	R	R′	Coupling constants, Hz J_{AB}	J_A[CH(CH₃)₂]	J_B[CH(CH₃)₂]	Chemical shifts, ppm A	B	1′	2′	3′	R	R′
erythro-1	CH_3	CH_3	4.0[b] (3.5)[c]			4.44	3.89	7.77	8.42	8.95	1.69	1.58
threo-1	CH_3	CH_3	3.2 (3.6)			4.34	3.90	7.72	8.47	9.03	1.60	1.57
erythro-2	CH_3	$CH(CH_3)_2$	7.3 (7.4		5.7	4.36	3.54	7.83	8.33	8.87	1.62	*a*
threo-2	CH_3	$CH(CH_3)_2$	4.2 (3.7)		6.7	4.51	3.52	7.83	8.40	8.94	1.72	*a*
erythro-3	$CH(CH_3)_2$	$CH(CH_2)_2$	10.5 (10.5)	2.2	3.1	4.04	3.67	7.82	8.43	8.95	*a*	*a*
threo-3	$CH(CH_3)_2$	$CH(CH_3)_2$	5.6 (~6)	5.2	6.3	4.16	3.72	7.98	8.47	8.93	*a*	*a*
erythro-4	CH_3	$C(CH_3)_3$	2.6 (2.7)			4.83	3.79	8.02	8.34	8.90	1.72	1.17
threo-4	CH_3	$C(CH_3)_3$	1.3 (1.3)			4.72	3.44	7.79	8.36	8.88	1.65	1.19

[a] Complex nonequivalent resonances of the methyls were observed. [b] *Ca.* 10% w/v solution in $CDCl_3$. [c] The data in parentheses refer to 10.0% w/v solutions in DMSO as solvent observed at 100 MHz.

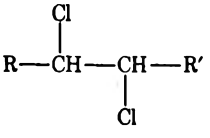
type of interaction may have a different origin from that present in the compounds of this study.

The present work concerns certain chloro sulfides having nitro substitutents in the aromatic ring (eq 2). The inductive effect of the nitro groups renders



(2)

1–4



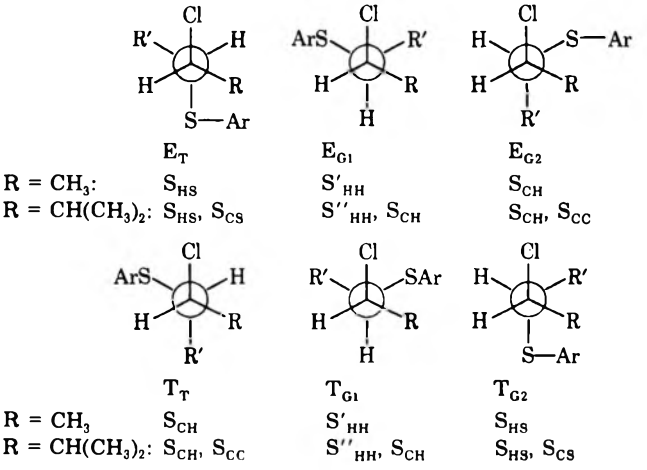
5

sulfur somewhat electron deficient. Thus, attempted observation of pseudocontact shifts using $Eu(fod)_3$ showed little or no displacement of the alkyl resonances in the nmr spectrum, although the aromatic resonances were shifted slightly.[15,16] The electron deficient nature of the sulfur should increase the probability of an attractive gauche interaction with the electron-rich chlorine.

The chloro sulfides were synthesized as shown in eq 2.[17] In this study, nmr and ir methods of determining conformational preferences will be compared. In addition to **1**–**4**, certain analogous dichlorides, **5**, will also be considered.

The nmr data for compounds in which R and R′ are alkyl groups are listed in Table I. The conformational preferences are approximated from vicinal nmr coupling constants (J_{AB}).[18] Large values for J_{AB} (10–13 Hz) are taken as indicative of predominately trans hydrogens, whereas small values for J_{AB} (1–4 Hz) indicate predominately gauche hydrogens. Intermediate values are thought to reflect weighted averages of the above conformations. Other work[19] has suggested that every conformer of every compound has distinct and separate values for J_{AB} (although these values are usually within the above ranges). Only a qualitative interpretation of the data will be attempted, in terms of the conformers shown in Scheme I. The infrared spectroscopic designations of the bands expected for each conformer are also given in Scheme I.

SCHEME I



	E_T	E_{G1}	E_{G2}
R = CH_3:	S_{HS}	S'_{HH}	S_{CH}
R = $CH(CH_3)_2$:	S_{HS}, S_{CS}	S''_{HH}, S_{CH}	S_{CH}, S_{CC}

	T_T	T_{G1}	T_{G2}
R = CH_3	S_{CH}	S'_{HH}	S_{HS}
R = $CH(CH_3)_2$:	S_{CH}, S_{CC}	S''_{HH}, S_{CH}	S_{HS}, S_{CS}

For *erythro*-**1**, a quite small value for J_{AB} (4.0 Hz) is noted. This value is substantially smaller than that found for the analogous dichloride (7.4 Hz), which suggests that the conformers having gauche heteroatoms, E_{G1} and/or E_{G2}, are more highly populated for **1** than for the dichloride.

(15) (a) C. C. Hinckley, *J. Amer. Chem. Soc.*, **91**, 5160 (1969); (b) P. DeMarco, T. Elzey, R. Lewis, and E. Wenkert, *ibid.*, **92**, 5734, 5737 (1970); (c) J. Sanders and D. Williams, *Chem. Commun.*, 422 (1970).

(16) Private observations have shown highly delocalized electron pairs do not complex well with $Eu(dpm)_3$.

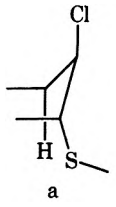
(17) (a) N. Kharasch, *J. Chem. Educ.*, **33**, 585 (1956); (b) W. H. Mueller and P. E. Butler, *J. Amer. Chem. Soc.*, **90**, 2075 (1968); (c) G. H. Schmid and V. M. Csizmadia, *Can. J. Chem.*, **44**, 1338 (1966); (d) G. H. Schmid, *ibid.*, **46**, 3757 (1968).

(18) (a) M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2870 (1963); (b) E. Garbisch, Jr., and M. Griffith, *ibid.*, **90**, 6543 (1968).

(19) (a) R. J. Abraham and G. Gatti, *J. Chem. Soc. B*, 961 (1969); (b) R. J. Abraham, L. Cavalli, and K. Pachler, *Mol. Phys.*, **11**, 471 (1966).

In studies on a considerable number of chlorine compounds, Mizushima and coworkers have developed,[20] and others have expanded, a correlation between ir absorption and conformation.[21] According to Altona,[21] the three types of ir absorption applicable to **1** are termed S_{HS}, S'_{HH}, and S_{CH}, which can be correlated with conformers E_T, E_{G1}, and E_{G2}, respectively (Scheme I).

These three absorptions are found at 701, 632, and 666 ± 20 cm^{-1}, respectively. The designation S_{HS} refers to an ir band expected from a secondary chlorine that is simultaneously trans to a sulfur atom and to a hydrogen (*i.e.*, structure a).



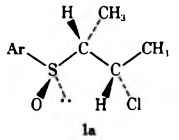
a

For *erythro*-**1** in CS_2 solution, absorptions at 714 (m) and at 653 (s) were observed. In the solid phase (KBr pellet), the latter band was also prominent. A strong band at 670–685 cm^{-1}, possibly an aromatic absorption, interferes with the S_{HS} or S_{CH} absorption in certain cases; so the identification of a band is not always straightforward. The strongest band (653 cm^{-1}) is closest to the region expected for the S_{CH} absorption, which suggests that the predominant conformer is E_{G2}. No ir band is noted near 632 cm^{-1}. Although this absence would seem to indicate that conformer E_{G1} is unpopulated, we feel that this indication is open to question.[22]

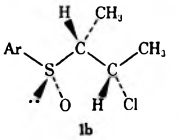
(20) S. Mizushima, T. Shimanouchi, K. Nakamura, M. Hayashi, and S. Tsuchiya, *J. Chem. Phys.*, **26**, 970 (1957).

(21) (a) C. Altona, *Tetrahedron Lett.*, 2325 (1968); (b) J. J. Shipman, V. Folt, and S. Krimm, *Spectrochim. Acta*, **18**, 1603 (1962); (c) P. N. Gates, E. Mooney, and H. Willis, *Spectrochim. Acta, Part A*, **23**, 2043 (1967).

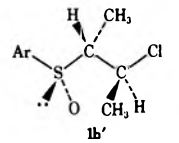
(22) It is instructive to consider the sulfoxides and the sulfone derived from the sulfide **1**. The sulfoxide **1a**, mp 139°, showed a lower vicinal coupling constant (3.2 Hz) than the original sulfide. The highly deshielded chemical shift for H_A (δ 4.73) suggests the configuration and conformation shown in structure **1a** in which the SO group is eclipsed with H_A. The second sulfoxide **1b** (an oil) showed a J_{AB} value of 6.9 Hz, indicative of mixed conformers. In conformer **1b**, dipolar and steric repulsions exist between oxygen and chlorine. In the alternate conformer **1b**, no 1,3 interactions exist, but the largest groups, methyl and sulfinyl, are gauche not trans. The chemical shift of H_A is less extreme (δ 4.5). The sulfone **1c** showed a J_{AB} value of 3.3 Hz. Thus, the progressive increase in size of the sulfur function in the series **1** → **1a** → **1c** involves a general strengthening of the preference for a conformer having gauche hydrogens (although part of the change in J_{AB} is due to an electronegativity effect). It is difficult to believe that the sulfone will tolerate a congested position as in conformer E_{G2}. More likely the sulfoxide and sulfone prefer conformer E_{G1}, in which the largest groups ($ArSO_2$ and CH_3) can be trans to one another. In the parent sulfide **1**, the general conformational purity is lower, but by analogy to **1a** and **1c** it seems likely that E_{G1} should have a significant population (the aromatic group is less hindered in E_{G1} than in E_{G2}). It is possible that the ir band at 653 cm^{-1} is a combination of S_{CH} and S'_{HH}, bands. It is also noteworthy that **1** is more complicated than the molecules used to establish the position of these bands. The referee is thanked for suggesting the study of the sulfone.



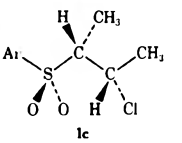
1a



1b



1b'

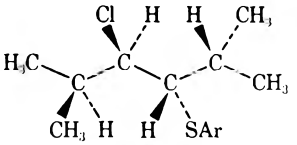


1c

The temperature effect on the spectrum of *erythro*-**1** was quite normal.[23] In benzonitrile solution, J_{AB} increased monotonically from 3.7 at *ca.* 40° to 4.7 at 130°. Unlike certain dihalides,[12] a change to a more polar solvent (DMSO) had little effect on the coupling constants of these chloro sulfides (Table I).

Moving from *erythro*-**1** to *erythro*-**2** involves a change in R′ from methyl to isopropyl. A corresponding change in J_{AB} to 7.3 Hz is observed, indicating an increased importance of E_T. However, the ir spectrum shows only a weak band at 711 cm^{-1} that can be correlated with E_T, in addition to a strong S_{CH} band, which is correlated with E_{G2}. A preference for E_{G2} rather than E_{G1} is more reasonable in this case, since the largest group (isopropyl) would be very hindered in E_{G1}. If one assumes the nmr evidence to be the more compelling, the growing preference for E_T is consistent with observations in other erythro isomers, in which the two alkyl groups seek a maximally separated orientation. The preference for E_T is stronger in the analogous dichloride (J_{AB} = 9.2 Hz), in which the chlorines probably also repel each other.

For *erythro*-**3**, R and R′ are both isopropyl. The very large J_{AB} (10.5 Hz) indicates a strong preference for conformer E_T, in which these groups are trans. The very small coupling constants for the isopropyl methine H_A and methine H_B protons (*ca.* 3 Hz), in contrast to J_{AB}, provides another illustration of the alternation of coupling constants. The alternation is the result of a preference for the conformation in which 1,3 interactions are minimized (structure b).



b

Thus, a large group at a given carbon is eclipsed only by a small group (hydrogen) at the carbon two atoms away.

The ir spectrum indicates a strong S_{HS} absorption, as expected for E_T. The ir spectrum also shows a S_{CS} band at 758 cm^{-1} (alternatively, this could be an S_{CC} absorption), which is consistent with conformer E_T but not consistent with structure b, since the S_{CS} absorption requires the sulfur to be eclipsed with carbon. At one time it was believed that such eclipsed conformations were highly improbable (by analogy to the *ca.* 3.5 kcal destabilization of eclipsed 1,3-diaxial groups in a cyclohexane system),[1-3] but recent force-field calculations have shown that 1,3-oxygen–carbon eclipsing interactions were indeed unfavorable, but not grossly so.[24] Nevertheless, structure b probably represents the major conformer.

In the series **1** → **2** → **3**, a progressive upfield shift of the nmr resonance for H_A is noted (Table I). Models show that the aromatic group is preferentially situated so that its face lies over H_A, particularly in conformer

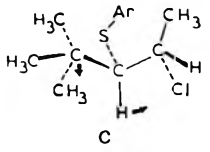
(23) J. R. Cavanaugh, *J. Amer. Chem. Soc.*, **89**, 1558 (1967), and later papers, reports an "abnormal" temperature effect. The energy difference between conformers was found to be temperature dependent.

(24) (a) C. Altona and J. Hirschmann, *Tetrahedron*, **26**, 2173 (1970); (b) see also N. L. Allinger, J. Hirsch, M. Miller, I. Tyminski, and F. VanCatledge, *J. Amer. Chem. Soc.*, **90**, 1199 (1968).

E_T. The ring current of the aryl group thus shields H_A.[25]

Like many *tert*-butyl compounds, *erythro*-**4** appears to occupy a grossly different conformation from *erythro*-**2**. The chemical shift of H_A in **4** is 0.47 ppm *downfield* from that in **2**. The very low J_{AB} suggests a preference for one of the gauche conformers. The strong S_{CH} ir band (CS_2 solution) suggests that the major conformer is E_{G2}. X-Ray structures of certain *tert*-butyl compounds by Altona and Faber have shown that the bond to the *tert*-butyl group is quite long compared to the normal C–C single bond.[26] Of greater importance is the spreading of the C–C–C(CH_3)$_3$ bond angle, which also tends to minimize the steric interactions of the *tert*-butyl group with other large groups.[26,27]

In *erythro*-**4**, the hydrogen at C_2 (structure c) would be expected to move toward C_1 as the C–C–C(CH_3)$_3$ angle spreads.[26] In conformation E_{G2}, this inward motion would be relatively facile since the hydrogen in question would approach the two smallest groups substituted at C_1, namely hydrogen and chlorine. In conformer E_T, which is less highly populated, the hydrogen at C_2 would approach methyl and chlorine upon moving inward, which should be more difficult. This deformation of the ethanic backbone would probably lead to abnormally low coupling constants, as, in fact, are observed for many *tert*-butyl compounds (*cf.* *threo*-**4**). Deviation of dihedral angles from 60°, which is an idealized value, seldom found, may also be *quite* pronounced in **4** in order that the most comfortable fit of groups may be achieved. This would also tend to lower the observed coupling constant.



C

The underlying causes for the conformations of compounds having the threo configuration is harder to evaluate, since these conformations frequently are the result of a balance between opposing effects. *threo*-**1** (R′ = CH_3) shows a very low value for J_{AB} (3.2 Hz) that is consistent with a preference for T_{G1} and/or T_{G2}.[28] The analogous dichloride shows a similarly low coupling constant. The dipole moment of the dichloride[29] indicates that the conformer with gauche chlorines, *i.e.*, T_{G1}, is quite important. However, for *threo*-**1**, the ir spectrum shows a sizable S_{HS} absorption, which suggests that T_{G2} is preferred. Oxidation of *threo*-**1** gave a sulfone having a J_{AB} of 4.7 Hz. This higher value for J_{AB} suggests that T_T has become more important, probably because the bulkiest groups (Ar–SO_2 and CH_3) are trans in this conformer. However, it is surprising that T_T is not the major conformer. *erythro*- and *threo*-**1** and their respective sulfones[22] are an unusual class of compounds in that a preference exists in both isomers for a conformer having gauche hydrogens (*cf.* Allinger's rationale).[24b]

(25) F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy," Academic Press, New York, N. Y., 1969, pp 66–70. The referee suggests that the effect of the nitro group or C–C bond anisotropies are alternative ways of explaining the shielding effect.

(26) C. Altona and D. Faber, *Chem. Commun.*, 1210 (1971).

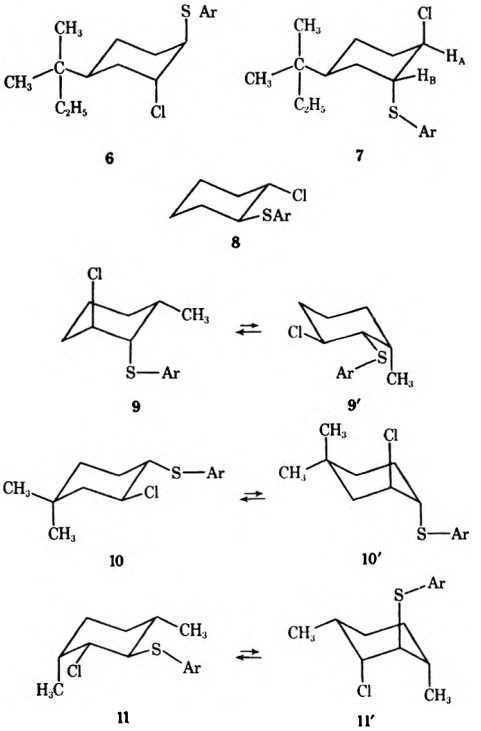
(27) C. Kingsbury and D. C. Best, *J. Org. Chem.*, **32**, 6 (1967). This paper states on the basis of ^{12}C–H coupling constants that angle spreading probably was not important on the basis of "normal" ^{13}C–H coupling constants. The $J_{^{13}C-H}$ values are no longer considered to be conclusive.

(28) The referee requested studies on cyclic molecules in order to more closely define the effects that determine conformation. Addition of 2,4-dinitrobenzenesulfenyl chloride to cyclic alkenes yields trans adducts, which are analogous to the threo diastereomers discussed above. We were unsuccessful in the synthesis of cis cyclic chloro sulfides. Addition of the sulfenyl chloride to 4-(1,1-dimethylpropyl)cyclohexene gave a mixture of **6** and **7** which resisted separation. It was possible to decouple H_A from all protons except H_B. Under these conditions, one compound, presumably **7**, showed a line separation for H_A that was independent of the exact decoupling frequency. This line separation (2.1 Hz) is probably close to the true coupling constant for gauche (equatorial–equatorial) hydrogens [see E. Garbisch, Jr., and M. Griffith, *J. Amer. Chem. Soc.*, **90**, 6543 (1968)]. The spectrum of the other compound could not be adequately decoupled, but it was clear that J_{AB} must be of similar magnitude. The conformationally mobile compound, **8**, which is analogous to *threo*-**1**, showed a J_{AB} of 7.2 Hz. The difference between *threo*-**1** (J_{AB} = 3.2 Hz) and **8** is partly due to the fact that one conformer having a low coupling constant, *i.e.*, T_{G1}, is impossible for the cyclic compound. More important, the other conformer having a low coupling constant, T_{G2}, is less probable for the cyclic compound because Cl and S–Ar are axial. Each of these axial groups is gauche to two carbon atoms, whereas if *threo*-**1** populates T_{G2}, Cl and S–Ar are each gauche to but one carbon atom.

Slight deviations from dihedral angles of 60° are common so that compounds may achieve the most comfortable fit of groups.[24] These deviations are very likely quite different in cyclic and acyclic compounds. Thus, in T_{G2} repulsions between R and R′ would tend to force these groups apart in acyclic molecules, but in cyclohexanes these "groups" move toward one another because of a slight flattening of the ring. Thus, a rigid, cyclic molecule is not necessarily a good model for an acyclic system.

However, the cyclic molecule **9**, mp 157°, shows a J_{AB} value (3.2 Hz) that is *smaller* than that of its open-chain analog, *threo*-**2**. The preference for **9** over **9′** strongly suggests that the Cl–S–Ar interaction cannot be strongly attractive and is probably repulsive. If a limiting value of *ca.* 12 Hz is assumed for a conformer having purely trans vicinal hydrogens, the conformational equilibrium may be calculated to be roughly 85% **9** and 15% **9′**. Using Hirsch's "best values" for conformational energies [*Top. Stereochem.*, **1**, 199 (1967)], and assuming no interaction of Cl and S–Ar, the equilibrium mixture is calculated to be roughly 70% **9** and 30% **9′**. The greater preference for **9** over **9′** that is observed may be ascribed to a roughly 0.5-kcal repulsion of gauche Cl and S–Ar groups.

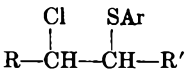
An attempt was made to synthesize a compound, *i.e.*, **10**, in which Cl and S–Ar would be almost completely equatorial. In spite of the 1,3-diaxial interaction present in **10′**, this conformer is substantially populated as shown by the fairly low J_{AB} value of 10.8 Hz. Compound **11** was synthesized to serve as an analog of *threo*-**3**. A J_{AB} value of 7.6 Hz was observed, which also suggests that **11′** has a surprisingly large population (*ca.* 40%). Thus, not only does chlorine readily tolerate an axial conformation [E. L. Eliel and R. Haber, *J. Amer. Chem. Soc.*, **81**, 1249 (1959)], but 1,3-diaxial interactions between chlorine and methyl groups appear to be much less repulsive than methyl–methyl interactions in these particular cases.



(29) A. L. McClellan, "Tables of Experimental Dipole Moments," W. H. Freeman, San Francisco, Calif., 1963, p 251.

TABLE II

INFRARED BANDS OF SULFIDE CHLORIDES 1–4 IN CS_2 SOLUTION AND AS A KBR PELLET



Compound	R	R′	S'_{HH} (632)[a]	S''_{HH} (685)	S_{CH} (666)	S_{CC} (742)	S_{HS} (700)	S_{CS} (765)
erythro-1	CH_3	CH_3		*b*	653, m	*b*	711, m	*b*
				(*b*)	(666, m)	(*b*)	(704, m)	(*b*)
threo-1	CH_3	CH_3		*b*	658, m	*b*	708, m	*b*
			(613 w)	(*b*)	(667, m)	(*b*)	(716, s)	(*b*)
erythro-2	CH_3	$CH(CH_3)_2$		*b*	653, s	*b*	711, w, sh	*b*
				(*b*)	(669, s)	(*b*)		(*b*)
threo-2	CH_3	$CH(CH_3)_2$	626, m	*b*	658, s	*b*	708, vw	*b*
			(623, s)	(*b*)	(664, s)	(*b*)		(*b*)
erythro-3	$CH(CH_3)_2$	$CH(CH_3)_2$	*b*	(694, s)[e]	650, w, sh	*d*	*e*	758, m[d]
			(*b*)	(696, s)[e]	(663, s)	(*d*)	*e*	(755, m)
threo-3	$CH(CH_3)_2$	$CH(CH_3)_2$	*b*	692, m[e]	667, sh	758, m	710 (w)	780, m
			(*b*)	(685, m)[e]	(*c*)		(*e*)	(783, m)
erythro-4	CH_3	*t*-C_4H_9		(*b*)	664, s, sh	*b*		*b*
				(*b*)	(663, m)	(*b*)	(691, s)	(*b*)
threo-4	CH_3	*t*-C_4H_9	636, s	*b*	658, w	*b*		*b*
			(633, m)	(*b*)	(665, s)	(*b*)		(*b*)

[a] The figures in parentheses refers to the expected position of the band (±20 cm^{-1}). [b] Not applicable. [c] Either superimposed on other absorptions or absent. [d] The assignment of the band at *ca.* 755 as S_{CS}, not as S_{CC}, is arbitrary. [e] The assignment of the band at *ca.* 694 as S''_{HH}, not as S_{HS}, is arbitrary.

threo-2 (J_{AB} = 4.2 Hz) shows a stronger preference for conformer T_T than *threo*-1.[28] An S'_{HH} ir band is apparent for *threo*-2, which suggests that T_{G1} has become populated. The analogous dichloride strongly prefers T_{G1} (J_{AB} = 3.7 Hz; μ = 2.4 D).[27]

A further increase in the size of the R group, *i.e.*, going to *threo*-3, results in a still larger value for J_{AB} (5.6 Hz). This value is close to the "averaged coupling constant" indicative of no strong conformational preference. The ir spectrum also indicates that a variety of conformations are populated. The increased population of T_T in the sequence **1** → **2** → **3** is unusual, since as the alkyl groups increase in size a growing preference exists for a conformer in which these groups are gauche. Molecular models suggest that the freedom of motion of the S–Ar group about the S–C and S–Ar bonds is severely restricted when R′ *and* R are isopropyl, especially in conformer T_{G1}. Thus, the isopropyl groups are most comfortable in T_{G1}, but the S–Ar is less restricted in T_T, and a mixture of these conformers results.[30]

threo-4 has a very small J_{AB} (1.3 Hz) indicative of a preference for one of the conformers having gauche hydrogens. The ir spectrum shows a strong S'_{HH} band, consistent with conformer T_{G1}; the extreme size of R appears to be dominate over the preference of S–Ar for an unrestricted position.

In summary, the ir (Table II) and nmr data are in fair agreement. Possible discrepancies have been noted for *erythro*-1 and -2, which points up the need for additional studies of the two methods. No evidence exists for an attractive Cl—S–Ar interaction in these compounds, but this interaction is not strongly repulsive.[28] The Br—S–Ar or I—S–Ar interaction, however, may be quite different, and it is regretable that compounds having these substituents are rather unstable and difficult to study.

Although a preference exists in *erythro*-1 for a conformer having gauche Cl and S–Ar groups, this preference probably is not the result of an attractive interaction between these groups. In the cyclohexane system[28] and in the threo isomers, no particular tendency for having gauche Cl and S–Ar groups was evident. In *erythro*-1, the preference for a conformer with gauche Cl and S–Ar groups probably is the consequence of minimized unfavorable interactions in these conformer(s). However, in the erythro set of compounds, gauche Cl and S–Ar groups are more tolerable than gauche Cl–Cl groups. The dichlorides show a much stronger preference for conformer E_T.

Although it is particularly difficult to pinpoint any one factor as strongly conformationally determinative in **1**–**4**, the restriction of motion of the S–Ar group seems to be fairly important. This was rather unexpected, since in a cyclohexane system the groups OH, OCH_3, OAc, and OTs have similar conformational preferences, as do SH and S–Ph groups. In the latter case, however, the Ph group is gauche to carbon and to hydrogen in either of the axial or equatorial conformations of sulfur. In an open chain compound, a greater choice of conformation is open to the aromatic group. In the S–Ar group of this study, the greater spatial requirements of the Ar group because of the ortho nitro function are also important.

(30) An increase in temperature of *ca.* 100° led to little or no change in vicinal coupling constant, which suggests that little difference in energy exists between the various conformers.

Experimental Section

Reaction of 2-Butenes with 2,4-Dinitrobenzenesulfenyl Chloride (12).—Into a solution of 12 (7.02 g, 0.03 mol) in dry acetic acid (75 ml) at room temperature was bubbled the appropriate isomer of 2-butene (*trans*-2-butene for the erythro adduct and *cis*-2-butene for the threo adduct). When the gas flow had started, the flask was cooled in an ice bath until the product solidified. The gas flow was then stopped, the flask corked, and the mixture allowed to stand for 2 hr, warming to room temperature. The mixture was then heated on the steam bath for 20 min and removed, and 2-butene again was bubbled into the solution while cooling to solidification. This process was repeated two more times. From the reactions were obtained the erythro adduct (7.91 g, 90%) with mp 75.5–76° (recrystallized from chloroform–pentane) (lit.[16b] 76.5–77.5°) and the threo adduct (6.44 g, 73%) with mp 140.3–149.7° (from chloroform–pentane) (lit.[16c] 128–129°).

erythro-2-Chloro-3-butyl 2,4-dinitrophenyl sulfide (1): ir (KBr) ~1590, ~1530, ~1505, 1448, 1394, 1387, 1381, ~1340, 1290, 1243, 1162, 1134, 1094, 1068, 1050, 983, 963, 916, 849, 833, 747, 735, 703, 676, 665, 605, 547, 518, 494, 416 cm^{-1}.

threo-2-Chloro-3-butyl 2,4-dinitrophenyl sulfide (1): ir (KBr) ~1590, ~1520, 1451, 1377, ~1340, 1244, 1156, 1138, 1100, 1052, 1014, 988, 917, 849, 834, 826, 762, 746, 735, 716, 708, 685, 667, 614, 590, 545, 529, 495, 480, 426 cm^{-1}.

Anal. Calcd for $C_{10}H_{11}ClN_2O_4S$: C, 41.31; H, 3.81. Found: C, 41.37, H, 3.88.

Reaction of 4-Methyl-2-pentenes with 12.—To a solution of the appropriate alkene (2.10 g, 0.025 mol) in dry acetic acid (10 ml) was added 12 (6.37 g, 0.027 mol). The reaction yielded 7.21 g (90%) of the erythro adduct (from trans alkene) with mp 89.0–89.5° (from dichloromethane–pentane) and 7.03 g (88%) of the threo adduct (from cis alkene) with mp 92.5–93.0° (from dichloromethane–pentane).

erythro-2-Chloro-4-methyl-3-pentyl 2,4-dinitrophenyl sulfide (2): ir (KBr) 1588, ~1520, 1471, 1462, 1451, ~1340, 1297, 1244, 1213, 1151, 1133, 1092, 1050, 1004, 918, 902, 882, 842, 830, 812, 744, 733, 728, 677, 669, 605, 548, 532, 502, 479, 434 cm^{-1}.

Anal. Calcd for $C_{12}H_{15}ClN_2O_4S$: C, 45.21; H, 4.74. Found: C, 45.21; H, 4.71.

threo-2-Chloro-4-methyl-3-pentyl 2,4-dinitrophenyl sulfide (2): ir (KBr) ~1585, ~1520, 1450, 1391, 1378, ~1340, 1152, 1135, 1093, 1054, 1045, 991, 957, 912, 895, 831, 820, 805, 754, 740, 732, 684, 664, 623, 595, 579, 549, 540, 522, 483, 472, 433, 413 cm^{-1}.

Anal. Calcd for $C_{12}H_{15}ClN_2O_4S$: C, 45.21; H, 4.74. Found: C, 45.09; H, 4.75.

Reaction of 2,5-Dimethyl-3-hexenes with 12.—To a solution of the appropriate alkene (2.12 g, 0.0190 mol) in dry acetic acid (10 ml) was added 12 (4.90 g, 0.0208 mol). The reactions formed 5.89 g (89%) of the erythro adduct (from trans alkene) with mp 97.5–98.0° (chloroform–pentane) and 5.82 g (88%) of the threo adduct (from cis alkene) with mp 69.5–70.0° (chloroform–pentane).

erythro-3-Chloro-2,5-dimethyl-4-hexyl 2,4-dinitrophenyl sulfide (3): ir ~1590, ~1515, 1471, 1460, 1389, ~1340, 1182, 1149, 1137, 1102, 1091, 1051, 615, 837, 831, 804, 760, 755, 740, 731, 696, 675, 664, 601, 548, 531, 520, 498, 471 cm^{-1}.

Anal. Calcd for $C_{14}H_{19}ClN_2O_4S$: C, 48.48; H, 5.52. Found: C, 48.29; H, 5.38.

threo-3-Chloro-2,5-dimethyl-4-hexyl 2,4-dinitrophenyl sulfide (3): ir (KBr) 1590, 1515, 1463, 1390, ~1340, 1302, 1244, 1145, 1101, 1052, 918, 913, 832, 820, 783, 742, 732, 685, 667, 612, 601, 536, 515, 475 cm^{-1}.

Anal. Calcd for $C_{14}H_{19}ClN_2O_4S$: C, 48.48; H, 5.52. Found: C, 48.66; H, 5.40.

Preparation of *erythro*-2-Chloro-4,4-dimethyl-3-pentyl 2,4-Dinitrophenyl Sulfide (4).—To a solution of *trans*-4,4-dimethyl-2-pentene (2.0 g, 0.0204 mol) in dry acetic acid (10 ml) was added 12 (5.00 g, 0.0213 mol). The reaction formed 5.51 g (81%) of yellow plates: mp 106.0–106.5° (from chloroform–pentane); ir (KBr) ~1590, ~1520, 1481, 1465, 1459, 1396, 1389, 1375, ~1340, 1251, 1243, 1220, 1146, 1134, 1116, 1098, 1047, 1016, 994, 916, 907, 862, 833, 830, 775, 746, 737, 731, 690, 674, 663, 594, 545, 533, 520, 498, 471, 433, 422, 411 cm^{-1}.

Anal. Calcd for $C_{13}H_{17}ClN_2O_4S$: C, 46.92; H, 5.15. Found: C, 46.83; H, 5.18.

Preparation of *threo*-2-Chloro-4,4-dimethyl-3-pentyl 2,4-Dinitrophenyl Sulfide (4).—To a solution of *cis*-4,4-dimethyl-2-pentene (2.6 g, 0.026 mol) in DMF (10 ml) was added 12 (6.6 g, 0.028 mol). The reaction formed 6.44 g (74%) of yellow plates: mp 107.5–108.0° (from dichloromethane–pentane); ir (KBr) 1596, 1589, 1520, ~1515, 1500, 1488, 1478, 1471, 1463, 1451, 1436, 1242, 1144, 1133, 1094, 1050, 1031, 917, 904, 870, 842, 836, 773, 762, 741, 732, 689, 664, 632, 593, 549, 531, 522, 507, 471 cm^{-1}.

Anal. Calcd for $C_{13}H_{17}ClN_2O_4S$: C, 46.92; H, 5.15; N, 8.42. Found: C, 46.81; H, 5.19; N, 8.22.

The nmr data were taken on a A-60D or XL-100 instrument at normal probe temperature. Coupling constants were determined from the average of two to three traces of 100-Hz expansions of the region in question. The concentration of the samples was *ca.* 10% ($CDCl_3$) or 10.0% (DMSO). The correctness of the nmr parameters was verified by simulation of the spectrum using the LAOCOON III computer program[31] equipped with a California Computer Products plot of the simulation. The parameters were varied until the simulated plot was superimposible on the original spectrum.

The infrared data were determined on Perkin-Elmer 231 or 621 instruments, usually the latter. The spectra were run at a concentration of *ca.* 0.2–0.6% w/v in CS_2 solution. The KBr spectra were run by the usual method. Nmr spectra were run in CS_2 solution at the same concentration as the ir spectra were taken. Only minor differences from the data given in Table I were noted.

Registry No.—*erythro*-1, 38434-69-4; *threo*-1, 38434-70-7; *erythro*-2, 38434-71-8; *threo*-2, 38434-72-9; *erythro*-3, 38434-73-0; *threo*-3, 38434-74-1; *erythro*-4, 38434-75-2; *threo*-4, 38434-76-3; 12, 528-76-7; *cis*-butene, 590-18-1; *trans*-butene, 624-64-6; *cis*-4-methyl-2-pentene, 691-38-3; *trans*-4-methyl-2-pentene, 674-76-0; *cis*-2,5-dimethyl-3-hexene, 10557-44-5; *trans*-2,5-dimethyl-3-hexene, 692-70-6; *cis*-4,4-dimethyl-2-pentene, 762-63-0; *trans*-4,4-dimethyl-2-pentene, 690-08-4.

Acknowledgments.—The award of the Texaco fellowship to G. M. U. is gratefully acknowledged. Partial funds for the purchase of the XL-100 nmr instrument were provided by NSF GP-10293, which is gratefully acknowledged.

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The Photochemistry of Aromatic Thiol Esters

JOHN R. GRUNWELL,*[1] NEIL A. MARRON, AND SALIBA I. HANHAN

Hughes Laboratories, Miami University, Oxford, Ohio 45056

Received August 31, 1972

The photolysis of a variety of aromatic thiol esters was investigated in cyclohexane using a 254-nm light source. The photochemical reaction proceeds initially by cleavage of the *S*-acyl bond, giving rise to the corresponding aromatic thiyl radical and an acyl radical which sometimes decarbonylates. The resulting radicals recombine to give disulfides, sulfides, and hydrocarbons. Acyl radicals which are less prone to decarbonylation abstract hydrogen to form aldehydes. No photo-Fries rearrangement and a minor amount of Norrish type II cleavage were observed. Sulfide formation appears to be intermolecular.

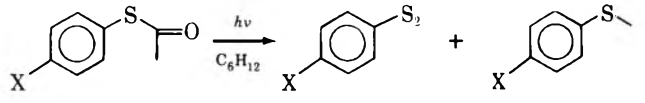
We found that the photolysis of 4-tolyl thiolacetate gave 4-tolyl disulfide and methyl 4-tolyl sulfide but no 4-toluenethiol nor any photo-Fries rearrangement.[2] Subsequently, Bradshaw and coworkers[3] reported the major products of the photolysis of phenyl thiolacetate to be phenyl disulfide, methyl phenyl sulfide, and thiophenol, which arises from secondary photolysis of phenyl disulfide without the intervention of solvent,[4] plus minor amounts of the corresponding photo-Fries products.

The purpose of this paper is to report the photochemistry of several aryl thiol esters in an effort to uncover partially the nature of the excited state responsible for the photoreaction, to discover whether or not sulfide formation is intramolecular, and to explain the lack of photo-Fries rearrangement in thiol esters.

Results

Irradiation of approximately 1% solutions of 4-substituted phenyl thiolacetates **1** in cyclohexane for 3 hr using a 254-nm light source produced the corresponding diphenyl disulfides **2** and methyl phenyl sulfides **3** as shown in Scheme I. In no case were the

SCHEME I

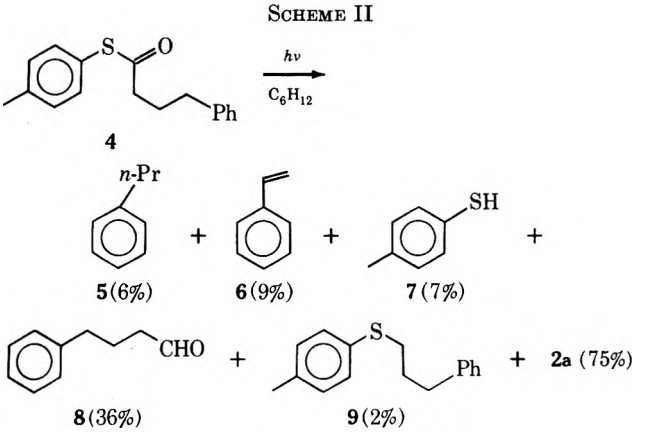


1a, X = CH_3	**2a**, 77%	**3a**, 7%
b, X = $(CH_3)_2N$	**b**, 77%	**b**, 7%
c, X = NO_2	**c**, 90%	**c**, 8%

4-substituted thiophenol or the photo-Fries rearrangement products found, a result which is in striking contrast to the reported photolysis of phenyl thiolacetate.[3] While esters **1a** and **1b** were 75 and 78% photolyzed after 3 hr, the nitro ester **1c** was only 47% gone because precipitation of the disulfide **2c** coated the vessel wall.

Irradiation of 4′-tolyl thiol-4-phenylbutyrate (**4**) with 254-nm light in cyclohexane solution (Scheme II) gave propylbenzene (**5**), styrene (**6**), 4-toluenethiol (**7**), 4-phenylbutanal (**8**), 3-phenylpropyl 4′-tolyl sulfide (**9**), 4-tolyl disulfide (**2a**), and a trace of 4-tolyl thiolacetate (**1a**). Clearly, the Norrish type II reaction is relatively inefficient as compared to cleavage of the *S*-acyl bond.

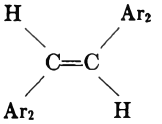
SCHEME II



To determine whether or not sulfide formation is intramolecular, photolysis of the esters phenyl 4-toluenethiolacetate (**10**) and 4′-tolyl benzenethiolacetate (**11**) was examined (Table I) because the expected

TABLE I[a]

PRODUCT YIELDS FOR *hν* OF ESTERS 10 AND 11

Products		*hν* of $Ar_1SC(=O)CH_2Ar_2$	*hν* of $Ar_2SC(=O)CH_2Ar_1$	*hν* of 10 + 11
$(Ar_1CH_2)_2$	12		28	6
$(Ar_2CH_2)_2$	14	18		3
$Ar_1CH_2CH_2Ar_2$	22			2
$(Ar_1S)_2$	16	25		16
$(Ar_2S)_2$	2a		35	40
Ar_1SSAr_2	23			5
$Ar_1CH_2SAr_2$	13		13	5
$Ar_2CH_2SAr_1$	15	3		2
$Ar_1CH_2SAr_1$	20			6
$Ar_2CH_2SAr_2$	21			11
Ar_2CH_3	17	8		
Ar_1SH	18	18		
	19	19		

[a] Yields are given in per cent; $Ar_1 = C_6H_5$; $Ar_2 = 4\text{-}CH_3C_6H_4$.

acyl radicals readily decarbonylate. The photolysis of **10** gave 1,2-diphenylethane (**12**), benzyl 4-tolyl sulfide (**13**), and the disulfide **2a**. Thiol ester **11** formed not only 1,2-di(4′-tolyl)ethane (**14**), 4-tolyl phenyl sulfide (**15**), and diphenyl disulfide (**16**), but also 4-xylene (**17**), thiophenol (**18**), and *trans*-4,4′-dimethylstilbene (**19**). After 3 hr the esters **10** and **11** have photolyzed 85 and 87%, respectively. However, when an equimolar solution of **10** and **11** was photolyzed for

(1) Summer Faculty Research Fellow, Miami University, 1971.

(2) J. R. Grunwell, *Chem. Commun.*, 1437 (1969).

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3 hr in cyclohexane, **10** disappeared about twice as fast as **11**. In addition to products **12**–**16**, the mixed sulfides **20** and **21**, the mixed hydrocarbon **22**, and the mixed disulfide **23** were also formed. Sulfide formation appears to be intermolecular for these esters. Laarhoven and coworkers have shown that benzyl sulfides photodissociate to benzyl and thiyl radicals.[5a,b] However, this reaction is slower than the photodissociation of the thiol esters. For instance, the sulfide **15** disappeared 40% after 3 hr of photolysis under identical conditions as **10** and **11**.[5c] Therefore, the "cross" sulfides arise only partially from secondary photolysis of **13** and **15**. The product ratios for the photolysis of **10** and **11** are shown in Table II and are all between 2 and 2.5, while the ratio **10**/**11** = 2.22 for the disappearance of **10** and **11**.

TABLE II
PRODUCT RATIOS

Product	Ratio
10/11	2.22
12/14	2.00
2a/16	2.48
13/15	2.50
21/20	1.88

Another series of experiments which has bearing on the intramolecularity of sulfide formation is summarized in Table III. When 4-tolyl thiolacetate (**1a**) and an equimolar amount of thiophenol (**18**) dissolved in cyclohexane were photolyzed for 3 hr, phenyl thiolacetate (**24**), methyl phenyl sulfide (**25**), and 4-tolenethiol (**7**) in addition to the disulfides **16**, **2a**, and **23** were formed. Unfortunately, we were unable to observe the photo-Fries products.

TABLE III[a]
PHOTOLYSIS OF ARYLTHIOL ESTER WITH ARYLTHIOL

Compd		$Ar_1SC(=O)CH_3$ **1a** + Ar_1SH **18**	$Ar_1SC(=O)CH_3$ **24** + Ar_2SH **7**
Ar_1SH	18	4	8
Ar_2SH	7	5	6
Ar_1SCOCH_3	24	3	28
Ar_2SCOCH_3	1a	9	11
Ar_1SCH_3	25	5	0
Ar_2SCH_3	3a	<1	0
$(Ar_1S)_2$	16	32	4
$(Ar_2S)_2$	2a	14	22
Ar_1SSAr_2	23	16	9
Ar_1S-c-C_6H_{11}	27	2	<1
Ar_2S-c-C_6H_{11}	26	1	2

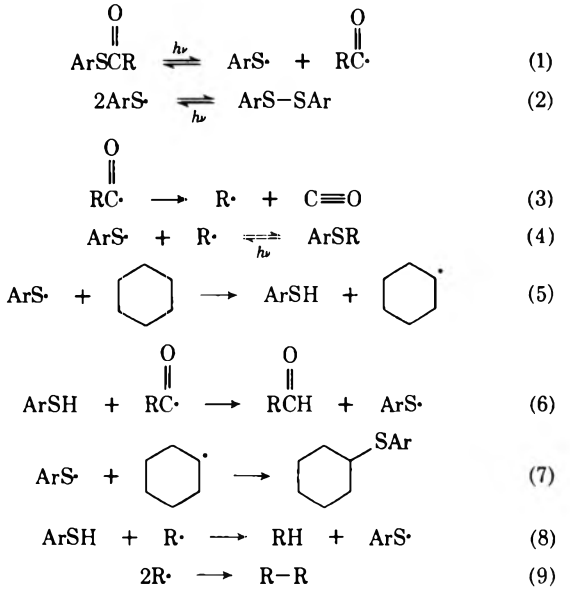
[a] Yields are given in per cent; $Ar_1 = C_6H_5$; $Ar_2 = 4\text{-}CH_3C_3H_4$.

When phenyl thiolacetate (**24**) and 4-toluenethiol (**7**) were photolyzed, the ester **1a** was formed in addition to the other products with the exception of the sulfides **3a** and **25**. The formation of methyl phenyl sulfide (**25**) from **1a** and **18** does not arise from secondary photolysis of **24**, since we found more **25** than **24**, and at no time does the sulfide **25** exceed the amount of ester **24** when **24** is irradiated in the absence of the thiol **7**, as shown by Bradshaw.[3] Therefore, sulfide formation appears to be intermolecular. Further, the acetyl radical has sufficient stability and lifetime to diffuse away from its original partner and then combine with another thiyl radical to generate a new ester. It seems possible that the photo-Fries rearrangement observed by Bradshaw may be intermolecular.

Discussion

The products of the photolyses seem best accounted for by homolytic cleavage of the S–acyl bond of the excited thiol ester followed by a series of dark reactions typical of the radicals produced. The proposed mechanism is summarized in Scheme III. The acyl radical is reduced to the corresponding aldehyde but will decarbonylate when the resulting radical is stabilized by a phenyl group. The acyl radical also reacts with the thiyl radical chiefly at sulfur, since the spin density of an aryl thiyl radical is largely localized on sulfur according to esr measurements.[6]

SCHEME III



The observed Norrish II cleavage[7] is inefficient as compared to the α cleavage of the S–acyl bonds. There is much less 4-tolyl thiolacetate than styrene. Two explanations are possible: (1) the concentration of the ester **1a** is reduced by secondary photolysis; or (2) most of the styrene is formed from a Norrish II cleavage of the phenylaldehyde **8**. The first hypothesis is unlikely, since the sulfide **3a** is not found. The second explanation seems plausible, since aldehydes are known to undergo Norrish II cleavage.[7] The inefficient Norrish II reaction of the phenylthiobutyrate ester **4** is mirrored by the lack of the corresponding McLafferty rearrangement in the mass spectrum of **4**.

The lack of a photo-Fries rearrangement for 4-substituted phenyl thiyl radicals is not strictly due to localization of spin on sulfur, since phenyl thiyl radical gives some photo-Fries products. Electron-donating and -withdrawing substituents will stabilize benzyl

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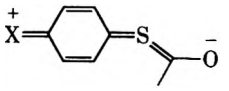
radicals by delocalization, and therefore it seems probable that what spin density is localized on the ortho position is diminished by the para substituent, thus rendering the ortho position of the thiyl radical unreactive.

While it seems likely that the photo-Fries rearrangement occurs by a radical mechanism,[8] the possibility exists that rearrangement proceeds through an intimate contact 1,3-sigmatropic change of order;[9] *i.e.*, the acyl group remains bonded to the rest of the molecule during rearrangement. If structures of the quinoid type such as **28** were important in the excited state



28

of 4-substituted (electron-donating substituents) as proposed by Cilento[10] and Baliah,[11] then the photo-Fries rearrangement would be hindered, since the phenyl and acyl groups would be coplanar. However, we can find no evidence which establishes the importance of **28** in the excited state of phenyl thiolacetates.[12] Therefore we prefer the explanation based on a free-radical mechanism.

Experimental Section

Boiling and melting points are uncorrected. All uv spectra were recorded on a Cary 14 spectrophotometer, ir spectra on a Perkin-Elmer 237 spectrophotometer, nmr spectra on a Jeolco C-60H spectrometer, and mass spectra on a Hitachi RMU-6 spectrometer. Gas chromatograms were obtained from a Hewlett-Packard 700 chromatograph equipped with a 4-ft 10% Carbowax 20M (Chromosorb P), a 6-ft 10% Carbowax 20M (Chromosorb W), or a 6-ft 15% SE-30 (Chromosorb P) column. Microanalyses were performed by Galbraith Laboratories, Inc. Cyclohexane was purified by washing with 18 *N* sulfuric acid and then distilled water followed by distillation from barium oxide. Acetonitrile and 1,4-dioxane were Matheson spectroquality reagents. All photolysis experiments were conducted in a Rayonet photochemical reactor equipped with 2537-Å mercury vapor lamps. All photochemical yields are based on the amount of ester which has disappeared.

4-Tolyl Thiolacetate (1a).—From acetyl chloride, 70.0 g (0.90 mol), 107.0 g (0.86 mol) of 4-toluenethiol, and 110.0 g of triethylamine, there was obtained 120.0 g (85%) of **1a**: bp 122° (10 mm) [lit.[13] bp 120° (11 mm)]; ir (neat) 3490 (w), 3020 (w), 2910 (w), 2860 (w), 1710 (s), 1590 (w), 1490 (w), 1350 (m), 1120 (s), 1090 (m), 1020 (m), 950 (m), and 910 cm^{-1} (s); uv max (cyclohexane) 233 mμ (ε 12,000); mass spectrum (80 eV) *m/e* (rel intensity) 166 (3), 124 (61), 123 (21), 91 (32), and 43 (100).

Photolysis of 1a.—Oxygen was removed from a solution of 3.0 g (0.0018 mol) of **1a** in 600 ml of cyclohexane by bubbling dry prepurified N_2 gas into the solution, which was irradiated for 10 hr and evaporated to give 2.39 g of a residue which was a mixture of **1a**, **2a**, and **3a**. Yields of **2a** and **3a** were determined using *n*-hexadecane as internal standard on glpc. **2a**[14] (77%) had ir (KBr) 2917 (m), 1491 (s), 1085 (m), and 805 cm^{-1} (s); mass spectrum (80 eV) *m/e* (rel intensity) 246 (52), 124 (31), 123 (100), 91 (47), and 45 (59). **3a**[15] (7%) had ir (neat) 3022 (w), 2917 (s), 1498 (s), 1443 (s), 1099 (s), 810 (s), 729 (w), and 709 cm^{-1} (w); mass spectrum (80 eV) *m/e* (rel intensity) 138 (100), 137 (19), 123 (36), 91 (16), and 45 (43).

4-*N*,*N*-Dimethylaminophenyl Thiolacetate (1b).—A solution of **2b** (5 g, 0.017 mol), 20 ml of acetic anhydride, and 20 ml of acetic acid was refluxed for 3 hr over 5 g of Zn and gave white crystals (recrystallized from EtOH): 4.3 g (67%); mp 81° (lit.[11] mp 80–81°); ir (KBr) 2884 (s), 1691 (s), 1597 (s), and 637 cm^{-1} (s); uv max (cyclohexane) 270 mμ (ε 26,000); mass spectrum (80 eV) *m/e* (rel intensity) 195 (32), 154 (13), 153 (100), 152 (90), and 120 (39).

Photolysis of 1b.—A deoxygenated solution of 0.237 g (0.0012 mol) of **1b** in 15 ml of cyclohexane was irradiated for 3 hr to give a mixture of **1b**, **2b**, and **3b**. The yield of **3b** was determined by glpc using benzyl tolyl sulfide as internal standard. **3b**[16] (7%) had mass spectrum (80 eV) *m/e* (rel intensity) 167 (52), 166 (29), 153 (14), 152 (100), 151 (61), and 45 (29). The mixture was triturated with ethanol and the yellow precipitate isolated was **2b**: 0.11 g (77%); mp 117° (lit.[17] mp 118°); ir (KBr) 2895 (m), 1579 (s), 1359 (s), and 808 cm^{-1} (s); mass spectrum (80 eV) *m/e* (rel intensity) 304 (8), 273 (36), 254 (10), 240 (30), 154 (13), 153 (94), 152 (100), 136 (30), and 120 (38).

4-Nitrophenyl Thiolacetate (1c).[18]—Acetic anhydride (16.5 g, 0.16 mol) was added to 25 g (0.16 mol) of 4-nitrothiophenol together with 5 drops of triethylamine. After 5 hr the yellow solid was recrystallized (50:50 NC_6H_{14}–THF) to 12 g (48%) of **1c**: mp 76–78°; ir (KBr) 3116 (m), 1716 (s), 1607 (s), 1480 (m), 1405 (m), and 747 cm^{-1} (s); uv max (cyclohexane) 285 mμ (ε 11,000) and 227 (5600); mass spectrum (80 eV) *m/e* (rel intensity) 197 (48), 156 (10), 155 (77), 139 (40), 125 (87), 43 (61), and 42 (60).

Photolysis of 1c.—A deoxygenated solution of 0.0213 g (0.108 mmol) of **1c** in 15 ml of cyclohexane was irradiated for 3 hr. The disulfide **2c** precipitated to give 0.0070 g (90%): mp 176–178° (lit.[19] mp 179–181°); ir (KBr) 1575 (m), 1490 (s), 1450 (m), 1330 (s), 850 (s), and 730 cm^{-1} (s). The solution was evaporated and analyzed on glpc, which showed the sulfide **3c** (8%) (lit.[20] mp 72°): mass spectrum (70 eV) *m/e* (rel intensity) 153 (100), 152 (93), 137 (30), 120 (64), and 109 (20).

4′-Tolyl Thiol-4-phenylbutyrate (4).—4-Phenylbutyryl chloride[21] (**29**) was prepared from thionyl chloride and 4-phenylbutanoic acid. A solution of 14.8 g (0.0815 mol) of **29** in 100 ml of dry ether was added to a solution of 10.1 g (0.0815 mol) of **7** and 6.4 g (0.0815 mol) of pyridine in 250 ml of ether maintained at 0°. The ether was washed (5% HCl, H_2O), dried ($MgSO_4$), filtered, and evaporated. The distilled residue was the ester **4**: 17.6 g (80%); bp 187° (5 mm); ir (CCl_4) 3030 (s), 2930 (s), 1705 (s), 1450 (s), and 1160 cm^{-1} (s); nmr δ 2.13 (quintet, 2, J = 7.0 Hz), 2.40 (s, 3), 2.60 (t, 4, J = 7.0 Hz), and 7.22 (s, 9); mass spectrum (70 eV) *m/e* (rel intensity) 270 (10), 147 (75), 124 (24), 123 (10), 91 (100), and 77 (10).

Anal. Calcd for $C_{17}H_{18}OS$: C, 75.51; H, 6.71; S, 11.86. Found: C, 75.51; H, 6.75; S, 12.06.

Photolysis of 4.—A deoxygenated solution of **4** (0.119 g, 0.436 mmol) in 15 ml of cyclohexane was irradiated for 3 hr and then evaporated to give a residue which was analyzed with glpc using triphenylmethane as internal standard. The residue contained **5** (6%), **6** (9%), **7** (7%), **8**[22] (36%), **2a** (75%), and **9** (2%). The compounds **5**, **6**, **7**, **8**, and **2a** were identified by comparison of mass spectral data with those of authentic samples. **5** had mass spectrum (70 eV) *m/e* (rel intensity) 120 (19), 118 (13), 117 (17), and 91 (100); **6**, 104 (100), 103 (41), and 78 (31); **7**, 124 (100), 91 (26), and 78 (32); **8**, 148 (5), 104 (100), and 91 (53). The sulfide **9** and **2a** were not separable on glpc but the yield of **9** was estimated from mass spectral analysis.

3-Phenylpropyl 4′-Tolyl Sulfide (9).—A solution of 10.7 g (0.054 mol) of 3-bromopropylbenzene in 80 ml of ethanol was added to a solution of 3.03 g (0.054 mol) of KOH and 6.7 g (0.054 mol) of **7** in 175 ml of EtOH at 0°. The mixture was stirred overnight and filtered and the filtrate was evaporated to give a residue which was dissolved in ether and washed (5% HCl, H_2O), dried ($MgSO_4$), filtered, and evaporated. The residue was dis-

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tilled to give an oil 9: 10.2 g (78%); bp 150° (0.18 mm); ir (CCl_4) 3070 (s), 2900 (s), 1600 (m), 1480 (s), and 1430 cm^{-1} (s); nmr δ 1.95 (quintet, 2, J = 7.0 Hz), 2.27 (s, 3), 2.75 (t, 4, J = 7.0 Hz), 7.07 (s, 4), 7.15 (s, 5); mass spectrum (70 eV) m/e (rel intensity) 242 (33), 137 (10), 124 (91), 91 (100), and 77 (18).

Anal. Calcd for $C_{16}H_{18}S$: C, 79.31; H, 7.49; S, 13.20. Found: C, 79.38; H, 7.56; S, 12.81.

Phenyl 4-Toluenethiolacetate (10).—To an ethereal solution of 7.04 g (0.05 mol) of **7** and 5.8 g of Et_3N at 0° was added 8.81 g (0.057 mol) of phenylacetyl chloride to give 10.4 g (80%) of **10**: mp 60–62° (lit.[23] mp 59–61°); ir (CCl_4) 3030 (s), 2920 (m), 1700 (s), 1600 (m), 1480 (s), and 1460 cm^{-1} (s); nmr (CCl_4) δ 2.43 (s, 3), 3.85 (s, 2), 7.25 (s, 4), and 7.35 (s, 5); mass spectrum (70 eV) m/e (rel intensity) 242 (7), 124 (42), 118 (100), and 91 (93).

Photolysis of 10.—A deoxygenated solution of 0.142 g (0.59 mmol) of **10** in 15 ml of cyclohexane was irradiated for 3 hr and then evaporated, and the residue was analyzed in glpc with triphenylmethane was internal standard. The mixture contained **12** (28%), **13** (13%), and **2a** (35%). The compounds were identified by mass spectrometry: **12**, mass spectrum (70 eV) m/e (rel intensity) 182 (53), 91 (100), and 77 (17); **13**, mp 65–66° (lit.[24] mp 64–66°), mass spectrum (70 eV) m/e (rel intensity) 200 (19), 109 (6), and 91 (100).

4'-Tolyl Benzenethiolacetate (11).—The ester **11** was prepared by a similar procedure as reported for **10**. We obtained 3.3 g (20%) of **11**: mp 35–37° (lit.[23] mp 36–37°); ir (CCl_4) 3050 (m), 2950 (s), 1710 (s), 1475 (s), and 1415 cm^{-1} (s); nmr (CCl_4) δ 2.43 (s, 3), 3.85 (s, 2), 7.17 (s, 5), and 7.37 (s, 4); mass spectrum (70 eV) m/e (rel intensity) 242 (3), 133 (9), 110 (5), 109 (9), 105 (100), and 77 (13).

Photolysis of 11.—A deoxygenated solution of 0.151 g (0.62 mmol) of **11** in 15 ml of cyclohexane was irradiated for 3 hr and evaporated to give a residue which was analyzed by glpc with triphenylmethane as standard. The residue contained **14** (18%), **15**[24] (3%), **16** (25%), **17** (8%), **18** (11%), and **19**[25] (7%). The products were identified by mass spectrometry. **14** had mass spectrum (70 eV) m/e (rel intensity) 210 (16), 105 (100), 79 (10), and 77 (12); **15** had mass spectrum (70 eV) m/e (rel intensity) 214 (15), 109 (5), 105 (100), and 77 (12); **16** had mass spectrum (70 eV) m/e (rel intensity) 218 (77), 109 (100), and 77 (25); **17** had mass spectrum (70 eV) m/e (rel intensity) 106 (48), 105 (25), 91 (100) and 77 (14); **18** had mass spectrum (70 eV) m/e (rel intensity) 110 (100), 109 (31), 84 (23), and 77 (21); **19** had mass spectrum (70 eV) m/e (rel intensity) 208 (100), 178 (61), and 91 (17).

Photolysis of 10 and 11.—A solution of 0.076 g (0.31 mmol) of **10** and **11** in 15 ml of cyclohexane was irradiated for 3 hr and evaporated to give a residue which was analyzed on glpc. The mixture contained **12** (6%), **14** (3%), **22** (2%), **13** (5%), **15** (2%), **20**[26] (6%), **21**[24] (11%), **16** (16%), **3a** (40%), and **23**[27] (5%). The products were identified by mass spectrometry. **20** had mass spectrum (70 eV) m/e (rel intensity) 200 (19), 109 (6), 91 (100), and 77 (4); **21** had mass spectrum (70 eV) m/e (rel intensity) 228 (65), 123 (17), 105 (100), 91 (21), 79 (51), and 77 (56).

Photolysis of 18 and 1a.—A deoxygenated solution of 0.14 g (1.3 mmol) of **18** and 0.22 g (1.3 mmol) of **1a** in 15 ml of cyclohexane was irradiated for 3 hr, evaporated, and analyzed using glpc with p-xylene as standard. The mixture contained **7** (5%), **18** (4%), **3a** (1%), **25** (5%), **1a** (9%), **24** (3%), **16** (32%), **2a** (14%), **23** (16%), **26** (2%), and **27** (1%). The products were identified by mass spectrometry. **26**[28] had mass spectrum (70 eV) m/e (rel intensity) 192 (23), 110 (100), 109 (16), and 83 (14); and **27**[28] had mass spectrum (70 eV) m/e (rel intensity) 206 (20), 124 (100), and 91 (56).

Photolysis of 7 and 24.—A solution of 0.19 g (1.5 mmol) of **7** and 0.22 g (1.5 mmol) of **24** was photolyzed and analyzed in the same way as **18** and **1a**. The mixture contained **7** (6%), **18** (8%), **1a** (11%), **24** (28%), **16** (4%), **2a** (22%), **23** (9%), **26** (1%), and **27** (2%).

Phenyl Thiolacetate (24).—The ester **24** was prepared by a method similar to that for **1c**. We obtained 8.6 g (57%): bp 110–111° (11 mm) [lit.[13] bp 91° (7 mm)]; mass spectrum (80 eV) m/e (rel intensity) 152 (33), 110 (91), 109 (53), 77 (16), and 43 (100). Other spectral data are the same as reported by others.[3,13]

Registry No.—**1a**, 10436-83-6; **1b**, 14297-63-3; **1c**, 15119-62-7; **2a**, 103-19-5; **2b**, 5397-29-5; **3a**, 623-13-2; **3b**, 2388-51-4; **4**, 38644-96-1; **7**, 106-45-6; **9**, 38644-97-2; **10**, 38644-98-3; **11**, 18241-65-1; **18**, 108-98-5; **14**, 934-87-2; 4-phenylbutyryl chloride, 18496-54-3; 3-bromopropylbenzene, 637-59-2.

(23) J. Morgenstern and R. Mayer, *Z. Chem.*, **8**, 146 (1968).
(24) R. F. Brooks, N. G. Clark, J. E. Cranshaw, D. Greenwood, J. R. Marshall, and H. A. Stevenson, *J. Sci. Food Agr.*, **9**, 111 (1958).
(25) R. N. Sieber, *Justus Liebigs Ann. Chem.*, **730**, 31 (1969).
(26) E. A. Lehto and D. A. Shirley, *J. Org. Chem.*, **22**, 989 (1957).
(27) A. B. Sullivan and K. Boustany, *Int. J. Sulfur Chem., Part A*, **1**, 121 (1971).
(28) J. I. Cuneen, *J. Chem. Soc.*, 36 (1947).

Synthesis of Octahydrothiopyrano[3,2-*b*]thiopyran and Certain Derivatives[1]

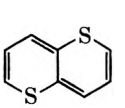
THOMAS E. YOUNG* AND LAURENCE J. HEITZ[2]

William H. Chandler Chemistry Laboratory, Lehigh University, Bethlehem, Pennsylvania 18015

Received June 23, 1972

Octahydrothiopyrano[3,2-*b*]thiopyran (**10a**) has been prepared by a multistep synthesis in which the enamine, 3-pyrrolidinothiacyclohex-2-ene (**6**), served as a key intermediate. The title compound (**10a**), isolated from a liquid mixture of isomeric materials, was obtained as a pure crystalline isomer (mp 68.5–70°) and assigned the trans configuration on the basis of nmr spectral parameters. Sodium metaperiodate oxidation of **10a** yielded a well-defined monosulfoxide (**11**) which underwent a Pummerer dehydration in acetic anhydride to afford a mixture of two isomeric hexahydrothiopyrano[3,2-*b*]thiopyrans (**12a** and **12b**).

The synergistic interaction of theoretical[3] and synthetic investigations during the past several years has led to an unusual variety of new heterocyclic sulfur compounds, of which cyclopenta[*c*]thiopyran,[4] 1-phenyl-1-thianaphthalene,[5] and thienothiapyrylium cations[6,7] have been of particular interest as nonclassical 10-π-electron systems. Among other novel thia heterocycles, whose syntheses have not yet been realized, thiopyrano[3,2-*b*]thiopyran (**1**) appeared to be an especially attractive goal for synthesis, since this



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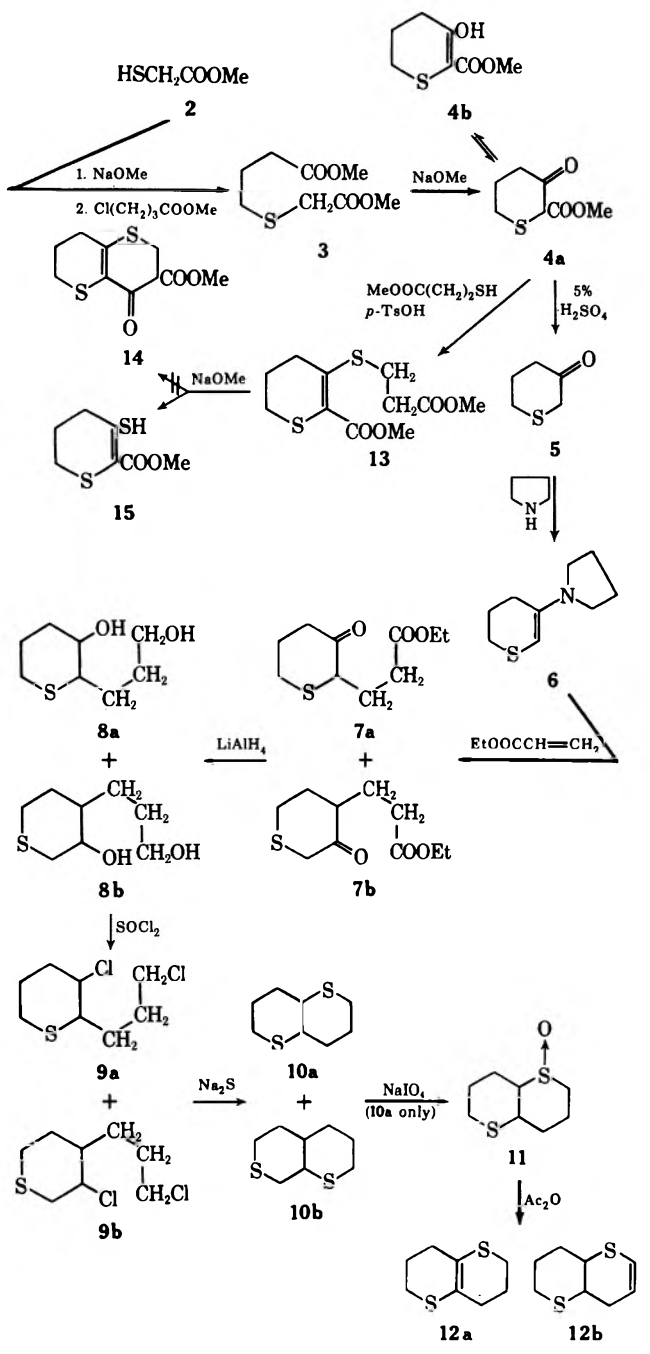
(1) Based in part on the Ph.D. dissertation of Laurence J. Heitz, Lehigh University, 1971. Supported by National Science Foundation Grant GP-8597.
(2) National Defense Education Act Fellow, 1966–1969; Research Assistant, 1969–1971.
(3) R. Zharadńik, *Advan. Heterocycl. Chem.*, **5**, 1 (1965).
(4) A. G. Anderson, Jr., W. F. Harrison, and R. G. Anderson, *J. Amer. Chem. Soc.*, **85**, 3488 (1963).
(5) C. C. Price, M. Hori, T. Parasaran, and M. Polk, *ibid.*, **85**, 2278 (1963).
(6) I. Degani, R. Fochi, and G. Spunta, *Ann. Chim. (Rome)*, **58**, 263 (1968).
(7) T. E. Young and C. R. Hamel, *J. Org. Chem.*, **35**, 821 (1970).

structure, although formally iso-π-electronic with the somewhat elusive and unstable heptalene,[8] is expected to have a weakly bonding HOMO and a delocalization energy of 2.26 β.[3,9] When a literature search revealed that not even the skeletal structure of **1** was known, we undertook exploratory syntheses of this bicyclic system, and report here a multistep preparation of octahydrothiopyrano[3,2-*b*]thiopyran (**10a**), along with some preliminary attempts to dehydrogenate **10a** to **1**. The synthetic sequences investigated are illustrated in Scheme I.

SCHEME I



An initial alkylation of methyl thioglycolate (**2**) with methyl 4-chlorobutyrate gave an 84% yield of methyl 4-(carbomethoxymethylmercapto)butyrate (**3**), which underwent Dieckmann cyclization with sodium methoxide to afford a 57% yield of 2-carbomethoxythiacyclohexan-3-one (**4**).[10-12] The nmr spectrum of this keto ester (**4**) clearly defined its structure and further revealed an enolic proton (OH of **4b**) and a methinyl proton (2-H of **4a**) in a 60:40 ratio, an enol:keto ratio which remained virtually unchanged on prolonged storage of the compound.

The keto ester **4** reacted with methyl 3-mercaptopropionate in the presence of *p*-toluenesulfonic acid with azeotropic separation of water (refluxing benzene) to give a 42% yield of 2-carbomethoxy-3-(2-carbomethoxyethylmercapto)thiacyclohex-2-ene (**13**), which exhibited infrared and nmr spectra consistent with the assigned structure. In particular, the nmr spectrum was devoid of vinyl proton signals, indicating absence of the isomeric 3-ene.

The diester **13** was then treated with sodium methoxide in an attempted Dieckmann cyclization to the bicyclic keto ester **14**, which would have functionality suitable for introduction of further ring unsaturation. However, no detectable cyclization occurred. The sole sulfur-containing product isolated was a liquid, bp 98° (0.13 mm), exhibiting an nmr spectrum [CCl_4, δ 9.48 (s, 1, SH), 3.78 (s, 3, Me), 2.90 (m, 2, CH_2), 2.58 (m, 2, CH_2), and 2.08 ppm (m, 2, CH_2), the various methylene groups not being uniquely assignable] and an infrared spectrum [neat, 2520 (SH) and 1730 cm^{-1} (C=O)] consistent with the mercapto ester structure **15**. This product, apparently resulting from a retro-Michael reaction of **13**, could not be obtained in satisfactory analytical purity even after repeated distillation, hence was of no further immediate interest. We therefore turned our attention to the following sequence.

2-Carbomethoxythiacyclohexan-3-one (**4**) was hydrolyzed and decarboxylated with 5% sulfuric acid solution to give a 73% yield of the previously known thiacyclohexan-3-one (**5**).[11] This ketone, on refluxing with excess pyrrolidine in benzene under a water separator, was converted to 3-pyrrolidinothiacyclohex-2-ene (**6**) in 88% yield. Enamine **6** showed a single olefinic absorption in the infrared and an nmr spectrum in which a lone vinyl proton appeared as a singlet at δ 4.39 ppm, thus characterizing the material as a pure isomer (**6**), uncontaminated by the isomeric 3-ene, which would have shown its vinyl proton (H-4) as a triplet.

Despite the singular structure of this enamine **6**, its alkylation with ethyl acrylate in dioxane solution afforded a 53% yield of mixed keto esters **7a** and **7b**. The dominance of the expected isomer, 2-(2-carbethoxyethyl)thiacyclohexan-3-one (**7a**), was clearly confirmed by the nmr spectrum, which showed the 2-methinyl proton of **7a** as an isolated triplet (J = 7.0 Hz) centered at δ 3.55 ppm and integrating for *ca.* 0.8 proton. The only hint of isomeric impurity was a singlet (integration 0.2 proton) at δ 3.35 ppm, assignable to H-2 of **7b**. Glpc analysis confirmed the presence

(8) H. J. Dauben, Jr., and D. J. Bertelli, *J. Amer. Chem. Soc.*, **83**, 4658 (1961).

(9) R. Zharadńik and C. Párkányi, *Collect. Czech. Chem. Commun.*, **30**, 3016 (1965).

(10) The methyl esters **3** and **4**, quite surprisingly, have not been previously reported (although the corresponding ethyl esters are known[11]) and were used here because of the availability of high-quality commercial sodium methoxide and also to simplify the nmr spectra of certain compounds encountered in this series.

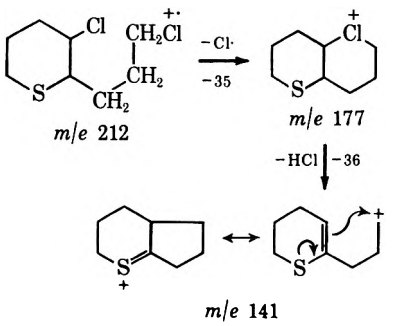
(11) E. A. Fehnel, *J. Amer. Chem. Soc.*, **74**, 1569 (1952).

(12) The thiacyclohexane nomenclature preferred here for **4** and several ensuing derivatives seems less cumbersome than names based on the alternative tetrahydrothiopyran.

of the two compounds in a ratio of 79:21. Since further fractional distillation did not improve the ratio significantly, the remaining synthetic steps were carried out from the mixture with the hope that the predominant isomer **7a** would ultimately lead to a purifiable end product.

Reduction of keto esters **7** with lithium aluminum hydride gave a 70% yield of the corresponding diols (**8a,b**) as an exceptionally viscous oil which could not be provoked to crystallize.[13] Although such a reduction of either cyclic ketone **7a** or **7b** would be expected to yield the more stable trans isomer if unhindered or alternately the cis isomer if the side chain carbethoxyethyl group exerts significant hindrance,[14] the steric effect cannot be evaluated *a priori;* hence cis and trans isomers of both **8a** and **8b** would be expected. Indeed, glpc of the exhaustively silylated diol mixture (*cf.* Experimental Section) showed the presence of four components. Surprisingly, however, the two major components comprised 74 and 17% of the mixture, suggesting that the reduction had been highly stereoselective. The nmr spectrum of the diol mixture was not clearly interpretable, hence the stereochemistry of the major product could not be directly defined.[15]

Reaction of the diols **8** with excess thionyl chloride in refluxing chloroform yielded a black reaction mixture which on distillation gave a 67% yield of the corresponding dichlorides **9**, as a somewhat unstable liquid, which even on storage at room temperature was transformed into a black, solid material. Repeated distillation of the dichlorides afforded analytically pure material as a mobile, nearly colorless liquid, whose mass spectrum showed a parent peak for the molecular ion at *m/e* 212 (calcd 212) and P + 2 and P + 4 peaks having intensities of 61 and 13%, respectively, of the parent, as expected[16] for a dichloride. The primary fragmentation pattern, a portion of which is illustrated below for **9a**, was also in accord with the behavior of other known primary and secondary halides.[16] Glpc analysis of the chloride mixture was prohibited by decomposition of the material at required column temperatures; however, the dominance of isomer **9a** is logically consistent with the glpc results for the precursor diols.



m/e 212 *m/e* 177 *m/e* 141

The mixture of isomeric dichlorides reacted smoothly with an equimolar amount of sodium sulfide in refluxing ethanol to give a 43% yield of a mixture of isomeric octahydrothiopyranothiopyrans as a liquid that partially solidified on standing. The colorless, crystalline fraction (18% yield), after recrystallization from hexane and sublimation at 55° (0.05 mm), had mp 68.5–70°, was homogeneous by glpc, and showed a molecular ion parent peak at *m/e* 174 (calcd 174) in the mass spectrum. This pure compound also comprised 27% of the residual liquid sample, which additionally contained three other closely related components (by glpc) that could not be identified, but which were ostensibly isomeric materials. While the preponderance of the crystalline compound suggests its derivation from the a series precursors, confirmation of its structure as octahydrothiopyrano[3,2-*b*]thiopyran (**10a**) was based on its 100-MHz nmr spectrum.[17]

The 100-MHz nmr spectrum of the crystalline isomer (**10a** in CCl_4) showed three groups of multiplets centered at δ 3.05, 2.45, and 1.95 ppm, integrating in the ratio 1:2:4, and clearly assignable to the bridgehead methinyl protons (H-4a and -8a), the α-methylenes (2-CH_2 and 6-CH_2), and the remaining β- and γ-methylene groups (3, 4, 7, and 8-CH_2), respectively, of structure **10a**.[18] These chemical shifts are sequentially comparable with those observed (in $CDCl_3$) for 1,4-dithiane (δ 2.90 ppm),[19] the α-CH_2 of thiane (δ 2.57 ppm), and the β- and γ-methylene groups of thiane (δ 1.5–1.9 ppm).[20] The bridgehead methinyl absorption was especially revealing and appeared essentially as a doublet ($J_{4,4a} = J_{8,8a} = 8$ Hz) with fine splitting of 3 Hz as expected for a rigid[21] *trans*-decalin-like structure in which an axial bridgehead proton (in *trans*-**10a**) would experience one axial–axial coupling and one axial–equatorial coupling from the adjacent methylene protons (*e.g.*, C-4). The observed magnitudes of $J_{axial-axial}$ and $J_{axial-equatorial}$ (8 and 3 Hz, respectively) are comparable with those of other six-membered systems existing primarily in chair conformation,[22] and the ratio ($R = J_{trans}/J_{cis} = 8/3 = 2.67$) is comparable with that of thiane ($R = 8.51/3.26 = 2.61$), which is known to exhibit a preference for the chair conformation.[23,24] Finally, it

(13) C. Ganter and J. F. Moser, *Helv. Chim. Acta*, **51**, 300 (1968), obtained 54 mg of the cis isomer of diol **8a** (reported mp 74–75°) by lithium aluminum hydride reduction of *cis*-3-acetoxy-2-(2-carbomethoxyethyl)thiacyclohexane, obtained in turn *via* photolysis of 2-oxo-6-acetoxy-9-thiabicyclo[3.3.1]-nonane.

(14) N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience, New York, N. Y., 1956, p 150.

(15) In attempts to characterize the stereochemistry of the major diol component, similar reductions of the keto esters **7** were carried out with lithium aluminum hydride–aluminum chloride followed by post-reaction equilibration with acetone or excess ketone. E. L. Eliel and M. N. Rerick [*J. Amer. Chem. Soc.*, **82**, 1367 (1960)] have reported that this method reduces simple substituted cyclohexanones with thermodynamic control of products and preponderant formation of trans alcohols. However, in the present application none of the diols **8** were obtained at all, but a whole new set of nonhydroxylic products which are currently under further investigation.

(16) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, Chapter 12.

(17) The 60-MHz nmr spectrum was not sufficiently resolved for detailed interpretation, and the introduction of 76 mg/ml of Eu(fod)$_3$-d_{27} caused insignificant downfield shifts. For comparison, the singlet resonance of 1,4-dithiane, with the same concentration of shift reagent, showed a downfield shift of only 0.08 ppm.

(18) On the basis of a similar analysis, structure **10b** is excluded, since it should show three analogous groups of protons integrating in a ratio of 3:4:7.

(19) The 1,4-dithiane was analyzed reagent grade material from the Aldrich Chemical Co.

(20) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "NMR Spectra Catalog," Vol. I, Varian Associates, Palo Alto, Calif., 1962, spectrum 118.

(21) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, pp 279–281.

(22) L. M. Jackman and S. Sternell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Elmsford, N. Y., 1969, p 288.

(23) J. B. Lambert, R. G. Keske, and Donnas K. Weary, *J. Amer. Chem. Soc.*, **89**, 5921 (1967).

(24) C. H. Bushweller, "Mechanisms of Reactions of Organic Sulfur Compounds," Vol. 5, Intrascience Research Foundation, Santa Monica, Calif., 1970, p 76.

should be noted that the cis configuration of **10a** (again assuming chair–chair preference) can exist in two conformations, one having both sulfur atoms equatorial and one having both sulfur atoms axial. Examination of Dreiding models suggests that the bridgehead methinyl splitting pattern in the cis case would be considerably more complex than that observed in the present instance, in which the nmr evidence favors assignment of the structure of crystalline **10a** (mp 68.5–70°) as *trans*-octahydrothiopyrano[3,2-*b*]thiopyran.

Attempts to dehydrogenate the octahydro compound **10a** directly to the fully conjugated system **1** with high potential quinones such as *p*-chloranil or dichlorodicyanoquinone yielded only complex, intractable products, while treatment of **10a** with palladium on charcoal at 200° afforded recovered starting material. As an alternate means of introducing ring unsaturation, the octahydro compound **10a** was converted by Leonard's sodium metaperiodate method[25] to octahydrothiopyrano[3,2-*b*]thiopyran 1-oxide (**11**) in 46% yield. This monosulfoxide underwent a Pummerer dehydration[26] by reaction with acetic anhydride at 100° to yield a mixture of the monoenes **12a** and **12b** as a liquid which exhibited a strong olefinic absorption at 1620 cm^{-1} in the infrared and an nmr spectrum (CCl_4) in which the vinyl protons of **12b** (*i.e.*, SCH=CH) appeared respectively as a doublet (δ 5.93 ppm) and a multiplet (δ 5.55 ppm) of equal intensity. The integrated intensities also indicated an approximate ratio of **12a**:**12b** of *ca.* 3:1.

Paucity of this last material **12** prohibited further experiments leading to the fully unsaturated system **1** *via* this lengthy pathway. Consequently, shorter alternative routes to the theoretically interesting thiopyrano[3,2-*b*]thiopyran (**1**) are currently under investigation. The octahydro compound (*trans*-**10a**) herein defined will serve as a suitable reference compound for structural definition of other related derivatives of this bicyclic system.

Experimental Section[27]

Methyl 4-(Carbomethoxymethylmercapto)butyrate (3).—To 1.5 l. of anhydrous methanol cooled to ice-bath temperature was added 210 g (3.75 mol) of commercial sodium methoxide during 30 min. Then 400 g (3.78 mol) of methyl mercaptoacetate was added over a period of 30 min followed by 500 g (3.66 mol) of methyl 4-chlorobutyrate over 30 min. The ice bath was removed, a thermometer was inserted in place of the dropping funnel, and stirring was continued under ambient conditions. After the temperature had risen to its maximum (41°) the solution was stirred for another 2 hr and then allowed to stand overnight. The precipitated sodium chloride was filtered off and washed with anhydrous methanol. The combined filtrates were concentrated by rotary evaporation and the viscous residue (containing more precipitated NaCl) was taken up in 1.5 l. of a 1:1 ether–water mixture. The ether layer was separated, washed with water, dried ($MgSO_4$), and filtered. The solvent was removed by rotary evaporation and the residual oil was distilled through a Vigreux column to give a small forerun, bp 40–107° (0.15 mm), followed by 634 g (84%) of water white methyl 4-(carbomethoxymethylmercapto)butyrate (**3**), bp 108–115° (0.1 mm). Redistillation gave an analytical sample: bp 118° (0.15 mm); ir (neat) 3000–2850, 1740 broad (C=O), 1440, 1370, 1300–1120, 1010 cm^{-1}.

Anal. Calcd for $C_8H_{14}O_4S$: C, 46.58; H, 6.84; S, 15.55. Found: C, 46.81; H, 7.11; S, 15.66.

2-Carbomethoxythiacyclohexan-3-one (4).—To a mechanically stirred, ice-cooled suspension of 54 g (1.0 mol) of commercial grade sodium methoxide in 500 ml of anhydrous ether was added 103 g (0.500 mol) of methyl 4-(carbomethoxymethylmercapto)-butyrate (**3**) during 10 min. The reaction mixture partially coagulated when approximately half of the diester had been added but gradually turned to a fine suspension by the end of the addition period. After the addition was complete, the mixture was stirred for 1 hr at ice-bath temperature followed by 2 hr at room temperature. Then the mixture was hydrolyzed with 200 ml of water containing 60 ml of glacial acetic acid. The ether layer was separated, washed with sodium bicabonate solution, dried ($MgSO_4$), and filtered, and the solvent was removed on a rotary evaporator. The residual oil was distilled through a Vigreux column to give 49.7 g (57%) of water-white 2-carbomethoxythiacyclohexan-3-one (**4**), bp 80–84° (0.15 mm). Redistillation gave an analytical sample: bp 84° (0.15 mm); ir (neat) 2940, 1745 (ester C=O), 1715 (ketone C=O), 1645 (chelated C=O), 1600 (C=C), 1435, 1370, 1330, 1295, 1280, 1220, 1175, 1075 cm^{-1}; nmr (neat) δ 12.13 (s, 0.6, OH), 4.20 (s, 0.4, H-2), 3.80 (two closely spaced singlets, 3, $COOCH_3$ of keto and enol forms), 2.80 (m, 2, CH_2), 2.30 ppm (m, 4, CH_2's).

Anal. Calcd for $C_7H_{10}O_3S$: C, 48.26; H, 5.79; S, 18.41. Found: C, 48.21; H, 5.96; S, 18.24.

Thiacyclohexan-3-one (5).—A mechnically stirred mixture of 156 g (0.895 mol) of 2-carbomethoxythiacyclohexan-3-one (**4**) and 500 ml of 5% H_2SO_4 solution was refluxed for 10 hr, cooled, and then adjusted to pH 6 with 10% sodium hydroxide. This mixture was extracted with several portions of ether and the combined extracts were washed with water. The ether solution was then dried ($MgSO_4$) and filtered, and the solvent was removed on a rotary evaporator. The residual oil was distilled through a Vigreux column to give 76.1 g (73%) of thiacyclohexan-3-one (**5**), bp 55–60° (0.10 mm) [lit.[11] bp 101–102° (18 mm). The infrared spectrum (neat), 2920, 1720–1710 (C=O), 1440, 1410, 1325, and 1235 cm^{-1}, was identical with that of an authentic sample; nmr (CCl_4) δ 3.17 (s, 2, 2-CH_2), 2.80 (m, 2, CH_2), 2.43 ppm (m, 4, CH_2's) [lit.[28] nmr δ 3.09 (s, 2), 2.73 (m, 2) 2.40 (s, 2), and 2.38 ppm (m, 2)].

3-Pyrrolidinothiacyclohex-2-ene (6).—A mixture of 11.6 g (0.10 mol) of thiacyclohexan-3-one (**5**) and 8.5 g (0.12 mol) of pyrrolidine in 150 ml of benzene was refluxed for 2 hr, during which time 2.5 ml of water was collected in a Dean–Stark trap. The solvent was removed on a rotary evaporator and the residual oil was distilled through a Vigreux column to give 13.92 g (88%) of 3-pyrrolidinothiacyclohex-2-ene (**6**), bp 98–103° (0.10 mm). Redistillation gave an analytical sample: bp 100° (0.10 mm); ir (neat) 2960–2800, 1600 (C=C), 1385, 1350, 1265 cm^{-1}; nmr (neat) δ 4.39 (s, 1, H-2), 2.95 (t, 4, CH_2's), 2.63 (m, 2, CH_2), 2.17 (m, 4, CH_2's), 1.80 ppm (m, 4, CH_2's).

Anal. Calcd for $C_9H_{15}NS$: C, 63.85; H, 8.93; N, 8.28; S, 18.94. Found: C, 63.62; H, 8.91; N, 8.25; S, 19.04.

2- and 4-(Carbethoxyethyl)thiacyclohexan-3-one (7a and 7b).—To a stirred solution of 57.0 g (0.337 mol) of 3-pyrrolidinothiacyclohex-2-ene (**6**) in 300 ml of *p*-dioxane at room temperature was added dropwise 37.0 g (0.370 mol) of ethyl acrylate during 20 min. The solution was refluxed for 10 hr and cooled, and 150 ml of water was added. Stirring was continued for 0.5 hr and then another 150 ml of water was added, at which point an oil separated. The mixture was extracted with two 200-ml portions of benzene, and the benzene extracts were washed with water, dried ($MgSO_4$), and filtered. The solvent was evaporated and the residual oil was distilled through a Vigreux column to give the

(25) N. J. Leonard and C. R. Johnson, *J. Org. Chem.*, **27**, 282 (1962).

(26) W. E. Parham and M. D. Bhavsar, *ibid.*, **28**, 2686 (1963).

(27) Melting points were determined on a Mel-Temp apparatus (Laboratory Devices, Cambridge, Mass.) which was calibrated with a standard series of compounds of known corrected melting point. The microanalyses were performed by the late Dr. V. B. Fish (Lehigh University), Galbraith Microanalytical Laboratories, Knoxville, Tenn., and by Dr. G. I. Robertson, Florham Park, N. J. Infrared spectra were recorded on a Perkin-Elmer Model 257 instrument. Nmr spectra were determined on a Varian A-60 or a Perkin-Elmer R20A spectrometer using tetramethylsilane as internal standard. The 100-MHz spectrum was run by Sadtler Laboratories, Philadelphia, Pa. Data are presented in the order δ (multiplicity, number of protons, assignment). The mass spectra were run by Dr. J. E. Sturm (Lehigh University) on a Hitachi RMU-6E high-resolution instrument equipped with double-focusing sector. Glpc analyses were performed on an F & M (Hewlett-Packard) Model 5750 research chromatograph equipped with a TC detector and an 8 ft × 0.125 in. column containing ethylene glycol succinate packing (LP-71). Helium flow rates were 25 ml/min and column temperature was generally at 210° except where otherwise noted.

(28) K. Sato, S. Inoue, and K. Kondo, *J. Org. Chem.*, **36**, 2077 (1971).

following: a, 14.34 g of forerun, bp up to 61° (0.30 mm); b, 1.00 g of liquid, bp 61–131° (0.30 mm); c, 38.73 g (53% yield) of product **7**, bp 131–133° (0.30 mm); and d, 9.55 g of viscous amber residue; combined wt 62.62 g. Fraction c was redistilled with 91% recovery to give analytically pure **7**: bp 117–117.5° (0.13 mm); ir (neat) 2975, 2950, 2930 (CH), 1735 (ester C=O), 1710 (C=O), 1448, 1422, 1372, 1260, 1185, 1095, and 1030 cm^{-1}; nmr (CCl_4) δ 4.27 (q, J = 7.0 Hz, 2, CH_2CH_3), 3.55 (t, J = 7.0 Hz, 0.8, H-2 methinyl), 3.35 (s, 0.2), 3.1–1.6 (complex m, 10), and 1.22 ppm (t, J = 7.0 Hz, 3, CH_2CH_3).

Anal. Calcd for $C_{10}H_{16}O_3S$: C, 55.53; H, 7.46; S, 14.83. Found: C, 55.62; H, 7.44; S, 14.76.

Glpc analysis of pure material at 210° showed two peaks: retention time, min (%) 43.6 (79) and 49.5 (21), which on the basis of the nmr spectrum (*cf.* especially the δ 3.55 ppm triplet) must be assigned to **7a** and **7b**, respectively.

2- and 4-(3-Hydroxypropyl)thiacyclohexan-3-ol (8a and 8b).—To a mechanically stirred slurry of 4.00 g (0.105 mol) of lithium aluminum hydride in 500 ml of anhydrous ether was added dropwise 21.6 g (0.100 mol) of the foregoing keto ester mixture (**7a,b**) over a period of 30 min. The mixture was refluxed for 0.75 hr and cooled, and 15 ml of ethyl acetate was added dropwise to destroy the excess hydride. Just enough water was then added to coagulate the solids. The mixture was filtered and the solids were extracted thoroughly with ether. The combined ether extracts were dried ($MgSO_4$) and filtered, and the solvent was removed on a rotary evaporator. The residual oil (14.65 g) was distilled to give about 1 ml of forerun, bp up to 135° (0.30 mm), then the diols **8**, 12.21 g (70%), as a very viscous oil, bp 140–143° (0.10 mm), leaving a semisolid residue (1.12 g.) Redistillation of the diols gave an analytical sample: bp 150° (0.25 mm); ir (neat) 3370 broad (H-bonded hydroxyl), 2930–2860, 1950–1150, 1050, 940, and 900 cm^{-1}; nmr ($CDCl_3$) δ 3.92 (m, 1, CHOH), 3.68 (s + m, 4, two OH and CH_2OH), 2.85 (m, 1, SCH), 2.53 (m, 2, CH_2S), 1.70 ppm (m, 8, remaining four CH_2's).

Anal. Calcd for $C_8H_{16}O_2S$: C, 54.51; H, 9.15; S, 18.19. Found: C, 54.31; H, 8.94; S, 18.15.

This diol mixture was exhaustively silylated with hexamethyldisilazane and trimethylchlorosilane in pyridine;[29] the resulting bistrimethylsilyl derivatives were analyzed by glpc (140°). Four peaks were observed, retention time, min (%), 7.2 (74), 8.9 (17), 9.4 (6), and 10.2 (3), of which the first, preponderant peak must be derived from 2-(3-hydroxypropyl)thiacyclohexan-3-ol (**8a**), whose structure accounts for the principal features of the nmr spectrum.

3-Chloro-2- and -4-(3-chloropropyl)thiacyclohexane (9a and 9b).—To a mechanically stirred solution of 59 g (0.50 mol) of thionyl chloride in 250 ml of chloroform was added dropwsie 39.3 g (0.223 mol) of the above diols **8** in 50 ml of chloroform over a period of 0.5 hr. The resulting mixture was refluxed for 5.5 hr, cooled, and left to stand overnight. The solution was poured into 1 l. of ice water and stirred for 20 min. The layers were separated; the chloroform layer was dried ($MgSO_4$) and filtered and the solvent stripped on the rotary evaporator. Distillation of the residual oil gave 32.0 g (67%) of the dichlorides **9**, bp 108–112° (0.35 mm). Several redistillations were required to give analytical material: bp 96–97° (0.07 mm); ir (neat) 2950, 2860, 1450, 1285, 790, 740, and 650 cm^{-1}; nmr (CCl_4) δ 3.58 (m, 3, CHCl and CH_2Cl), 2.70 (m, 3), 1.95 ppm (m, 8).

Anal. Calcd for $C_8H_{14}Cl_2S$: C, 45.08; H, 6.62; Cl, 33.26; S, 15.04. Found: C, 45.29; H, 6.65; Cl, 33.00; S, 15.35.

Octahydrothiopyrano[3,2-*b*]thiopyran (10a).—A stirred solution of 34.7 g (0.163 mol) of the dichlorides **9** and 39.0 g (0.163 mol) of sodium sulfide nonahydrate in 300 ml of 95% ethanol was refluxed for 19 hr, cooled, and diluted with an equal volume of water. This mixture was extracted with four 100-ml portions of benzene, the benzene extracts were washed with saturated sodium chloride solution and then with water, and the solution was dried ($MgSO_4$) and filtered. The solvent was removed on a rotary evaporator and the residual oil (28.4 g) was distilled through a Vigreux column. The combined fractions, bp 75–79° (0.05 mm), weighed 13.1 g (46% crude yield) and solidified to a great extent after overnight refrigeration or on standing several days at room temperature. Only a few drops of higher boiling distillate had been collected, bp 131–154° (0.25 mm), when the pot residue, comprising about half of the original charge, began to decompose extensively with loss of vacuum. Recrystallization of the solid fraction from hexane gave 5.0 g (18%) of octahydrothiopyrano-[3,2-*b*]thiopyran (**10a**), mp 60–66°. Sublimation at 55° (0.05 mm) and further recrystallization gave an analytical sample: mp 68.5–70°; ir (KBr) 2930, 2850, 1440, 1100, 1065, and 725 cm^{-1}; nmr (CCl_4) δ 3.05 (q, 2), 2.45 (m, 4), and 1.95 ppm (m, 8); mass spectrum m/e 174 (M^+) (calcd 174).

Anal. Calcd for $C_8H_{14}S_2$: C, 55.12; H, 8.10; S, 36.79. Found: C, 54.91; H, 7.92; S, 36.56.

The pure crystalline compound was homogeneous by glpc and had a retention time of 12.1 min at 210°. The residual oil, after separation of the solid fraction, weighed 6.86 g and on glpc at 210° showed four well-defined peaks, retention time, min (%), 8.6 (34), 9.9 (6), 12.1 (27), and 13.8 (33). The peak at 12.1 min was identical with that of pure crystalline **10a** on the basis of both retention time and peak enhancement. Although no further separation was achieved by either fractional distillation or chromatography on silica gel, this four-component mixture showed an ir spectrum similar to that of the crystalline product.

Octahydrothiopyrano[3,2-*b*]thiopyran 1-Oxide (11).—A solution of 2.00 g (0.0115 mol) of octahydrothiopyrano[3,2-*b*]-thiopyran (**10a**) in 50 ml of *p*-dioxane was added to 2.45 g (0.0115 mol) of sodium metaperiodate in 50 ml of water. The resulting mixture became immediately cloudy and a white, fluffy solid precipitated. The mixture was stirred at room temperature for 24 hr, the solid was removed by filtration, and the filtrate was diluted with 150 ml of water. This solution was extracted with chloroform and the chloroform extracts were dried ($MgSO_4$) and filtered. Removal of the solvent on the rotary evaporator gave 1.8 g of an orange solid which was recrystallized from petroleum ether (bp 30–60°) to give 1.0 g (46%) of octahydrothiopyrano-[3,2-*b*]thiopyran 1-oxide (**11**), mp 100–106°. Three more recrystallizations gave an analytical sample: mp 112–114°; ir (KBr) 2920, 1430, 1060, 1030 (S→O), 1000, 930 cm^{-1}.

Anal. Calcd for $C_8H_{14}OS_2$: C, 50.49; H, 7.41; S, 33.69. Found: C, 50.64; H, 7.47; S, 33.45.

2,3,4,6,7,8-Hexahydrothiopyrano[3,2-*b*]thiopyran (12a) and 4,4a,6,7,8,8a-Hexahydrothiopyrano[3,2-*b*]thiopyran (12b).—A mixture of 4.85 g (0.0255 mol) of octahydrothiopyrano[3,2-*b*]-thiopyran 1-oxide (**11**) and 20 ml of acetic anhydride was heated at 100° for 66 hr. The solvent was then removed on a rotary evaporator and the residual oil was distilled on a short-path apparatus to give 3.40 g (77%) of crude product, bp 68–75° (0.05 mm). Redistillation afforded an oil, bp 68–70° (0.03 mm), whose spectra were consistent with the products **12a** and **12b**: ir (neat) 2930, 2840, 1620 (C=O), 1440, 1295, 1255, 1185, 940, 780, 690, 670 cm^{-1}; nmr (CCl_4) δ 5.93 (d, 0.25, SCH=CH), 5.55 (m, 0.25, SCH=CH), 2.70 (m, 5), 2.08 ppm (m, 7); mass spectrum m/e 172 (M^+).

Anal. Calcd for $C_8H_{12}S_2$: C, 55.76; H, 7.02; S, 37.22. Found: C, 56.03; H, 7.30; S, 36.97.

2-Carbomethoxy-3-(2-carbomethoxyethylmercapto)thiacyclohex-2-ene (13).—A solution of 20.0 g (0.115 mol) of 2-carbomethoxythiacyclohexan-3-one (**4**), 17.5 g (0.115 mol) of methyl β-mercaptopropionate, and 1 g of *p*-toluenesulfonic acid monohydrate in 150 ml of benzene was refluxed under a Dean–Stark trap for 9 hr, during which time 2.3 ml of water was collected. The benzene solution was cooled, then washed successively with water, 5% sodium bicarbonate, and again with water, and dried over $MgSO_4$. Benzene was removed on a rotary evaporator and the residual oil was distilled to give 14.64 g (46%) of crude product, bp 165–175° (0.40 mm). Redistillation gave analytically pure **13**: bp 153–154° (0.10 mm); ir (neat) 2985, 2940, 2920 sh, 2830, 1735 (C=O), 1430, 1355, 1240, 1050 cm^{-1}; nmr (CCl_4) δ 3.73 (s, 3) and 3.66 (s, 3), both CH_3's of ester groups, 3.0–2.0 ppm (m, 10, various methylenes).

Anal. Calcd for $C_{11}H_{16}O_4S_2$: 47.80; H, 5.84; S, 23.21. Found: C, 47.73; H, 5.99; S, 23.16.

Registry No.—**3**, 38555-40-7; **4**, 38555-41-8; **5**, 19090-03-0; **6**, 38555-43-0; **7a**, 38555-44-1; **7b**, 38555-45-2; **8a**, 38555-46-3; **8b**, 38555-47-4; **9a**, 38555-48-5; **9b**, 38555-49-6; **10a**, 36910-78-8; **11**, 38555-51-0; **12a**, 38555-52-1; **12b**, 38555-53-2; **13**, 38555-54-3; methyl mercaptoacetate, 2365-48-2; methyl 4-chlorobutyrate, 3153-37-5; methyl β-mercaptopropionate, 2935-90-2.

(29) C. C. Sweeley, R. Bentley, M. Makita, and W. W. Wells, *J. Amer. Chem. Soc.*, **85**, 2497 (1963), developed optimal conditions for the use of these reagents for carbohydrate analysis.

Synthesis of 2,3,4,10-Tetrahydrothiopyrano[3,2-*b*]-1-benzothiopyran and Its Reaction with *o*-Chloranil[1]

THOMAS E. YOUNG,* LAURENCE J. HEITZ,[1,2] AND DAVID J. STEKLENSKI[1]

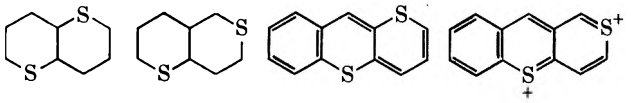
William H. Chandler Chemistry Laboratory, Lehigh University, Bethlehem, Pennsylvania 18015

Received July 13, 1972

2,3,4,10-Tetrahydrothiopyrano[3,2-*b*]-1-benzothiopyran-10-one (**9**), the first example of a new fused-ring heterocyclic system, has been synthesized *via* a stepwise condensation sequence from thiophenol and 2-carbomethoxythiacyclohexan-3-one (**5**). Reduction of this ketone (**9**) with aluminum hydride afforded 2,3,4,10-tetrahydrothiopyrano[3,2-*b*]-1-benzothiopyran (**11**), which was inert to further catalytic (Pd/C) dehydrogenation up to 200°. Dehydrogenation of **11** with *o*-chloranil yielded a product characterized as a 1:1 adduct (**12**) of thiopyrano[3,2-*b*]-1-benzothiopyran (**3**) with *o*-chloranil.

In view of the many thousands of heterocyclic ring systems known in the literature, it is quite surprising that virtually no attention has been given to the thiopyranothiopyrans having various modes of ring fusion. Indeed, prior to our recently completed syntheses of *trans*-octahydrothiopyrano[3,2-*b*]thiopyran (**1**)[3] and of octahydrothiopyrano[4,3-*b*]thiopyran (**2**)[4] only one example of this general class, *viz.*, 1,2,3,4-tetrahydro-8-amino-5-methyl-2,10-dithiaxanthone, had been disclosed as an incidental item in a patent.[5]

Interest in these kinds of structures stems from the potential aromaticity of fully conjugated, nonclassical dithia heterocycles such as thiopyrano[3,2-*b*]-1-benzothiopyran (**3**) and the dicationic species, 2,10-dithioniaanthracene (**4**), as well as analogs derived from **1** and **2**.

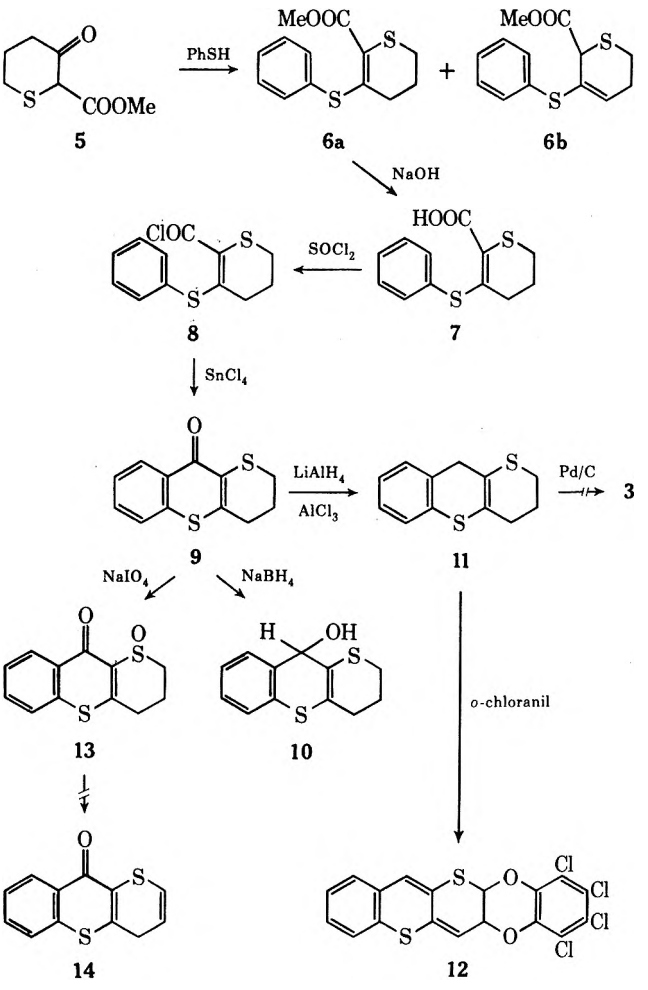


1 **2** **3** **4**

As a prelude to further studies of such theoretically interesting systems, we have explored syntheses of the prerequisite skeletal structures, and report here an explicit preparation of 2,3,4,10-tetrahydrothiopyrano-[3,2-*b*]-1-benzothiopyran (**11**), along with the response of this compound toward selected dehydrogenating reagents.

The reactions investigated are summarized in Scheme I, in which 2-carbomethoxythiacyclohexan-3-one (**5**)[3] was first condensed with thiophenol in benzene in the presence of *p*-toluenesulfonic acid as catalyst and with azeotropic separation of water. The products, obtained in 46% yield, were comprised of a mixture of methyl 3-phenylmercaptothiacyclohex-2-ene-2-carboxylate (**6a**) and the isomeric 3-ene (**6b**) whose presence was evident from a vinyl triplet (H-4, δ 6.50 ppm, J = 4 Hz) in the nmr spectrum. The ratio of **6a**:**6b** was about 4:1 as estimated from the integrated intensities of the separate methyl (ester) resonance bands. Fractional distillation of the isomeric esters and recrystallization of the higher boiling fraction from hexane afforded

SCHEME I



pure crystalline samples of the conjugated isomer **6a** whose structure was verified by its nmr spectrum, which clearly lacked the vinyl proton absorption characteristic of the unconjugated isomer **6b**.

Saponification of pure ester **6a** gave a 69% yield of the corresponding carboxylic acid **7**, which was used in subsequent cyclization experiments. Reaction of this acid with thionyl chloride gave the acid chloride **8**, which underwent ring closure on treatment with stannic chloride to yield (86% for two steps) 2,3,4,10-tetrahydrothiopyrano[3,2-*b*]-1-benzothiopyran-10-one (**9**). This yellow crystalline ketone (**9**) exhibited an nmr spectrum consistent with the assigned structure and displayed an intense carbonyl stretching band at 1600 cm^{-1} in the infrared spectrum. This carbonyl frequency, which is comparable with that of 4*H*-thio-

(1) Based in part on the Ph.D. dissertation of L. J. Heitz, 1971, and the senior B.S. thesis of D. J. Steklenski, 1969, both at Lehigh University. Supported by National Science Foundation Grant GP-8597.

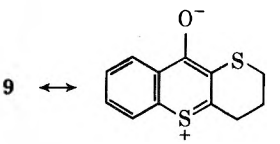
(2) National Defense Education Act Fellow, 1966–1969; Research Assistant, 1969–1971.

(3) T. E. Young and L. J. Heitz, *J. Org. Chem.*, **38**, 1562 (1973).

(4) T. E. Young and L. J. Heitz, unpublished work.

(5) Farbenfabriken Bayer, A.-G., British Patent 803,803 (Nov 5, 1958); *Chem. Abstr.*, **53**, 11412*h* (1959); *cf.* F. Bossert and R. Goennert, *Med. Chem. Abhandl. Med. Chem. Forschungstaetten Farbwerke Hoechst A.-G.*, **7**, 36 (1963); *Chem. Abstr.*, **60**, 9236*g* (1964).

pyran-4-one (1609 cm^{-1}),[6a] is indicative of an unusually low double-bond character of the carbonyl group, probably resulting from delocalization *via* a thiopyrylium-like structure as illustrated by the following canonical form.[6b]



The resulting redistribution of charge would account for the low carbonyl reactivity of ketone **9**, which could not be derivatized with hydroxylamine or phenylhydrazine in the usual manner. Furthermore, repeated attempts to reduce the ketone **9** by variations of the Huang-Minlon and Meerwein–Ponndorf reductions all yielded varying amounts of unreacted ketone but no reduction products. Reaction with lithium aluminum hydride was also ineffective, yielding about 30% of the expected weight of a solid, noncrystalline product which could neither be crystallized nor sublimed. However, sodium borohydride in aqueous ethanol gave a trace of the carbinol **10**, isolated as white crystals which showed a broad, hydrogen-bonded hydroxyl absorption at 3310 cm^{-1} in the infrared spectrum, but virtually no olefinic absorption in the expected region above 1600 cm^{-1}. Possible reduction of the ring-juncture double bond was excluded, however, since the mass spectrum of **10** showed the correct molecular ion parent peak at *m/e* 236 (calcd 236). In any case, the exceedingly poor yield of the carbinol **10** obviated further synthetic experiments with this material, and variations of the reduction procedure did not improve its availability.

The cyclic ketone **9** was finally reduced by aluminum hydride generated *in situ* from lithium aluminum hydride and aluminum chloride in ether solution. This procedure, based on a similar one devised by Urberg and Kaiser[7] for reduction of thioxanthones, gave a 70% yield of 2,3,4,10-tetrahydrothiopyrano[3,2-*b*]-1-benzothiopyran (**11**) as a viscous yellow oil whose infrared and nmr spectra clearly confirmed the assigned structure.

Attempts to dehydrogenate the tetrahydro compound **11** directly to the fully conjugated system **3** with palladium on charcoal at 200° yielded only recovered starting material, while reaction of **11** with *o*-chloranil in acetic acid solution afforded a colorless, crystalline compound which appeared to be a 1:1 adduct of thiopyrano[3,2-*b*]-1-benzothiopyran (**3**) with *o*-chloranil (*i.e.*, **12** or possibly an isomer thereof). Although this product was too insoluble in available solvents (*cf.* Experimental Section) to permit nmr characterization, it had an acceptable elemental analysis and showed a molecular ion parent peak at *m/e* 460 (calcd 460) in the mass spectrum, and an intensity ratio [(P + 2):P] of 1.35, about that expected for a tetrachloro compound.[8] In addition, this substance exhibited an intense infrared absorption band at 1450 cm^{-1}, which is comparable with the strong band (*ca.* 1428 cm^{-1}) characteristic of other 1,4-dioxin adducts of *o*-chloranil with olefins.[9] The high degree of unsaturation of this compound was further substantiated by an exceedingly weak aliphatic C–H stretching frequency at 2920 cm^{-1}, while the low frequency of the olefinic absorption (1600 cm^{-1}) strongly favored assignment of the conjugated structure **12** to this adduct. The ostensible intermediacy of **3** in the formation of this product **12** cannot, of course, be verified on the basis of the present experiments. Hence, unambiguous characterization of the theoretically interesting, but elusive, **3** must await its ultimate isolation by other means.

As a possible alternative route to introducing further unsaturation into the terminal thiopyran ring, the intermediate ketone **9** was converted by reaction with sodium metaperiodate[10] in dioxane to the 1-oxide **13** in 81% yield. The infrared spectrum of this product showed a typical sulfoxide stretching frequency at 1030 cm^{-1} and an intense absorption at 1610 cm^{-1} characteristic of the carbonyl group of the thiochromen-4-one system, thus confirming the assigned site of oxidation at S-1. Attempts to effect a Pummerer dehydration[11] of the sulfoxide with acetic anhydride, in the hope of obtaining **14**, yielded poorly defined products which could not be characterized, while a variation involving the use of benzoic anhydride afforded only recovered starting material.

Experimental Section[12]

Methyl 3-Phenylmercaptothiacyclohex-2-ene-2-carboxylate (6a) and Methyl 3-Phenylmercaptothiacyclohex-3-ene-2-carboxylate (6b).—A solution of 87.0 g (0.500 mol) of 2-carbomethoxythiacyclohexan-3-one (**5**),[3] 55.1 g (0.500 mol) of thiophenol, and 6.0 g (0.035 mol) of *p*-toluenesulfonic acid monohydrate in 500 ml of benzene was refluxed for 18 hr under a Dean–Stark trap. A total of 9.0 ml of water was collected. The solution was cooled and washed with four 150-ml portions of 10% sodium hydroxide, followed by two 150-ml portions of water. The benzene fraction was dried ($MgSO_4$) and filtered, and the solvent was removed on a rotary evaporator. The viscous, straw-yellow residual oil (108.7 g) was fractionally distilled to give 73.6 g of crude product, bp 150–175° (0.2–0.3 mm). Redistillation of this material gave two major fractions.

Fraction 1 (21.1 g), bp 138–145° (10.10 mm), whose nmr spectrum showed two distinct methyl ester peaks at δ 3.83 and 3.71 ppm for **6a** (*vide infra*) and **6b**, respectively, in about a 1:1 ratio, yielded a middle cut, bp 139.5–140° (0.10 mm), which was analyzed.

Anal. Calcd for $C_{13}H_{14}O_2S_2$: C, 58.61; H, 5.30; S, 24.08. Found: C, 58.81; H, 5.36; S, 24.15.

Fraction 2 (39.4 g), bp 146–156° (0.10 mm), showed an nmr spectrum with only a trace of vinyl absorption and consisted mainly of isomer **6a**. Redistillation gave pure **6a**, bp 159–160° (0.10 mm), which crystallized on cooling. Recrystallization from

(6) (a) D. S. Tarbell and P. Hoffman, *J. Amer. Chem. Soc.*, **76**, 2451 (1954). (b) On the basis of more detailed infrared studies, A. R. Katritzky and R. A. Jones, *Spectrochim. Acta*, **17**, 64 (1961), concluded that similarly polarized canonical forms are important contributors to the structure of 4*H*-thiopyran-4-one.

(7) M. M. Urberg and E. T. Kaiser, *J. Amer. Chem. Soc.*, **89**, 5931 (1967).

(8) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967.

(9) L. M. Jackman in R. A. Raphael, E. C. Taylor, and H. Wynberg, Ed., "Advances in Organic Chemistry. Methods and Results," Vol. 2, Interscience, New York, N. Y., 1962, pp 334–335.

(10) N. J. Leonard and C. R. Johnson, *J. Org. Chem.*, **27**, 282 (1962).

(11) W. E. Parham and L. D. Edwards, *ibid.*, **33**, 4150 (1968).

(12) Melting points were determined using a Mel-Temp apparatus, precalibrated with a standard series of compounds having known corrected melting points. The microanalyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn., and by Dr. George I. Robertson, Florham Park, N. J. Infrared spectra were recorded on a Perkin-Elmer Model 257 instrument. Solids were run at 1% weight concentration in KBr disks, and liquids were run neat between NaCl plates. Nmr spectra were determined on a Varian A-60 or a Perkin-Elmer Hitachi R-20A spectrometer using tetramethylsilane as internal standard. Data are presented in the order δ (multiplicity, coupling constant, number of protons, assignment). Mass spectra were run by Dr. J. E. Sturm (Lehigh University) on a Hitachi RMU-6E high-resolution instrument equipped with double-focusing sector.

hexane yielded white needles: mp 48–48.5°; ir (neat) 2950–2920, 1730 and 1710 (C=O), 1585 (C=C), 1480, 1440, 1290–1210, 1190, 1055, 1030, 750, and 695 cm^{-1}; nmr ($CDCl_3$) δ 7.38 (m, 5, ArH), 3.83 (s, 3, CH_3), 2.90 (t, J = 4.5 Hz, 2, 6-CH_2), 2.05 ppm (m, 4, 4- and 5-CH_2).

Anal. Calcd for $C_{13}H_{14}O_2S_2$: C, 58.61; H, 5.30; S, 24.08. Found: C, 58.40; H, 5.21; S, 24.32.

3-Phenylmercaptothiacyclohex-2-ene-2-carboxylic Acid (7).—A mechanically stirred mixture of 165 g (0.619 mol) of methyl 3-phenylmercaptothiacyclohex-2-ene-2-carboxylate (**6a**) and 600 ml of 10% sodium hydroxide solution was refluxed for 5 hr. The resulting solution was cooled in an ice bath and acidified to pH 1–2 with 10% hydrochloric acid. The foul-smelling brown precipitate was collected by filtration, air dried, and then recrystallized from 600 ml of benzene to yield 108 g (69.1%) of pale yellow acid (**7**): mp 122–125°; nmr ($CDCl_3$) δ 11.02 (s, 1, COOH), 7.58 (m, 5, ArH), 2.87 (t, J = 6 Hz, 2, 6-CH_2), 2.03 ppm (m, 4, 4- and 5-CH_2).

Anal. Calcd for $C_{12}H_{12}O_2S_2$: C, 57.11; H, 4.79; S, 25.41. Found: C, 57.40; H, 4.83; S, 25.51.

2,3,4,10-Tetrahydrothiopyrano[3,2-*b*]-1-benzothiopyran-10-one (9).—To a mechanically stirred solution of 23.2 g (0.092 mol) of 3-phenylmercaptothiacyclohex-2-ene-2-carboxylic acid (**7**) in 250 ml of anhydrous ether was added 34.5 ml (0.52 mol) of thionyl chloride and 5 drops of pyridine. A condenser and drying tube were attached and the mixture was then refluxed for 2 hr. The ether and excess thionyl chloride were then removed on a rotary evaporator, leaving the crude acid chloride **8** as a dark brown oil. The acid chloride was dissolved in 250 ml of anhydrous benzene, the solution was cooled in an ice bath, and 23.4 ml (0.200 mol) of stannic chloride was added. The mixture was allowed to come to room temperature during 2 hr, after which it was poured into a mixture of 250 ml of concentrated hydrochloric acid and 700 g of ice. The resulting mixture was stirred thoroughly and the solid was collected by filtration. Benzene extraction of the mother liquor yielded more brown solid upon evaporation of the solvent. The combined solids were recrystallized from absolute ethanol to give 8.60 g (40%) of 2,3,4,10-tetrahydrothiopyrano[3,2-*b*]-1-benzothiopyran-10-one (**9**) as yellow crystals, mp 174–176°. Further recrystallization produced an analytical sample: mp 178–180°; ir (KBr) 1600 (C=O), 1580, 1560, 1530, 1430, 1320, 1145, 830, 810, and 750 cm^{-1}; nmr ($CDCl_3$) δ 8.50 (m, 1, H-9), 7.55 (m, 3, H-6, 7, and 8), 3.07 (t, J = 6 Hz, 2, 2-CH_2), 2.78 (t, J = 6 Hz, 2, 4-CH_2), 2.20 ppm (m, 2, 3-CH_2).

Anal. Calcd for $C_{12}H_{10}OS_2$: C, 61.50; H, 4.30; S, 27.27. Found: C, 61.30; H, 4.48; S, 27.28.

2,3,4,10-Tetrahydrothiopyrano[3,2-*b*]-1-benzothiopyran-10-ol (10).—To a suspension of 1.00 g (0.00428 mol) of ketone **9** in 130 ml of 95% ethanol was added a solution of 3.00 g (0.079 mol) of sodium borohydride in 20 ml of 3% sodium hydroxide solution. The mixture was then stirred under reflux for 5.5 hr, cooled, and diluted with 500 ml of water. The resulting emulsion was acidified with acetic acid to pH *ca.* 6, and the yellow precipitate was collected and dried. This material weighed 0.52 g and gelled around 115–120°, but could neither be crystallized nor sublimed. Concentration of the filtrates yielded 50 mg of cream-colored solid which on sublimation at 110° (0.15 mm) afforded white crystals of the carbinol **10**: mp 133–135°; ir (KBr) 3310 broad (OH), 3050 (ArH), 2935, 2910, 2850 (CH aliphatic), 1590, 1565, 1470, 1430, 1270, 1040, and 750 cm^{-1}; mass spectrum m/e 236 (calcd 236 for M^+).

Anal. Calcd for $C_{12}H_{12}OS_2$: C, 60.98; H, 5.12; S, 27.13. Found: C, 60.81; H, 5.06; S, 26.92.

2,3,4,10-Tetrahydrothiopyrano[3,2-*b*]-1-benzothiopyran (11).—To a mechanically stirred slurry of 1.29 g (0.034 mol) of lithium aluminum hydride in 50 ml of anhydrous ether (distilled from NaH) was added slowly a solution of 9.10 g (0.0685 mol) of anhydrous aluminum chloride in 75 ml of dry ether. After the mixture was cooled in an ice bath, 4.00 g (0.0171 mol) of 2,3,4,10-tetrahydrothiopyrano[3,2-*b*]-1-benzothiopyran-10-one (**9**) was added portionwise during 10 min. The resultant solution was refluxed for 0.5 hr and cooled, and the excess lithium aluminum hydride was carefully destroyed by addition of ethyl acetate. Water was then added dropwise to coagulate the solids. The mixture was filtered, and the solids were washed with three 50-ml portions of ether. The combined ether extracts were dried ($MgSO_4$), filtered, and evaporated. The residual oil was distilled through a short-path column to give 2.85 g (76%) of 2,3,4,10-tetrahydrothiopyrano[3,2-*b*]-1-benzothiopyran (**11**) as a pale yellow oil: bp 133–136° (0.15 mm); ir (neat) 3060 (ArH), 2920, 2860, 2840, 2820 (CH aliphatic), 1620 (C=C), 1590, 1575, 1470, 1450, 1440, and 750 cm^{-1}; nmr (CCl_4) δ 7.08 (m, 4, ArH), 3.20 (s, 2, 10-CH_2), 2.75 (t, J = 5.5 Hz, 2, 2-CH_2), 2.08 ppm (m, 4, 3- and 4-CH_2).

Anal. Calcd for $C_{12}H_{12}S_2$: C, 65.41; H, 5.49; S, 29.10. Found: C, 65.50; H, 5.58, S, 28.90.

Reaction of 2,3,4,10-Tetrahydrothiopyrano[3,2-*b*]-1-benzothiopyran (11) with *o*-Chloranil.—To a magnetically stirred refluxing solution of 2.20 g (0.01 mol) of 2,3,4,10-tetrahydrothiopyrano-[3,2-*b*]-1-benzothiopyran (**11**) in 30 ml of glacial acetic acid was added dropwise 4.90 g (0.02 mol) of *o*-chloranil in 20 ml of acetic acid over a period of 15 min. After the addition was complete, the resulting mixture was refluxed for 2 hr. The mixture was then cooled to room temperature and the precipitate was collected by filtration go give 4.00 g of white solid, mp 260° dec. The very low solubility of this material in all of the usual solvents, including such powerful media as DMSO, DMF, pyridine, trifluoroacetic acid, and hexamethylphosphoramide, dictated purification[13] by extraction of impurities with refluxing xylene to give an analytical sample of white powder: mp 265° dec; ir (KBr) 3060 w (ArH), 2920 w (CH aliphatic), 1600 (C=C), 1450 s, 1385, 1310, 1285, 1230, 1165, 1110, 1090, 1010, 1000, 865, 835, and 755 cm^{-1}; mass spectrum m/e (rel intensity) 460 (29), 203 (100), 171 (51), 91 (49), and 69 (70) (calcd for M^+, 460). Additionally, the molecular ion cluster, m/e (rel intensity normalized to total unity) 460 (0.125), 461 (0.060), 462 (0.290), 463 (0.070), 464 (0.207), 465 (0.045), 466 (0.079), 467 (0.017), 468 (0.017), yielded a molecular weight value of 462.6 (calcd 462.2).

Anal. Calcd for $C_{18}H_8Cl_4O_2S_2$: C, 46.78; H, 1.74; Cl, 30.68; S, 13.87. Found: C, 47.03; H, 2.06; Cl, 30.45; S, 14.17.

2,3,4,10-Tetrahydrothiopyrano[3,2-*b*]-1-benzothiopyran-10-one 1-Oxide (13).—To a magnetically stirred solution of 2.72 g (0.0128 mol) of sodium metaperiodate in 50 ml of water was added in one portion a solution of 3.00 g (0.0128 mol) of **9** in 50 ml of dioxane. The solution immediately became cloudy with precipitation of a white solid occurring after a few minutes. Stirring was continued overnight at room temperature. The mixture was then diluted with 100 ml of water and extracted with three 75-ml portions of chloroform. The combined extracts were dried ($MgSO_4$) and filtered, and the solvent was removed on a rotary evaporator. The resulting crude solid was recrystallized from absolute ethanol to give 2.60 g (81%) of 2,3,4,10-tetrahydrothiopyrano[3,2-*b*]-1-benzothiopyran-10-one 1-oxide (**13**), mp 166° dec. Two more recrystallizations afforded an analytical sample of **13**: mp 166° dec; ir (KBr) 3050 (ArH), 2900 (CH aliphatic), 1610 (C=O), 1590, 1565, 1530, 1440, 1315, 1050, 1030 ($^+SO^-$), 990, and 750 cm^{-1}; nmr (CF_3COOD) δ 8.55 (m, 1, H-9), 7.83 (m, 3, H-6, 7, 8), 4.2–2.2 ppm (m, 6, 2-, 3-, and 4-CH_2).

Anal. Calcd for $C_{12}H_{10}O_2S_2$: C, 57.57; H, 4.03; S, 25.62. Found: C, 57.36; H, 4.19; S, 25.41.

Registry No.—**5**, 38555-41-8; **6a**, 38555-58-7; **6b**, 38555-59-8; **7**, 38555-60-1; **8**, 38555-61-2; **9**, 38555-62-3; **10**, 38555-63-4; **11**, 38555-64-5; **12**, 38555-65-6; **13**, 38555-66-7; thiophenol, 108-98-5; *o*-chloranil, 2435-53-2.

(13) Confidence in the purity of this product rests on the concordance of four different elemental analyses, the m/e value for the molecular ion, and the molecular weight based on the molecular ion cluster.

Thionyl Chloride–Pyridine Chemistry. II.[1] Synthesis and Reactions of *N*-α-Styrylpyridinium Salts

HOWARD M. RELLES

General Electric Research and Development Center, Schenectady, New York 12301

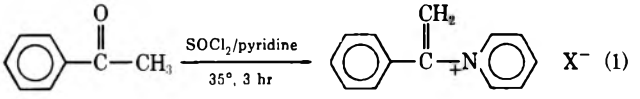
Received November 15, 1972

Acetophenone was readily converted to *N*-α-styrylpyridinium salts by treatment with thionyl chloride in pyridine. The synthesis, mechanism of formation, spectra, and some chemical reactions of these salts are discussed. The thermal reaction of **1b** led specifically to 1-phenylnaphthalene and pyridinium tetrafluoroborate. The mechanism of the latter transformation is also discussed.

The recent publication[2a] of the synthesis of *N*-α-styrylpyridinium iodide (**1c**) from styrene, iodonium nitrate, and pyridine prompts us to report on a new synthetic method for the production of **1** and related derivatives and on some of the chemical and spectral properties of **1**.

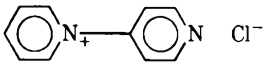
Results and Discussion

Synthesis.—When a solution of acetophenone and thionyl chloride in pyridine was prepared and maintained at room temperature or slightly above for a short time, the acetophenone was converted to *N*-α-styrylpyridinium chloride (**1a**) in very high yield (eq 1).



1a, X = Cl
b, X = BF_4
c, X = I

The integration of the ^1H nmr spectrum of the crude reaction product, after separation from the reaction solvent, showed that the relative integrals for phenyl: olefinic protons were 5:2; none of the original methyl protons nor those of an observed methyl-containing intermediate (*vide infra*) remained. The other observable product of this transformation was HCl; it was seen as pyridinium hydrochloride by ^1H nmr spectroscopy. Direct isolation of **1a** proved somewhat tedious because of its contamination by pyridinium hydrochloride and a small amount of **2**, a product



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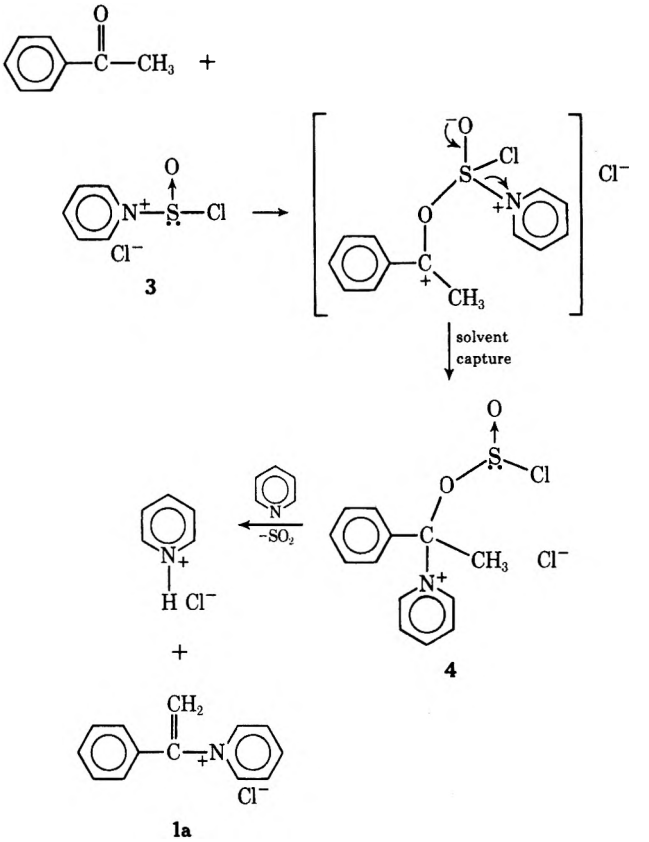
known[2b] to arise from a slow side reaction between thionyl chloride and pyridine. However, it was quite easy to isolate the desired product as the tetrafluoroborate salt, **1b**. Subsequently, it was found that, if desired, **1a** could be readily regenerated using a chloride ion exchange resin.

When the reaction was monitored by ^1H nmr spectroscopy, one could observe that as the methyl (δ 2.0) of acetophenone gradually disappeared a new methyl group at 2.4 appeared,[3] increased to some maximum value, and then also gradually disappeared, thus giving rise to the terminal olefinic carbon of **1a**. Since thionyl chloride has been reported[4,5] to lead to entirely different kinds of products with a similar ketone in the *absence* of pyridine, we suggest that **3** may be the reactive species in the present case and that one possible mechanistic description, therefore, could be that shown in Scheme I.

SCHEME I



1a

The nmr observations are satisfied if one assumes that the last step in this scheme is the slowest. Attack on one of the protons of the methyl group of **4** by pyridine as SO_2 and Cl^- are eliminated might in fact be expected to be slow as a consequence of the degree of crowding around that carbon.

Interestingly, the capture of the carbonium ion center by solvent has to be very rapid compared to capture by a chloride ion, since the latter should lead to α-chlorostyrene, which was not observed.[6] Indeed, it might

(1) Paper I: H. M. Relles, *J. Org. Chem.*, **37**, 3630 (1972).

(2) (a) U. E. Diner and J. W. Lown, *Chem. Commun.*, 333 (1970); (b) R. F. Evans, H. C. Brown, and H. C. van der Plas. *Org. Syn.*, **43**, 97 (1963).

(3) Not 1,1-dichloroethylbenzene (see Experimental Section, Table III).

(4) C. J. Ireland and J. S. Pizey, *J. Chem. Soc., Chem. Commun.*, 4 (1972).

(5) In fact, we have observed that acetophenone, in thionyl chloride, is rapidly converted to as yet unidentified products + HCl: H. M. Relles, unpublished results.

(6) However, preliminary results using quinoline as solvent indicate that *ca.* 15% of α-cholorostyrene is produced: H. M. Relles, unpublished results.

be expected that, as bonding begins between sulfur and the carbonyl oxygen, bonding between pyridine and the carbonyl carbon could simultaneously be taking place.

^{1}H Nmr Spectra.—The spectra of several α-substituted vinyltrimethylammonium salts have been reported.[7] Uniformly in D_2O, the proton cis to the positive nitrogen occurred further downfield (further from TMS) than the one trans to it, the difference ($\Delta\delta$) being 22.4 ± 4.3.Hz. In the spectra of **1a** or **1b**, it seems appropriate to make the same relative assignments, especially since the $\Delta\delta$ is of the same order in D_2O: 20.3 ± 0.3 Hz. Of greater interest is the fact that this $\Delta\delta$ for the vinyl protons varies considerably with solvent (see Table I).

TABLE I
SOLVENT EFFECT ON THE DIFFERENCE IN CHEMICAL SHIFTS FOR THE OLEFINIC PROTONS OF 1

Solvent	Salt	$\Delta\delta$, Hz[a]
$CDCl_3$[b]	**1a**	3.0
1:1 Pyridine-CH_2Cl_2[c]	**1a**	6.0
Pyridine[c]	**1a**	7.0
Pyridine	**1b**	11.0
CD_3COCD_3	**1b**	15.5
CH_3COCH_3	**1b**	16.0
CH_3CN	**1a**	16.0
CH_3COOH	**1b**	17.0
$(CH_3)_2NCHO$	**1b**	18.0
20% DCl in D_2O	**1b**	19.0
CH_3OH	**1b**	20.0
2:1 CD_3OD:D_2O	**1b**	20.0
D_2O	**1a**	20.0
D_2O	**1b**	20.5
H_2O	**1a**	20.5
H_2O	**1b**	21.5

[a] Measured at *ca.* 35°; accurate to ±0.5 Hz. [b] **1b** was completely insoluble in $CDCl_3$. [c] A reaction mixture, which also contained some $SOCl_2$ and pyridinium hydrochloride.

As can be seen, the $\Delta\delta$ for **1** is small in poorly ionizing media, such as deuteriochloroform, large, up to *ca.* 21 Hz, in ionizing media such as water and methanol, and intermediate for solvents of intermediate ionizing ability. Although the variation may result from the fluctuation of δ for only one of the olefinic protons, this cannot be stated with certainty, since all of the δ values for **1** vary somewhat with solvent. However, it is reasonable to assume that varying degrees of solvent separation of the ion pairs of **1** would lead to differences in the effective positive charge on nitrogen and that this charge would influence the δ values of the olefinic protons to different extents.

Mass Spectra.—It was not possible to obtain the mass spectra of **1a** and **1b** at low temperatures because of their lack of sufficient vapor pressure. On warming, however, it was possible, in the case of **1a**, to obtain a strong ion at *m/e* 182 corresponding to the cationic portion of the salt, although the spectrum was complicated by the presence of additional compounds. With **1b**, which presumably has even lower volatility and therefore had to be warmed even further, these additional compounds essentially dominated the spectrum and the *m/e* 182 peak was very weak. These spectra are tabulated in Table II.

(7) M. Ohtsuru, K. Tori, J.-M. Lehn, and R. Seher, *J. Amer. Chem. Soc.*, **91**, 1187 (1969).

TABLE II
MASS SPECTRA[a] OF **1a** AND **1b**

	Relative intensities[b]	
m/e	**1a** (160°)[c]	**1b** (210°)[c]
362	4	*d*
286	19	*d*
285	83	2
284	17	*d*
283	7	*d*
282	9	*d*
281	10	*d*
271	17	*d*
270	7	*d*
269	16	*d*
206	8	*d*
205	5	16
204	27	95
203	18	65
202	14	48
201	*d*	9
200	*d*	10
183	42	*d*
182	96	3
181	42	*d*
180	39	*d*
106	12	*d*
105	11	*d*
104	26	12
103	90	8
102	18	8
101	9	28
100	*d*	7
80	84	11
79	100	100
78	27	17
77	63	6
76	12	7
75	8	6

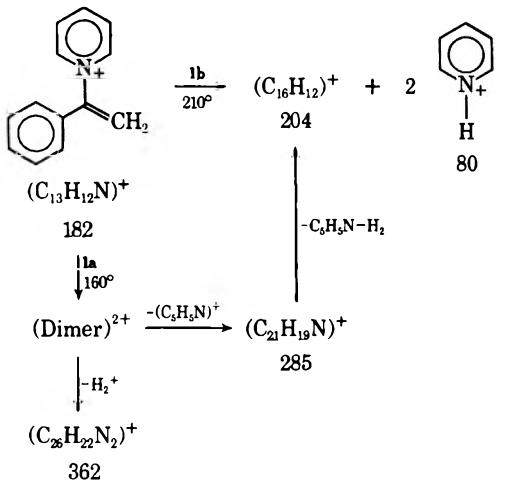
[a] Additional peaks found for **1a** were *m/e* (rel intensity) 169 (9), 168 (8), 167 (15), 154 (8), 153 (7), 152 (11), 63 (10), 53 (17), 52 (77), 51 (64), 50 (32), 39 (19), 38 (32), 37 (8), 36 (92), and 35 (15). Additional peaks for **1b** were *m/e* (rel intensity) 53 (9), 52 (69), 51 (38), 50 (24), 49 (36), and 39 (13). [b] Per cent of *m/e* 79 peak, the most intense peak in each system. [c] Probe temperature. [d] The peak was totally absent or present at less than 1% relative intensity.

Interestingly, the dominant peak in the spectrum of **1b** appeared at *m/e* 204. This corresponds to a dimer of the cationic portion of this salt minus the elements of two pyridinium ions ($2 \times 182 - 2 \times 80$) or, potentially, to a hydrocarbon having the empirical formula $C_{16}H_{12}$. Indeed, the spectrum of **1a** showed a minor peak at *m/e* 362, a major one at 285, and one at 204 which could correspond to a dimer minus two hydrogens, a dimer minus pyridine, and a dimer minus the elements of two pyridinium ions (as in **1b**), respectively. These observations are summarized schematically in Scheme II.

Cleavage of the bond between the pyridinium nitrogen and the olefinic carbon to which it is attached in the cation was also apparently significant, leading to the very strong peak for **1a** at *m/e* 103 ($C_8H_7^+$). Presumably the cluster observed around this latter *m/e* value arose from hydrogens gained or lost during this cleavage. Finally, peaks for $(C_5H_6N)^+$, $(C_5H_5N)^+$, $(C_6H_6)^+$, and $(C_6H_5)^+$ were very prominent as well.

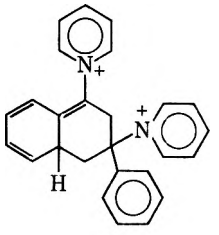
Chemical Reactions.—A few reactions of **1** have been studied. These are described in some detail in the following sections.

SCHEME II



Thermolysis.—The mass spectral results (above) suggested that it might be possible to heat the salt **1** and cause it to undergo a chemical transformation leading to a $C_{16}H_{12}$ hydrocarbon. Indeed, when **1b** was heated at 215° under reduced pressure in a sublimation apparatus or at 300° in a sealed tube there were formed just two observable products in high yield: pyridinium tetrafluoroborate and 1-phenylnaphthalene ($C_{16}H_{12}$); no 2-phenylnaphthalene or any other hydrocarbon product could be detected. The exclusive formation of 1-phenylnaphthalene places severe constraints on any mechanistic description of this reaction and one which would appear to be a likely possibility in the face of this constraint is given in Scheme III.

We believe that the six-membered ring formation depicted in the dimerization of **1** is best represented as a stepwise rather than a concerted reaction. If the reaction were a (4 + 2) concerted cyclization, one would surely expect to find some 2-phenylnaphthalene which would arise *via* **9**, the intermediate which would



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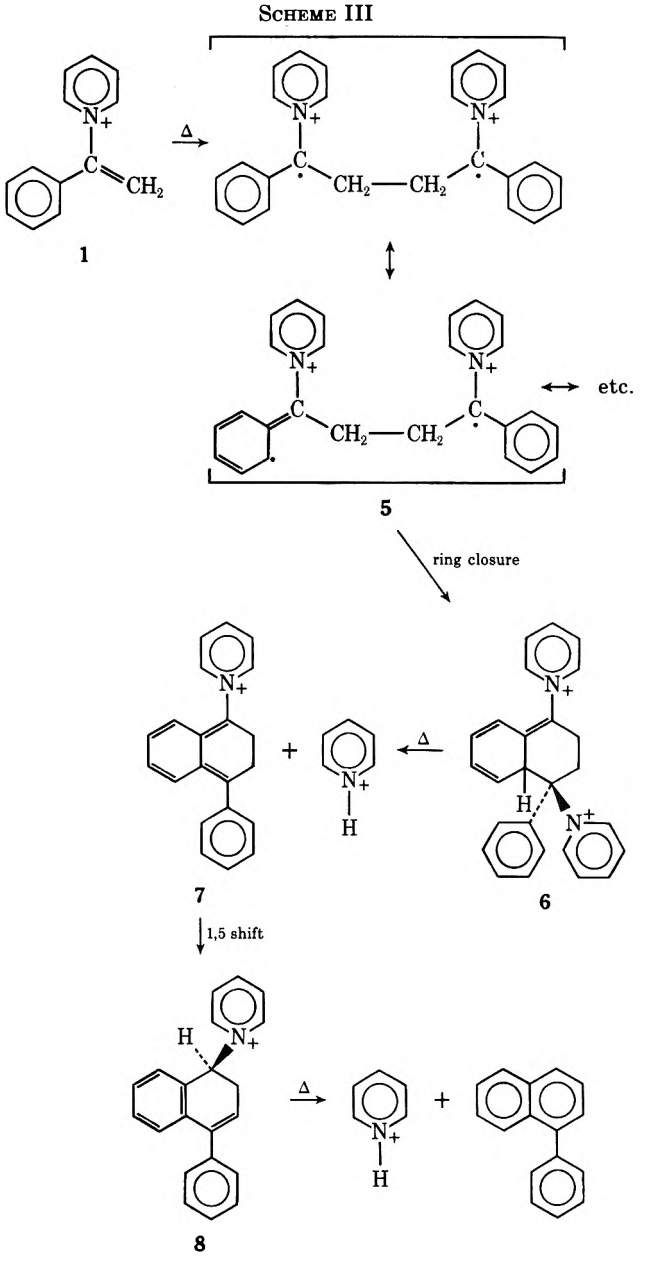
be highly favored (relative to **6**) on steric grounds. However, no 2-phenylnaphthalene was observed. On the other hand, if the cyclization occurred stepwise to give first the bisbenzyl radical cation **5**, the observed product identity would already have been established regardless of the eventual adverse steric effects which would be encountered in closing the ring to **6**. Formation of **7** from **6** simply requires a thermal heterolysis to give pyridine and a benzyl carbonium ion followed by the removal of a proton. The conversion of **7** to **8** can occur *via* protonation–deprotonation or by a thermally allowed 1,5-sigmatropic hydrogen shift. Either path should be energetically favorable, since a simultaneous rearomatization occurs.

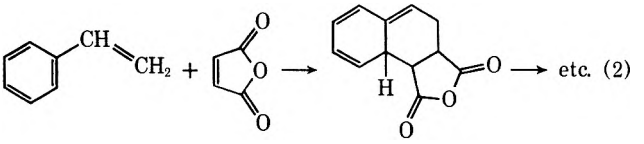
Also in favor of this mechanism is the report[8] that

(8) R. R. DiLeone, U. S. Patent 3,410,876 (Nov 12, 1968).

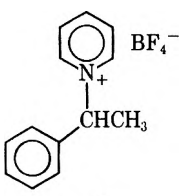
SCHEME III



a cyclization reaction similar to that proposed in Scheme III occurs between styrene and maleic anhydride (eq 2).



Hydrogenation.—The hydrogenation of **1b** with Pd/C readily led to **10b** in very high yield. We have

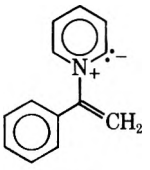


10b

found no previous reports of the synthesis of this very simple molecule, presumably because those methods,

which have been tried[9] involved the reaction of α-phenethyl halides with pyridine, a combination which resulted only in elimination of HX. Thus, not only does the isolation of **10b** serve as further evidence for the structure of its precursor, but it also completes a facile two-step sequence to a previously unknown type of pyridinium salt.

H–D Exchange.—When a solution of **1b** in D_2O was heated at 180°, hydrogen–deuterium exchange took place at only two carbons, the α-pyridinium carbons; no other protons in the molecule were exchanged. This we attribute to the inductive acidifying influence of the positive nitrogen on the α protons and suggest the intermediacy of a structure such as **11**, in accord with



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similar structures which have been invoked[10] under similar H–D exchange conditions for other pyridinium salts.

The extension of this thionyl chloride–pyridine reaction to other ketones and other carbonyl compounds is underway.

Experimental Section

All ^1H nmr spectra were recorded with a Varian Associates T-60 nmr spectrometer using tetramethylsilane as internal standard unless noted otherwise. All infrared spectra were taken as KBr pellets. Mass spectra were determined on a C. E. C. 21-104 analytical mass spectrometer at 70 eV.

Reagent grade acetophenone and thionyl chloride were redistilled before use.

N-α-**Styrylpyridinium Tetrafluoroborate (1b).**—To a solution of 2.40 g (0.0200 mol) of acetophenone in 40 ml of pyridine was added 11.9 g (0.100 mol) of thionyl chloride all at once and this solution was stirred at 35° for 2.5 hr. The reaction mixture was then stirred vigorously with four separate 100-ml portions of hexane (to remove most of the excess pyridine and thionyl chloride), the hexane layers being carefully decanted each time. The viscous residue which remained was dissolved in 20 ml of water and filtered free of a trace amount of brown, amorphous material. This clear solution was then mixed with a solution prepared from 5.0 g (0.045 mol) of $NaBF_4$ and 10 ml of water. This resulted rapidly in the precipitation of a tan, crystalline material. Filtration and drying *in vacuo* (60°, 2 days) gave 4.71 g (88%) of **1b**: ^1H nmr (CD_3OD–D_2O, external TMS) δ 5.67 (d, J = 3 Hz, 1, olefinic proton cis to phenyl), 6.00 (d, J = 3 Hz, 1, olefinic proton cis to pyridinium ring), 6.90–7.40 (m, 5, phenyl), 7.63–8.23 (m, 2, β-pyridinium), 8.23–8.83 (m, 3, α- and γ-pyridinium).

A 4.30-g portion of this product was recrystallized from 20 ml of water (including a charcoal treatment). After filtering and drying *in vacuo* (60°), there was obtained 2.23 g of **1b** as colorless crystals: mp 118.5–119.5°; ^1H nmr (CD_3COCD_3) δ 6.10 (d, J = 3 Hz, 1, olefinic), 6.37 (d, J = 3 Hz, 1, olefinic), 7.10–7.67 (m, 5, phenyl), 8.15–8.62 (m, 2, β-pyridinium), 8.62–9.32 (m, 3, α- and γ-pyridinium); ir 1627 (s),[11] 1493 (m), 1488 (m), 1474 (s),[11] 1446 (m), 927 (m), 788 (m), 773 (s),[11] 723 (m), 697 (m), 681 (s), and a very strong, broad band at 1050 cm^{-1} for BF_4^-.[12] dominated this spectrum; mass spectrum m/e (rel intensity) 182 (3), *N*-α-styrylpyridinium cationic part of salt **1b** (see complete mass spectrum and interpretation in Results and Discussion).

Anal. Calcd for $C_{13}H_{12}BF_4N$: C, 58.0; H, 4.5; N, 5.2. Found: C, 58.7; H, 4.5; N, 5.3.

N-α-**Styrylpyridinium Chloride (1a).**—A column of 20 g of anion exchange resin Amberlite IRA-400-chloride form was prepared in water (interstitial volume 18 ml) and eluted with 100 ml of water; the silver nitrate test for chloride ion was negative throughout this elution.

A solution of 0.50 g of **1b** was prepared in 15 ml of water by warming to 40° and this solution was placed on top of the resin bed. Elution with water was allowed to proceed at *ca.* 1.7 ml/min as 5 ml-fractions were collected. Fractions 3–11 showed positive chloride ion tests while fractions 1, 2, 12, and 13 were negative. Fractions 3–11 were combined and water was removed at 60° on a rotary evaporator. The residue, 0.39 g of a tan solid, was dissolved in 3 ml of $CDCl_3$ and its ^1H nmr was recorded: δ 6.14–6.33 (m, 2, olefinic), 7.14–7.70 (m, 5, phenyl), 8.43–8.80 (m, 2, β-pyridinium), 8.80–9.17 (m, 1, γ-pyridinium), 9.17–9.42 (m, 2, α-pyridinium); the latter three regions were distinct and characteristic in appearance for pyridinium compounds.[13] A small amount of water also appeared at δ 3.50 as a broadened singlet.

Solvent removal from the above nmr solution and two recrystallizations of the hygroscopic product from CH_2Cl_2–Et_2O gave 0.10 g of **1a**: mp 163–164.8°; ir very similar to that of **1b** except for absence of the large band due to BF_4^-, 1619 (s),[11] 1490 (m), 1466 (s),[11] 1447 (m), 942 (s), 800 (s), 774 (s),[11] 723 (m), 690 (s), 682 cm^{-1} (s); mass spectrum m/e (rel intensity) 182 (98), *N*-α-styrylpyridinium cationic part of salt **1a** (see complete mass spectrum and interpretation in Results and Discussion); ^1H nmr (D_2O, external TMS) δ 6.12 (d, J = 3 Hz, 1, olefinic cis to phenyl), 6.45 (d, J = 3 Hz, 1, olefinic cis to pyridinium), 7.41–7.90 (m, 5, phenyl), 8.23–8.62 (m, 2, β-pyridinium), 8.82–9.25 (m, 3, α- and γ-pyridinium).

N-α-**Phenethylpyridinium Tetrafluoroborate (10b).**—A solution of 2.00 g (0.0074 mol) of **1b** in 50 ml of anhydrous methanol was stirred with 0.1 g of 10% Pd/C at 30.0 psi pressure of hydrogen. After 2.5 hr, the pressure had dropped to 29.3 psi and then remained constant. The catalyst was removed by filtration and the solvent was evaporated. The residue, 2.02 g, which slowly crystallized on standing and was shown to be *ca.* 85% **10b** by ^1H nmr (*vide infra*), was triturated with 4:1 hexane–chloroform at 40° to remove 0.07 g of acetophenone (identified by ^1H nmr and vpc). The residual solid was dissolved in water and this solution, after it was extracted with hexane and 2.0 g of excess $NaBF_4$ was added, was stored overnight at *ca.* 0°. The long, needle-like crystals which separated were filtered, washed with ether, and dried *in vacuo*. In this way 0.90 g of **10b** was obtained: mp 68–85° dec; ^1H nmr (CD_3OD) δ 2.17 (d, J = 7 Hz, 3, methyl), 6.25 (q, J = 7 Hz, 1, methine), 7.27–7.76 (m, 5, phenyl), 7.90–8.40 (m, 2, β-pyridinium), 8.40–8.88 (m, 1, γ-pyridinium), 8.88–9.30 (m, 2, α-pyridinium); ir 1628 (s),[14] 1495 (s),[14] 1480 (s),[14] 1450 (m),[14] 1050 (vs) (tetrafluoroborate ion),[12] 768 (m), 730 (m), 698 (m), 680 cm^{-1} (s); mass spectrum m/e (rel intensity) 79 (100), pyridine$^+$, 105 (82), α-phenethyl$^+$, complex spectrum; no M^+ for cationic portion of **10b**.

Anal. Calcd for $C_{13}H_{14}BF_4N$: C, 57.6; H, 5.2; N, 5.2. Found: C, 56.9; H, 5.2; N, 5.1.

N-α-**Styrylpyridinium Chloride (1a). Experiment for Mechanistic Information.**—Six grams (0.05 mol) of thionyl chloride was added to a solution of 1.20 g (0.0100 mol) of acetophenone in 20 ml of pyridine. This system was then stirred at 35° for 3 hr. During this time, the progress of the reaction was monitored by frequent recording of the ^1H nmr spectrum of a sample which had been removed and stored also at 35°. These results are given in Table III.

Stirring the reaction mixture vigorously with four separate 50 ml-portions of hexane, each hexane layer being carefully decanted, led to a viscous liquid residue.

A.—A sample of this residue gave the following ^1H nmr spectrum ($CDCl_3$): δ 6.18 (d, J = 3 Hz, 1, olefinic cis to phenyl), 6.34 (d, J = 3 Hz, 1, olefinic cis to pyridinium), 7.18–7.73 (m, 5, phenyl), 8.12–9.48 (m, 16, very complex multiplet containing at least the pyridinium protons of **1a** and pyridinium hydrochlo-

(9) S. Hanai, *J. Chem. Soc. Jap.*, **63**, 352, 356 (1942); J. W. Baker, *J. Chem. Soc.*, 2631 (1932).

(10) J. A. Zoltewicz and L. S. Helmick, *J. Amer. Chem. Soc.*, **92**, 7547 (1970), and references cited therein.

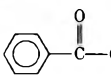
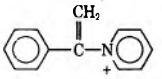
(11) Correspond to strongest peaks in ir spectrum of *N*-vinylpyridinium ion: 1632, 1480, and 758 cm^{-1}, respectively. See I. N. Duling and C. C. Price, *ibid.*, **84**, 578 (1962).

(12) Sadtler Inorganic Grating Spectral Catalog, Sadtler Research Laboratories, Inc., Philadelphia, Pa., 1967, Spectra Y 777 K and Y 955 K.

(13) See, for example, ref 1.

(14) Similar to the spectra of **1a** and **1b**.

TABLE III
^{1}H NMR OBSERVATIONS DURING THE REACTION OF ACETOPHENONE WITH THIONYL CHLORIDE AND PYRIDINE

Reaction time, min	Approximate relative molar amounts[a]  [b]	Unknown[c] CH_3 compd		Cl^- [d]	HCl[e]
0	100	0	0		0
42	12.6	31.2	56.2		*f*
49	7.1	27.3	65.6		66
63	3.4	16.6	80.0		80
72	3.1	11.9	85.0		86
87	2.1	6.6	91.3		*f*
102	0.4	3.9	95.7		*f*
120	0.0	2.0	98.0		*f*
174	0.0	0.0	100.0		102

[a] ±5%. [b] Determined from methyl integral ÷ 3. Chemical shift (*external TMS*) for methyl of acetophenone in this reaction mixture was δ 2.0. [c] Determined from integral of peak (at δ 2.4) ÷ 3. Assumed to be a new kind of methyl peak from its chemical shift and sharp singlet nature; shown not to be 1,1-dichloroethylbenzene by admixture and observing a new methyl singlet at δ 2.1. [d] Determined from olefinic integral ÷ 2; this occurred between δ 5.55 and 5.83. The rest of the spectrum of this molecule was obscured by solvent. [e] As pyridine hydrochloride. Determined from the acidic proton singlet at δ 18.0 after subtracting for the amount of water known to have been present in the pyridine. [f] The value was not determined.

ride, and probably those of some pyridine not extracted by the hexane treatment). An additional minor α-pyridinium type of multiplet (δ 9.80–10.02), probably due to some **2**[2], was also present. (A control experiment indicated that **2** might be produced to the extent of about 0.0006 mol under these reaction conditions.)

B.—When the nmr solution of A was shaken with water, no solutes were left in the $CDCl_3$ phase; all had been transferred to the water phase. ^{1}H nmr (H_2O) showed integrals for phenyl:vinyl (5:2).

C.—When some of the residue was dissolved in water, potentiometrically titrated to pH 6.9, and then extracted several times with ether to remove pyridine, the residual aqueous phase displayed a ^{1}H nmr spectrum in complete accord with **1a**.

Thermal Reaction of 1b. Experiment I.—A 1.00-g sample of **1b** was heated in a sublimation apparatus at 215° for 17.5 hr at *ca.* 0.10 mm pressure. The residue, 0.73 g, was shown by nmr to be unchanged **1b**. The sublimate, 0.23 g, was a pale yellow, oily solid which proved to be only partially soluble in water, only partially soluble in chloroform, but completely soluble in acetone. Its ^{1}H nmr spectrum (CD_3COCD_3, external TMS) showed no vinyl protons and was in accord with pyridinium tetrafluoroborate plus a $(C_6H_6)_x$ aromatic hydrocarbon: δ 6.4 [broad band, $W_{1/2}$ = 20 Hz, 0.91 (after subtracting for HDO of solvent), NH^+], 7.68–8.08 (m, 2.0, β-pyridinium), 8.26–8.83 (m, 3.0, α- and γ-pyridinium), and 6.89–7.68 (m, 5.8, aromatic).

Experiment II.—A 0.20-g sample of **1b** was heated in a sealed tube at 300° for 3.25 hr. The products were mixed with 1.5 ml of D_2O and 1.5 ml of $CDCl_3$, the layers were separated, and the ^{1}H nmr spectrum of each was recorded: D_2O phase, 86:14 mole ratio of pyridinium tetrafluoroborate:**1b**; $CDCl_3$ phase, only an aromatic multiplet essentially identical with that found for an authentic sample of 1-phenylnaphthalene ($C_{16}H_{12}$).

The contents of the $CDCl_3$ phase were examined further: vpc (6 ft 10% SE-30, 220°; retention time given in minutes) reaction product, 4.05; 1-phenylnaphthalene, 4.05; 2-phenylnaphthalene, 5.60; tlc on silica gel (1:9 benzene–hexane, R_f given) reaction product, 0.48; 1-phenylnaphthalene, 0.48; 2-phenylnaphthalene, 0.52; tlc on alumina (25:75 benzene–hexane) reaction product, 0.76; 1-phenylnaphthalene, 0.76; 2-phenylnaphthalene, 0.71. Trace components were also present (R_f 0.00–0.02) in the $CDCl_3$ phase.

Experiment III.—A 2.0-g sample of **1b** was heated at 300° for 4.5 hr in a sealed tube. The contents of the tube were stirred with 50 ml of hexane and extracted twice with 50-ml portions of water. The hexane solution was dried ($MgSO_4$), filtered, and freed of all solvent *in vacuo*, giving 0.41 g of a tan oil: ^{1}H nmr ($CDCl_3$) δ 7.33–8.13 (m, aromatic, superimposable on the spectrum of authentic 1-phenylnaphthalene), 7.08–7.33 (m, aromatic, minor portion of the spectrum, <5% of aromatic area, due to some other minor component); vpc again showed 1-phenylnaphthalene and indicated that, at the most, only 1% of the isolated material could be 2-phenylnaphthalene. The product was passed through a short alumina column in 1:3 benzene–hexane to remove some color and then analyzed further by its mass spectrum: *m/e* (rel intensity) 204 (100) M^+, 203 (66.7) $(M - 1)^+$, 202 (50.0) $(M - 2)^+$. Relative intensities found for the 204, 203, 202 sequence for authentic 1-phenylnaphthalene were 100:66.4:49.8; for authentic 2-phenylnaphthalene, these values were 100:17.0:30.2.

Deuterium Incorporation by 1b in D_2O.—A solution of 0.10 g of **1b** in 1.0 g of D_2O was heated in a sealed nmr tube at 180° for 3 days. After this time, the ^{1}H nmr spectrum indicated that H–D exchange had occurred essentially exclusively and nearly completely at the α-pyridinium carbons: δ 6.10 (d, J = 3 Hz, 0.98, olefinic), 6.43 (d, J = 3 Hz, 0.98, olefinic), 7.42–7.93 (m, 5.00, phenyl), 8.23–8.57 (d, slightly broadened, J = 7.5 Hz, 1.93, β-pyridinium protons, coupled only to γ proton), 8.75–9.20 (t, slightly distorted, $J \cong 7.5$ Hz, 1.16, γ-pyridinium protons + residual α-pyridinium protons); the HDO peak of solvent had increased, as expected, by the corresponding amount. This α-exchanged pyridinium ring gave virtually the identical ^{1}H nmr spectrum as found for the ring protons of 2,6-dimethylpyridinium hydrochloride.[15]

Registry No.—**1a**, 38434-89-8; **1b**, 579-54-4; **10b**, 38434-91-2; thionyl chloride, 7719-09-7; pyridine, 110-86-1; acetophenone, 98-86-2.

(15) H. M. Relles, unpublished results.

Bridgehead Nitrogen Heterocycles. II. Formation by Reaction of α-Amino N-Heterocyclic Compounds with Chlorothioformyl Chloride

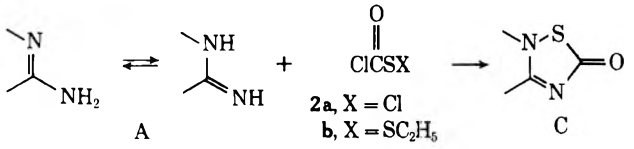
KURT PILGRAM* AND RICHARD D. SKILES

Biological Sciences Research Center, Shell Development Company, Modesto, California 95352

Received October 12, 1972

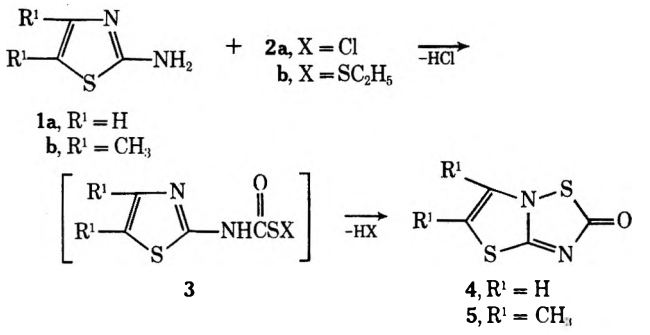
Cyclization of a variety of α-amino N-heterocyclic compounds (A) with chlorothioformyl chloride (**2a**) resulted in the formation of bicyclic bridgehead nitrogen heterocycles (C) in fair yield. A second method of synthesis of C, from A and ethyldithiocarbonyl chloride (**2b**), has also been established. Some preliminary studies of the chemical reactivity of 6-substituted 2*H*-[1,2,4]thiadiazolo[2,3-*b*]pyridazin-2-ones (**14**) and **15** have been carried out.

The preparation of bridgehead nitrogen heterocycles from α-amino N-heterocyclic compounds with 3-chloroacrylic and atropic acids (and acid chlorides) was investigated recently in this laboratory.[1] We have now investigated the reactions of α-amino N-heterocyclic compounds with chlorothioformyl chloride (**2a**) which build up novel nitrogen- and sulfur-containing heterocyclic ring systems with bridgehead nitrogen.



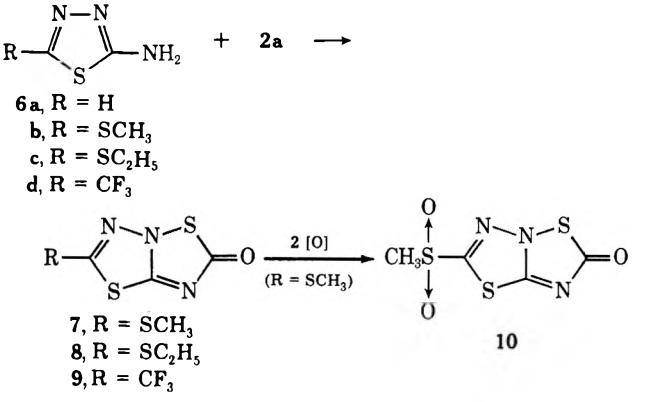
Results

Entry into the 2*H*-thiazolo[3,2-*b*][1,2,4]thiadiazol-2-one ring system was first obtained when 2-aminothiazole (**1a**) and its 4,5-dimethyl analog (**1b**) were allowed to react with **2a** in the presence of 2 molar equiv of triethylamine in tetrahydrofuran solution at temperatures between −10 and 60°. The reaction mixtures from these two amines were black tars, but it was possible to isolate and characterize **4** and **5**. The yields of **4** and **5**

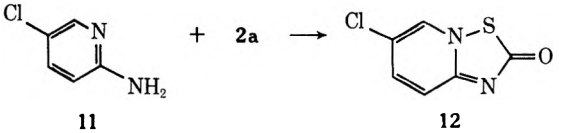


were in the order of 2–3%. This appears to be more of an unsatisfactory reaction than an isolation problem, as **5** was purified and readily isolated by silica chromatography.[2] Because of the inherent synthesis difficulty, an alternative route was sought. A suitable intermediate would be ethyldithiocarbonyl chloride (**2b**) which would be expected to undergo amination by the heterocyclic amine followed by a facile ring closure to the bicyclic ring system. It was found that **1a** reacted readily with **2b** and the yield of purified **4** was in the order of 25% without isolation of the intermediate **3** (R¹ = H; X = SC_2H_5). The formation of **3** (R¹ = H; X = SC_2H_5) in admixture with **4** at 0° was likely in light of tlc data (Experimental Section). However, attempted isolation of **3** at room temperature proved unsuccessful.

The 1,3,4-thiadiazole ring system has been the subject of numerous investigations.[4] It was anticipated that the most direct route to the 6*H*-[1,3,4]thiadiazolo-[3,2-*b*][1,2,4]thiadiazol-6-one system would be from 2-amino-1,3,4-thiadiazole (**6a**) and its 5-substituted analogs (**6b**, **6c**, and **6d**). Reaction of **6a** with **2a** led to the formation of tar which could not be resolved by chromatography. However, condensations of **6b**, **6c**, and **6d** with **2a** occurred readily, under the same reaction conditions used for the reactions of **2a** with **1**, to give the fused heterocyclic compounds **7**, **8**, and **9** in 10–53% yield. Oxidation of **7** with *m*-chloroperbenzoic acid gave the corresponding sulfone **10**.



Entry into the 2*H*-[1,2,4]thiadiazolo[2,3-*a*]pyridin-2-one system was obtained when **2a** was allowed to react with 2-amino-5-chloropyridine (**11**). Recrystallization of the reaction mixture afforded **12** in 48% yield.



2-Amino-6-chloropyridazine (**13**) also underwent ready reaction with **2a** to yield 6-chloro-2*H*-[1,2,4]-thiadiazolo[2,3-*b*]pyridazin-2-one (**14**) in 37% yield. The displacement of chlorine in **14** was quite facile, and reaction at ambient temperature of sodium methylmercaptide with **14** led to the 6-methylthio analog (**15**). Oxidation of **15** with peracetic acid gave the sulfone **16**,

(1) J. G. Kuderna, R. D. Skiles, and K. Pilgram, *J. Org. Chem.*, **36**, 3506 (1971).

(2) A possible explanation for the low yields may be the inherent instability of **3** (R¹ = H, CH_3; X = Cl). For example, *N*,*N*-dialkylcarbamoylsulfenyl chlorides readily decompose at 0° with elimination of sulfur to form *N*,*N*-dialkylcarbamoyl chlorides.[3]

(3) G. Zumach and E. Kühle, *Angew. Chem.*, **82**, 63 (1970); *Angew. Chem., Int. Ed. Engl.*, **9**, 54 (1970).

(4) L. L. Bambas, *Heterocycl. Compounds*, **4**, 81 (1952).

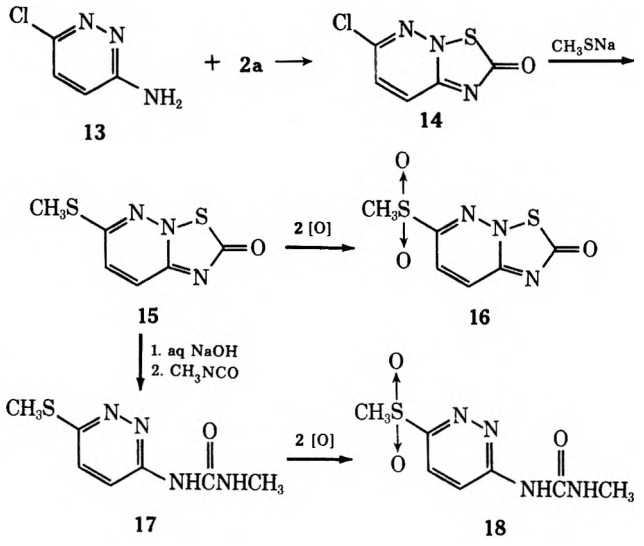
TABLE I
HETEROCYCLES OBTAINED BY REACTION OF α-AMINO N-HETEROCYCLIC COMPOUNDS WITH CHLOROTHIOFORMYL CHLORIDE (CTFC)[a]

Compd	Yield, %	Mp, °C	Formula	Nmr data, δ[b]	Solvent
4	3.3 25[c]	130–132	$C_4H_2N_2OS_2$	7.6 (1) (d, 1, 5-CH), 7.2 (1) (d, 6-CH)	DMSO-d_6
5	2.0	73–75	$C_6H_6N_2OS_2$	2.1 (1) (d, 3, 5-CH_3), 2.4 (1) (d, 3, 6-CH_3)	$CDCl_3$
7	10	149–152	$C_4H_2N_3OS_3$	2.75 (s, SCH_3)	$CDCl_3$
8	36.4	104–106	$C_5H_5N_3OS_3$	1.5 (t, 3, CH_3), 3.35 (q, 2, CH_2)	$CDCl_3$
9	53	83–85	$C_4F_3N_3OS_2$		
12	48	132–134	$C_6H_3ClN_2OS$	7.4 (m, 2, CH=CH), 8.1 (m, 1, 5-CH)	DMSO-d_6
14	37	164–166	$C_5H_2ClN_3OS$	7.45 (q, 1, CH=), 7.9 (q, 1, CH=)	DMSO-d_6
20	20	77–79	$C_5H_6N_2OS_2$	1.4 (m, 2, 6-CH_2), 3.1 (t, 2, 5-CH_2), 3.85 (t, 2, 7-CH_2)	$CDCl_3$

[a] Satisfactory analytical data (±0.3 for N) were reported for all compounds in this table; C and H analyses were reported for all except 7; S analyses were reported for 4, 7, 8, and 20; Cl analysis was reported for 14. [b] In parts per million (J in hertz) (multiplicity, number of protons, assignment). [c] From 2-aminothiazole and ethyldithiocarbonyl chloride.

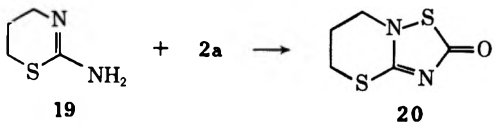
whereas alkaline hydrolysis afforded 3-amino-6-methylthiopyridazine isolated as its urea **17** by reaction with methyl isocyanate; oxidation of **17** gave sulfone **18** (Scheme I) in 90% yield. Displacement of chlorine

SCHEME I



in **14** by nucleophiles other than sodium methylmercaptide followed by hydrolysis of the resulting substituted bicyclic heterocycle may provide a convenient preparative method for 3-substituted 6-aminopyridazines which are difficult to prepare by other methods.[5,6]

5,6-Dihydro-2-amino-4*H*-1,3-thiazine (**19**) underwent ready reaction with **2a** to yield 5,6-dihydro-2*H*-[1,2,4]-thiadiazolo[3,2-*b*]thiazin-2-one (**20**), also a new heterocyclic system.

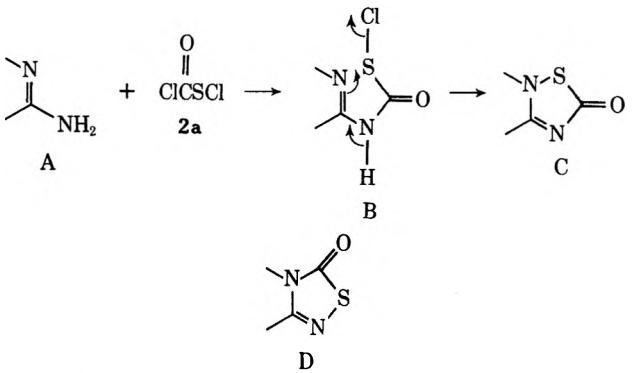


Discussion

Analytical and physical data of all bicyclic heterocycles prepared by reaction of an α-amino N-heterocyclic compound, **1**, with **2a** are summarized in Table I. A common feature of the mass spectra of the compounds described above is that the molecular ions are prominent peaks indicating a fairly great stability of these fused bicyclic compounds. The primary fragmentation path involves loss of the carbonyl group. In all cases, ions corresponding to $M^+ - 28$ (CO) can be observed which on further impact lose nitrogen and sulfur. However, certain substituents (*e.g.*, CF_3, RS, and RSO_2) influence the secondary pattern markedly.

In the ir spectra, carbonyl bands for all the bicyclic heterocycles are near 1700 cm^{-1}, whereas absorptions of the –C=N grouping are shown by all compounds in the 1640–1670-cm^{-1} region.

The chemistry of α-amino N-heterocyclic compounds (amidines) of general structure A is complicated by the presence in the molecule of two nitrogen atoms, and it is frequently difficult to present unequivocal chemical proof of structure of reaction products. The problem is still more complicated by the presence of two reactive centers in **2a**. Basically, the reaction of A with **2a** may give either one of the two heterocycles C and D. Structure D may be excluded from consideration on the basis of the following grounds. Firstly, in α-amino N-heterocyclic compounds of general structure A, monoacylation and carbamoylation occurs always on the exocyclic amino group.[5,7–11] Secondly, **2a** has been shown[3] to undergo reaction with amines selectively with the carbonyl group forming an amide bond leaving B as the only likely intermediate. Soft–hard acid–base theory[12,13] supports this view in that amidines such as A (the amino group is a hard base) would be expected



(5) M. Tisler and B. Stanovnik, *Advan. Heterocycl. Chem.*, **9**, 211 (1968).
(6) J. Druey, K. Meier, and K. Eichenberger, *Helv. Chim. Acta*, **37**, 121 (1954).
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(8) F. Kröhnke, B. Kickhöfer, and C. Thoma, *Ber.*, **88**, 1117 (1955).
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(10) J. Sandström, *ibid.*, **9**, 181 (1968).
(11) A. H. Land, *Heterocycl. Compounds*, **5**, 595 (1957).
(12) R. G. Pearson, *J. Amer. Chem. Soc.*, **85**, 3553 (1963).
(13) We are grateful to reviewer III who raised this point.

to react preferentially with the carbonyol group (carbonyl carbon centers which resemble carbonium centers are hard) of **2a**. The internal nitrogen atom in B would be expected to react more slowly with the sulfur atom (a soft acid) to give C.

In summary, synthetic procedures were developed to convert α-amino N-heterocyclic compounds to a variety of novel bridgehead nitrogen heterocycles by reaction with chlorothioformyl chloride. Detailed studies of the individual synthesis to optimize conditions were not performed.

Experimental Section

Melting points are uncorrected and were taken on a Thomas-Hoover capillary apparatus. Ir absorption spectra were determined on a Beckman IR-4 double beam instrument. The nmr spectra were determined on a Varian A-60 spectrometer. Mass spectra were recorded on a Perkin-Elmer Model 270 B double focusing mass spectrometer.

Materials.—2-Aminothiazole (**1a**) and 2-amino-5-chloropyridine (**11**) (Aldrich Chemical Co.) were used without further purification. The following α-amino N-heterocyclic compounds were prepared following procedures reported in the literature: 2-amino-1,3,4-thiadiazole (**6a**),[14] 2-amino-5-methylthio-1,3,4-thiadiazole (**6b**),[15] 3-amino-6-chloropyridazine (**13**),[16] 2-amino-5-trifluoromethyl-1,3,4-thiadiazole (**6d**),[17] 2-amino-4,5-dimethylthiazole (**1b**),[18] and 5,6-dihydro-2-amino-4*H*-1,3-thiazine (**19**).[8]

2-Amino-5-ethylthio-1,3,4-thiadiazole (6c).—Alkylation with ethyl iodide of the sodium salt of 2-amino-5-mercapto-1,3,4-thiadiazole proceeded smoothly in refluxing ethanol to give the title compound in 88% yield, mp 134–136°.

Anal. Calcd for $C_4H_7N_3S_2$: C, 41.4; H, 5.7; N, 16.1; S, 36.8. Found: C, 41.6; H, 6.0; N, 16.0; S, 36.5.

2*H*-Thiazolo[3,2-*b*][1,2,4]thiadiazol-2-one (4). A. From 2-Aminothiazole (1a) and Chlorothioformyl Chloride (2a).—To a cold (−10°) solution of 13.1 g (0.1 mol) of **2a** in 100 ml of tetrahydrofuran was added dropwise (75 min) with stirring a solution of 10.0 g (0.1 mol) of **1a** in 300 ml of tetrahydrofuran, followed by the dropwise (30 min) addition of 20.2 g (0.2 mol) of triethylamine. The mixture was then stirred at 60° for 2.5 hr and filtered. The filtrate was concentrated to dryness and the residual solid was recrystallized from methanol to afford 0.5 g (3.3%) of **4**: a brown crystalline solid; mp 130–132°; ir (KBr) 1735, 1645 cm^{-1}; mass spectrum (70 eV) 158 (M^+).

B. From 2-Aminothiazole (1a) and Ethyldithiocarbonyl Chloride (2b).—To a cooled (0°) solution of 14.4 g (0.1 mol) of **2b** in 100 ml of tetrahydrofuran was added dropwise with stirring a solution of 20.0 g (0.2 mol) of **1a** in 150 ml of tetrahydrofuran causing a tarry solid to precipitate. Tlc of the solution indicated the disappearance of starting materials and the appearance of two new reaction products. The intensity of the spot corresponding to the compound with smaller R_f value, presumably **3** (R^1 = H; X = SC_2H_5), decreased with time at the expense of the spot corresponding to **4** which has a greater R_f value. The mixture was stirred for 18 hr at ambient temperature, heated to 60° for 1 hr, and cooled to 25°. Filtration and concentration to dryness of the filtrate afforded a solid which was recrystallized from methanol to give 4.0 g (25%) of **4**, a light yellow crystalline solid, mp 130–132°, in admixture with A (see above), mmp 130–132°. R_f values of **3** (R^1 = H; X = SC_2H_5) (solvent no.): 0.09 (3),[19] 0.17 (9),[19] and 0.36 (10).[19] R_f values of **4** (solvent no.): 0.37 (3), 0.44 (9), and 0.56 (10).

5,6-Dimethyl-2*H*-thiazolo[3,2-*b*][1,2,4]thiadiazol-2-one (5).—To a solution of 7.2 g (0.05 mol) of **2a** in 100 ml of tetrahydrofuran was added at 5° dropwise and with stirring a solution of 7.0 g (0.055 mol) of **1b**. The temperature was maintained at 5° during the dropwise (1.5 hr) addition of 11.0 g (0.109 mol) of triethylamine. The mixture was stirred at ambient temperature for 1 hr and then heated to 60° for 1 hr. The warm reaction mixture was filtered and the filtrate was evaporated to a residue which upon purification by column chromatography afforded 0.2 g (2%) of **5**: mp 73–75°; ir (KBr) 1705 (C=O), 1670 cm^{-1} (C=); mass spectrum (70 eV) 186 (M^+).

2-Methylthio-6*H*-[1,3,4]thiadiazolo[3,2-*b*][1,2,4]thiadiazol-6-one (7).—To a solution of 13.1 g (0.1 mol) of **2a** in 150 ml of tetrahydrofuran was added at −5° with stirring a solution of 14.7 g (0.1 mol) of **6b** and 20.2 g (0.2 mol) of triethylamine in 350 ml of tetrahydrofuran. The mixture was warmed gently to reflux for 2.5 hr. The reaction mixture was filtered, concentrated to dryness, and purified by column chromatography over silica gel to give 2.0 g (10%) of **7**, a light yellow crystalline solid, mp 149–152°.

2-Methylsulfonyl-6*H*-[1,3,4]thiadiazolo[3,2-*b*][1,2,4]thiadiazol-6-one (10).—To a solution of 2.0 g (0.01 mol) of **7** in 25 ml of chloroform was added with stirring a solution of 6.1 g (0.03 mol) of 85% *m*-chloroperbenzoic acid in 25 ml of chloroform. The mixture was stirred at ambient temperature for 2.5 hr and left standing overnight. The reaction mixture was washed with aqueous (10%) sodium carbonate and then with cold water. The chloroform layer was dried and evaporated to dryness. The residual solid was recrystallized from methanol to give 0.5 g (22%) of **10**: a light yellow colored solid; mp 145–148°; ir (KBr) 1742, 1728, 1708, (C=O), 1560 (C=), 1160 cm^{-1} (SO_2); mass spectrum (70 eV) 237 (M^+), 221, 209, 123, 107, 102, 90, 79, 63, 44, 28, 15.

Anal. Calcd for $C_4H_3N_3O_3S_3$: C, 20.2; H, 1.3; N, 17.7. Found: C, 20.4; H, 1.4; N, 17.8.

6-Chloro-2*H*-[1,2,4]thiadiazolo[2,3-*b*]pyridazin-2-one (14).—To a chilled (5°) solution of 13.1 g (0.1 mol) of **2a** in 100 ml of tetrahydrofuran was added dropwise (2.5 hr) with stirring a solution of 12.9 g (0.1 mol) of **13** and 20.2 g (0.2 mol) of triethylamine in 600 ml of tetrahydrofuran. The mixture was heated to reflux for 6 hr, filtered while hot, and concentrated to dryness. The residual solid was recrystallized from methanol (charcoal) to give 7.0 g (37%) of **14**: a light yellow crystalline solid; mp 164–167°; ir (KBr) 1720 (C=O), 1660, 1620 cm^{-1} (C=).

6-Methylsulfonyl-2*H*-[1,2,4]thiadiazolo[2,3-*b*]pyridazin-2-one (16).—A solution of 4.0 g (21.4 mmol) of **14** and 1.5 g (21.4 mmol) of sodium methylmercaptide in 40 ml of dimethyl sulfoxide was left standing at ambient temperature for 1.5 hr. A solid precipitated during this time. The mixture was poured over ice and filtered. The filter cake was washed with water and dried to give 3.0 g (72%) of **15**.

Compound **15**, 1.5 g, was suspended in 25 ml of acetic acid and warmed to 50° until solution occurred. Hydrogen peroxide (35%, 10 ml) was added. The mixture was heated to 75°, left standing at ambient temperature for 2 hr, poured into ice water, and filtered to give 1.0 g (59%) of **16**: a light yellow crystalline solid; mp 183–186°; ir (KBr) 1710 (C=O), 1325 and/or 1310, 1145 and/or 1140 cm^{-1} (SO_2).

Anal. Calcd for $C_6H_5N_3O_3S_2$: N, 18.2; S, 27.7. Found: N, 17.9; S, 27.4.

1-Methyl-3-(3-methylthiopyridazin-6-yl)urea (17).—A suspension of 21.0 g (0.112 mol) of **14** and 7.9 g (0.112 mol) of sodium methylmercaptide in 100 ml of absolute methanol was stirred at 45° until a clear solution had formed (1 hr). After 18 hr the reaction mixture was poured into water and filtered to give 20 g of **15**, mp 141–144°. A suspension of 5 g (25 mmol) of **15** in 100 ml of 10% sodium hydroxide solution was placed on a steam bath for 30 min giving a clear solution. When a sample of this solution was acidified, hydrogen sulfide was liberated. After removal of water under reduced pressure, dimethylformamide and excess methyl isocyanate were added to the residual solid. After 24 hr this solution was diluted with water, and the product was filtered. Recrystallization from ethanol gave 1.0 g (20%) of **17**: a tan solid; mp 237–240°; ir (KBr) 3330, 3240 (NH), 1708 (C=O), 1555 and 1525 cm^{-1} (amide II).

Anal. Calcd for $C_7H_{10}N_4SO$: C, 42.5; H, 5.0; N, 28.3; S, 16.2. Found: C, 42.6; H, 4.9; N, 28.6; S, 16.5.

1-Methyl-3-(3-methylsulfonylpyridazin-6-yl)urea (18).—A mixture of **17**, 0.5 g (2.25 mmol), in 20 ml of 33% hydrogen peroxide and 15 ml of acetic anhydride was heated at 80° for 2 hr, poured into ice water, filtered, and dried to give 0.6 g (90%) of

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(15) M. Busch and H. Biebler, *J. Prakt. Chem.*, [2] **93**, 339 (1916).

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(17) I. Lalezari and N. Shargki, *J. Heterocycl. Chem.*, **3**, 336 (1966).

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(19) Solvent no. 3 (by volume): hexane (66), ethyl acetate (30), tetrahydrofuran (4). Solvent no. 9 (by volume): hexane (50), ethyl acetate (25), tetrahydrofuran (25). Solvent no. 10 (by volume): hexane (20), ethyl acetate (40), tetrahydrofuran (40).

18: a colorless crystalline solid; mp 257–260°; ir (KBr) 3330, 3250 (NH), 1710, 1700 (C=O), 1550 (amide II), 1350 or 1315, 1150 (SO_2).

Anal. Calcd for $C_7H_{10}N_4SO_3$: C, 36.5; H, 4.4; N, 24.4. Found: C, 36.4; H, 4.2; N, 23.9.

Registry No.—**1a**, 96-50-4; **1b**, 2289-75-0; **2a**, 2757-23-5; **2b**, 13221-50-6; **3** (R^1 = H; X = SC_2H_5), 38401-09-1; **4**, 38400-53-2; **5**, 38400-54-3; **6b**, 5319-77-7; **6c**, 25660-70-2; **6d**, 10444-89-0; **7**, 38400-58-7; **8**, 38400-59-8; **9**, 38400-60-1; **10**, 38400-61-2; **11**, 1072-98-6; **12**, 38400-63-4; **13**, 5469-69-2; **14**, 38400-66-7; **15**, 38400-67-8; **16**, 38400-65-6; **17**, 38400-68-9; **18**, 38400-69-0; **19**, 10416-84-9; **20**, 38400-71-4; sodium 2-amino-5-mercapto-1,3,4-thiadiazole, 38400-72-5; sodium methylmercaptide, 5188-07-8.

Acknowledgment.—We are indebted to Dr. S. B. Soloway for his constant encouragements and to Drs. B. C. Baker, W. J. McKinney, and G. E. Pollard for microanalyses and spectral measurements.

Bridgehead Nitrogen Heterocycles. III. Formation by Reaction of α-Ureido N-Heterocyclic Compounds with Chlorothioformyl Chloride

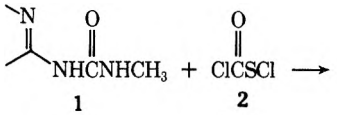
KURT PILGRAM* AND RICHARD D. SKILES

Biological Sciences Research Center, Shell Development Company, Modesto, California 95352

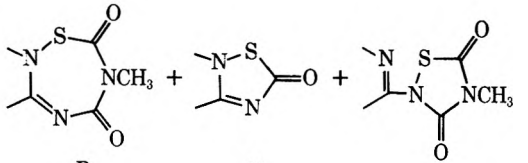
Received October 12, 1972

Condensation of α-ureido N-heterocyclic compounds (1) with chlorothioformyl chloride (2) is shown to give bicyclic bridgehead nitrogen heterocycles of general structure B and H as well as 2,4-disubstituted 1,2,4-thiadiazolidine-3,5-diones (D). The factors which control the course of the reaction and which determine the nature of the reaction product are discussed.

In the preceding article[1] it was shown that α-amino N-heterocyclic compounds (amidines) undergo reaction with chlorothioformyl chloride to give bicyclic bridgehead nitrogen heterocycles in fair yield. We now report the reactions of a series of α-ureido N-heterocyclic compounds (**1**) with chlorothioformyl chloride (**2**). Of

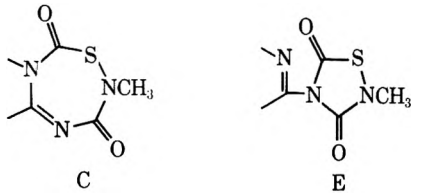


1 **2**



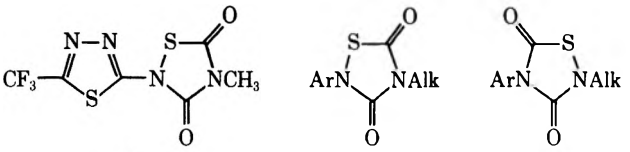
B H D

particular interest are the reactions of **2** with various **1** compounds in which the relative nucleophilicities of the exo- and endocyclic nitrogen atoms vary because theoretically these condensations can give fused thiatriazepinedione derivatives (*i.e.*, B and C) as well as 1,2,4-thiadiazolidinediones (*i.e.*, D and E). The result re-



C E

ported[2] for the condensation of 1-methyl-3-(5-trifluoromethyl-1,3,4-thiadiazol-2-yl)urea (**1g**) with **2**, which yielded 4-methyl-2-(5-trifluoromethyl-1,3,4-thiadiazol-2-yl)-1,2,4-thiadiazolidine-3,5-dione (**3**), does not indicate this variability in the direction of cyclization which can occur in these reactions. In agreement with the above result, however, it has been reported[3] that condensation of a series of 1-alkyl-3-arylureas yielded 4-alkyl-2-aryl-1,2,4-thiadiazolidine-3,5-diones (**4**); positional isomer **5** was not formed.

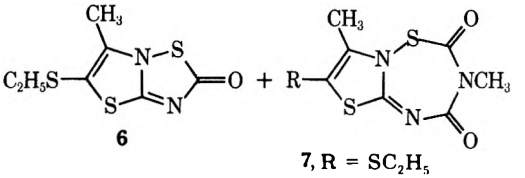


3 **4** **5**

Results and Discussion

When urea **1a** was allowed to react with **2** in xylene or *p*-dioxane in the presence of 2 molar equiv of triethylamine at 20–50°, there were obtained two compounds separated by silica chromatography and identified as 5-ethylthio-6-methyl-2*H*-thiazolo[3,2-*b*][1,2,4]-thiadiazol-2-one (**6**, 6.5%) and 3,8-dimethyl-7-ethylthio-2*H*-thiazolo[3,2-*b*][1,2,4,6]thiatriazepine-2,4(3*H*)-dione (**7**, 11.6%). However, when the reaction was carried out in refluxing xylene (4 hr), the only isolable product was **6** (6.5%); compound **7** could not be de-

1a, R = SC_2H_5
b, R = CH_3
c, R = $(CH_3)_2CHCH_2$



6

7, R = SC_2H_5
8, R = CH_3
9, R = $CH_2CH(CH_3)_2$

(1) K. Pilgram and R. D. Skiles, *J. Org. Chem.*, **38**, 1575 (1973).
(2) Farbenfabriken Bayer, A. G., Belgian Patent 746,833 (1970).
(3) G. Zumach and E. Kühle, *Angew. Chem.*, **82**, 63 (1970); *Angew. Chem., Int. Ed. Engl.*, **9**, 54 (1970).

TABLE I

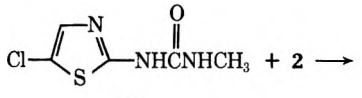
HETEROCYCLES OBTAINED BY REACTION OF α-UREIDO N-HETEROCYCLIC COMPOUNDS (1) WITH CHLOROTHIOFORMYL CHLORIDE (2)[a]

Compd	Yield, %	Mp, °C	Formula	Nmr Data, δ[b]	Solvent
6	6.5	78–81	$C_7H_8N_2OS_3$	1.3 (t, 3, CH_3CH_2), 2.8 (q, 2, CH_3CH_2)	$CDCl_3$
7	11.6	57–58	$C_9H_{11}N_3O_2S_3$	1.3 (t, 2, CH_3CH_2), 2.85 (q, 2, CH_3CH_2), 2.2 (s, 3, CH_3C=), 3.3 (s, 3, NCH_3)	$CDCl_3$
8	25	154–156	$C_8H_9N_3O_2S_2$	2.25 (d, 3, 7-CH_3), 2.35 (d, 3, 8-CH_3), 3.15 (s, 3, NCH_3)	DMSO-d_6
9	63	Oil	$C_{11}H_{15}N_3O_2S_2$	1.0 [d, 6, $(CH_3)_2$], 2.0 (m, 1, CH), 2.35 (s, 3, CH_3C=), 2.65 (d, 2, CH_2), 3.2 (s, 3, NCH_3)	$CDCl_3$
10	34	132–133	$C_4HClN_2OS_2$	7.2 (s, CH=)	$CDCl_3$
11	4.3	139–141	$C_6H_4ClN_3O_2S_2$	7.6 (s, 1, CH=), 3.3 (s, 3, NCH_3)	$CDCl_3$
12	25	210 dec	$C_3HN_3OS_2$		
13	63	149–152	$C_4H_3N_3OS_3$	2.75 (s, SCH_3)	$CDCl_3$
3	50	98–100	$C_6H_3F_3N_4O_2S_2$	7.0 (m, 4, C_6H_4), 3.3 (s, 3, NCH_3)	$CDCl_3$
16	60	162–165	$C_5H_2ClN_3OS$	7.45 (q, 1, CH=), 7.9 (q, 1, CH=)	DMSO-d_6

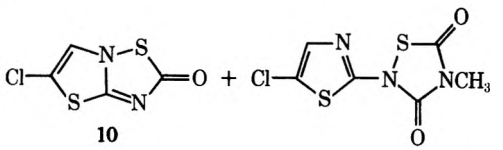
[a] Satisfactory analytical data (±0.3% for C, H, and N) were reported for all compounds in this table; S analyses were reported for all except 6, 7, and 12; Cl analyses were reported for 10 and 11. [b] In parts per million (multiplicity, number of protons, assignment).

tected (tlc) in the reaction mixture. The two ureas **1b** and **1c** reacted with **2** to give the fused thiatriazepinedione derivatives **8** (25%) and **9** (63%), and no further reaction products could be detected in the reaction mixture.

The reaction mixture obtained by treatment of **1d** with **2** in refluxing benzene (18 hr) contained two products which were separated by column chromatography and identified as 5-chloro-2*H*-thiazolo[3,2-*b*]-[1,2,4]thiadiazol-2-one (**10**, 34%) and 2-(5-chlorothiazol-2-yl)-4-methyl-1,2,4-thiadiazolidine-3,5-dione (**11**, 4.3%).



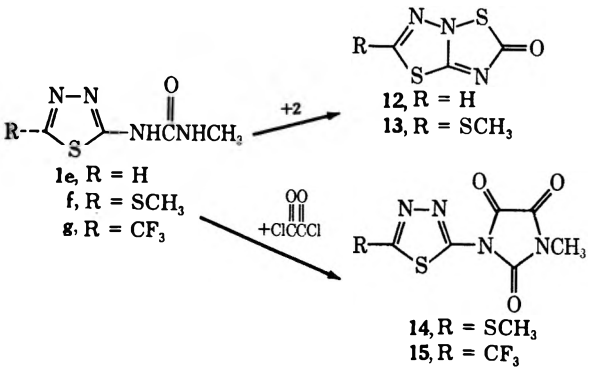
1d



10 **11**

The ureas **1e**, **1f**, and **1g** were allowed to condense with **2** in refluxing benzene or *p*-dioxane in the presence or absence of triethylamine to determine whether or not the direction of cyclization would be the same as with **1d** and **2**. The results of these three experiments indicated that the cyclizations occurred similarly to give either a 2*H*-1,3,4-thiadiazol[3,2-*b*][1,2,4]thiadiazol-2-one (**12**, 25%) and **13** (63%) or a 2,4-disubstituted 1,2,4-thiadiazolidine-3,5-dione derivative (**3**, 50%). Surprisingly, the reactions of both **1f** and **1g** with oxalyl chloride which were effected in refluxing xylene resulted in almost quantitative (94–98%) yields of the parabanic acid derivatives **14** and **15** (Scheme I); fused compounds analogous to **13** could not be detected. Compound **13** was identical (elemental analysis, melting point, mixture melting point, ir and nmr spectrum, and formation of an identical sulfone) with the product obtained earlier[1] in 10% yield as a result of the interaction of 2-amino-5-methylthio-1,3,4-thiadiazole with **2** in the presence of 2 molar equiv of triethylamine.

SCHEME I

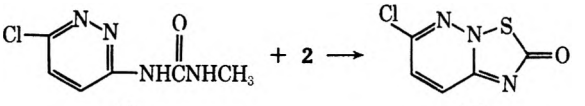


1e, R = H
f, R = SCH_3
g, R = CF_3

12, R = H
13, R = SCH_3

14, R = SCH_3
15, R = CF_3

The reaction of **1h** with **2** proceeded smoothly in refluxing xylene (18 hr) to give 6-chloro-2*H*-[1,2,4]-thiadiazolo[2,3-*b*]pyridazin-2-one (**16**) in 60% yield.



1h **16**

The identity of this compound with that obtained by reaction of 3-amino-6-chloropyridazine with **2**[1] was verified (elemental analysis, melting point, mixture melting point, nmr, and mass spectrum).

Table I lists data of compounds **3**, **6**–**13**, and **16**.

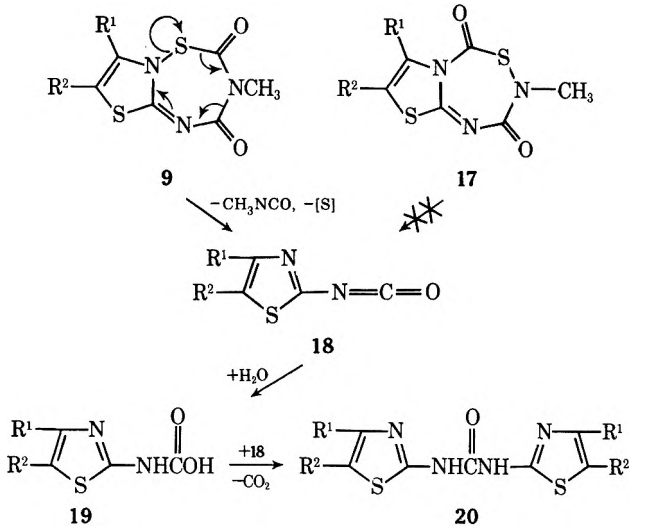
The identification of **7**, **8**, and **9** as thiatriazepinediones of general structure B is based upon the following observations. Elemental analyses indicate that ring closure occurred. Structure B is preferred over that of C, D, and E on chemical and spectroscopic grounds. Compounds of general structure D are thermally stable.[3,4] Compounds **7**, **8**, and **9** on the other hand undergo facile decomposition with elimination of methyl isocyanate and sulfur when heated or stored at ambient temperature over extended periods of time. In this respect, the behavior of these compounds resembles that of annelated 3-phenyl-1,3,5-triazine-2,4-diones which eliminate phenyl isocyanate on heating.[5]

(4) G. Zumach, L. Eue, W. Weiss, E. Kühle, and H. Hack, South African Patent 67/07491 (1968) [*Chem. Abstr.*, **70**, 47465r (1969)]; British Patent 1,115,350 (1968) [*Chem. Abstr.*, **69**, 96732p (1968)].

(5) U. v. Gizycki and G. Oertel, *Angew. Chem.*, **80**, 363 (1968); *Angew. Chem., Int. Ed. Engl.*, **7**, 381 (1968).

When **9** was exposed to moist air at 60° in a vacuum oven for 72 hr, the urea **20** was isolated in 50% yield in addition to elemental sulfur. The mechanism postulated to account for this mode of fragmentation is illustrated in Scheme II. A positional isomer such as **17**

SCHEME II



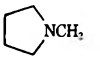
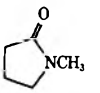
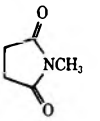
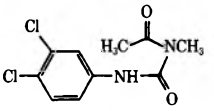
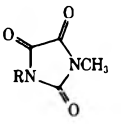
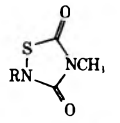
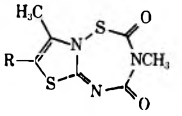
which has also been considered as the product from **1c** and **2** (*e.g.*, C), would not be expected to fragment readily to **18**. Water may intercept the unstable **19** to give the carbamic acid **21** which by loss of carbon dioxide[6] and addition to **19** gives the symmetrical urea **20**. In the absence of hydroxylic solvents, **18** would be expected to cyclodimerize.[5]

The NCH_3 chemical shift is predictive of whether the cyclization products derived from **1** with **2** have general structures B and D or C and E. For example, in nitrogen heterocycles, one or two carbonyl groups adjacent to the nitrogen atom have a pronounced effect on the nmr chemical shift of the substituent on the nitrogen atom; *e.g.*, in *N*-methylpyrrolidine[7] the chemical shift of the methyl group is δ 2.33 ppm. In *N*-methylpyrrolidone[7] and *N*-methylsuccinimide the corresponding chemical shifts are δ 2.82 and 3.00 ppm, respectively. The nmr data for the various cyclization products derived from **1** and **2** are consistent with those for heterocycles containing similar arrangements (Table II). The chemical shift of the *N*-methyl group is invariably observed at δ 3.15–3.33 ppm indicating the presence of the $-C(=O)N(CH_3)C(=O)-$ grouping in heterocycles such as **3**, **7**, **8**, **9**, and **11**.

The thiatriazepinedione cyclization products derived from **1** with **2** were further characterized by their ir spectra; peaks in the ir were assigned in the light of well-established correlations of C=O groups. Iminocarbonyl groups which are part of a ring system have C=O bands at 1790–1720 and 1710–1670 cm^{-1},[8] the lower frequency band being more intense. In conformity with general structure B, the compounds **7**, **8**, and **9** show two characteristic carbonyl bands at 1758–1741 and 1705–1695 cm^{-1} of which the higher frequency band

(6) C. W. van Hoogstraten, *C. R. Acad. Sci.*, **51**, 414 (1932).
(7) J. C. N. Ma and E. W. Warnhoff, *Can. J. Chem.*, **43**, 1849 (1965).
(8) L. J. Bellamy, "Advances in Infrared Frequencies," Vol. 130, Methuen and Co. Ltd., London, 1968, p 134.

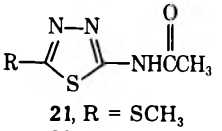
TABLE II
NUCLEAR MAGNETIC RESONANCE POSITIONS FOR *N*-METHYL GROUPS

Compd	Structure	δ in $CDCl_3$ (ppm)
		2.33[a]
		2.82[a]
		3.00
23		3.35
15, 16		3.1–3.2[b]
11, 14		3.30–3.33
7, 8, 9		3.15–3.30

[a] Reference 7. [b] In DMSO-d_6.

is weaker in intensity. Similarly, compounds of general structure D (*e.g.*, **3** and **11**) have two C=O bands at 1765–1740 and 1730–1710 cm^{-1}.

As depicted in Scheme III, the formation of H (*e.g.*, **6**, **10**, **12**, **13**, and **16**), which poses an interesting mechanistic problem, can be rationalized as proceeding *via* the corresponding α-amino N-heterocyclic compound, F. As these reactions of **1** with **2** leading to H are carried out at elevated temperature, the intermediate formation of F from **1** by loss of methyl isocyanate is not unexpected in view of the fact that almost all monomethylureas show the tendency to give off methyl isocyanate at elevated temperature.[9] For example, when **1f** and **1g** were treated with acetyl chloride in refluxing xylene or at 80° in the presence or absence of triethylamine, the corresponding acetamides **21** and **22** were isolated in fair (50%) yield.



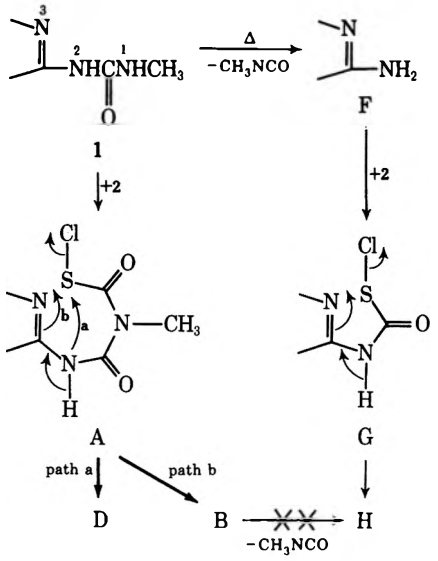
21, R = SCH_3
22, R = CF_3

The thermally unstable thiatriazepinedione B is not a precursor of H as evidenced by the failure to detect H (*e.g.*, **6**) in a refluxing solution of B (*e.g.*, **7**) in xylene. The formation of B and D is presumed to arise *via* the acylated urea A. Because N^1 (bearing a methyl group) is a better nucleophile than N^2 (exocyclic nitrogen) and

(9) S. Petersen, *Justus Liebigs Ann. Chem.*, **562**, 205 (1949).

N^3 (endocyclic nitrogen) for acylation,[10] the condensation should proceed through intermediate A to give B and D *via* the respective pathways a and b (Scheme III).

SCHEME III



Intermediate products arising from initial N-sulfenylation may be excluded from consideration on grounds previously discussed.[1]

In summary, the reactions of α-ureido N-heterocyclic compounds with chlorothioformyl chloride provide a convenient way to a variety of 2,3-fused 1,2,4,6-thiatriazepine-5,7-diones (B) 2,3-fused 1,2,4-thiadiazolin-5-ones (H), and 2,4-disubstituted 1,2,4-thiadiazolidine-3,5-diones (D).

Experimental Section

The usual general remarks[1] regarding apparatus are applicable.

Materials.—Procedures for the preparation of monomethylureas are well documented in the literature.[12] With the exception of **1d**, all other ureas were prepared from methyl isocyanate and the respective α-amino N-heterocyclic compound. Urea **1d** was obtained in 32% yield by chlorination with sulfuryl chloride of 1-methyl-3-(thiazol-2-yl)urea following a literature procedure.[13] Physical and analytical data of ureas prepared in context with the present work as precursor of novel heterocyclic compounds are listed in Table III.

5-Ethylthio-6-methyl-2*H*-thiazolo[3,2-*b*][1,2,4]thiadiazol-2-one (6) and 3,8-dimethyl-7-ethylthio-2*H*-thiazolo[3,2-*b*][1,2,4,6-]thiatriazepine-2,4(3*H*)-dione (7).—To a slurry of 19.9 g (86 mmol) of **1a** in 125 ml of xylene was added dropwise with stirring 12.5 g (95 mmol) of **2**, causing the temperature to rise from 20 to 25°. To this mixture was added dropwise a solution of 19.0 g (188 mmol) of triethylamine in 75 ml of xylene. After 24 hr, the reaction mixture was washed with water, dried ($MgSO_4$), and evaporated to dryness under reduced pressure. Separation by silica chromatography[14] of the residue gave 1.3 g (6.5%) of **6**: a light yellow crystalline solid; mp 78–81° (from hexane); ir (KBr) 1595 (C=), 1690 cm^{-1} (C=O); mass spectrum (70 eV) 232 (M^+). The second compound, 2.9 g (11.6%) of colorless solid, was identified as **7**: mp 57–58° (from hexane); ir (CH_2Cl_2) 1705, 1755 cm^{-1} (C=O).

In another experiment, a mixture of 15.5 g (67 mmol) of **1a** and 9.7 g (74 mmol) of **2** in 100 ml of xylnee was heated to reflux (4 hr). The reaction gave off hydrogen chloride and turned dark. The solvent was removed under reduced pressure and the residual black tar was purified by silica chromatography to give 1.0 g (6.5%) of **6**, identical with the product obtained above.

5-Chloro-2*H*-thiazolo[3,2-*b*][1,2,4]thiadiazol-2-one (10) and 2-(5-Chlorothiazol-2-yl)-4-methyl-1,2,4-thiadiazolidine-3,5-dione (11).—A suspension of 9.0 g (47 mmol) of **1d** in 100 ml of benzene and 6.9 g (52 mmol) of **2** was heated to reflux until hydrogen evolution ceased (18 hr). The solvent was removed and the residual solid was purified by silica chromatography to give 4.0 g (34%) of **10** [a colorless crystalline solid; mp 132–133° (from methanol); ir (CH_2Cl_2) 1720, 1690 cm^{-1} (C=O)] and 0.5 g (4.3%) of **11** [a tan crystalline solid; mp 139–141°; ir (CH_2Cl_2) 1740, 1710 cm^{-1} (C=O)].

2-Methylthio-6*H*-[1,3,4]thiadiazolo[3,2-*d*][1,2,4]thiadiazol-6-one (13).—A mixture of 8.0 g (39.2 mmol) of **1f**, 100 ml of toluene, and 5.8 g (44 mmol) of **2** was stirred and heated at reflux for 18 hr. The solvent was removed and the residual solid was recrystallized from methanol to give 5.0 g (63%) of **13**: a tan solid; mp 149–152°; ir (CH_2Cl_2) 1730, 1713, 1690 cm^{-1} (C=O). Oxidation with *m*-chloroperbenzoic acid in chloroform solution afforded a sulfone, mp 145–148°, identical (mixture melting point, ir, nmr) with the product obtained by reaction of **2** with 2-amino-5-methylthio-1,3,4-thiadiazole.[1]

1-Methyl-3-(5-methylthio-1,3,4-thiadiazol-2-yl)imidazolidinetrione (14).—A solution of 9.0 g (44.2 mmol) of **1f** and 6.2 g (48.6 mmol) of oxalyl chloride in 150 ml of toluene was refluxed for 18 hr. Recrystallization of the solid product from methanol gave 5.5 g (94%) of **14**: a cream-colored solid; mp 172–174°; ir (KBr) 1750 cm^{-1} (C=O); nmr (DMSO-d_6) δ 2.8 (s, 3, SCH_3), 3.1 ppm (s, 3, NCH_3).

Anal. Calcd for $C_7H_8N_4O_3S_2$: C, 32.6; H, 2.3; N, 21.7; S, 24.8. Found: C, 33.0; H, 2.4; N, 22.0; S, 24.9.

1-Methyl-3-(5-methylsulfonyl-1,3,4-thiadiazol-2-yl)imidazolidinetrione.—A solution of 4.5 g (22.4 mmol) of **14** and 9.1 g of 85% *m*-chloroperbenzoic acid (44.8 mmol) in 100 ml of chloroform was refluxed for 18 hr and, after filtration, washed with aqueous sodium carbonate and with water, dried ($MgSO_4$), and evaporated to dryness. Recrystallization from methanol afforded 5.0 g (77%) of a colorless crystalline solid: mp 247–250°; ir (KBr) 1740 (C=O), 1320 and 1160 (SO_2); nmr (DMSO-d_6) δ 3.15 (s, 3, NCH_3), 3.7 ppm (s, 3, SO_2CH_3).

Anal. Calcd for $C_7H_8N_4O_5S_2$: C, 29.0; H, 2.1; N, 19.3. Found: C, 29.2; H, 2.3; N, 19.2.

3-Methyl-1-(5-trifluoromethyl-1,3,4-thiadiazol-2-yl)imidazolidinetrione (15).—To a solution of 10.0 g (44.2 mmol) of 1g in 100 ml of toluene was added with stirring 6.2 g (48.6 mmol) of oxalyl

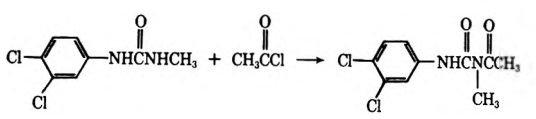
TABLE III

α-UREIDO N-HETEROCYCLIC COMPOUNDS, $RNHC(=O)NHCH_3$[a]

Compd	Yield, %	Mp, °C	Formula
1a	61	178–180, 188–190	$C_6H_{13}N_3OS_2$
1b	70	182–184	$C_7H_{11}N_3OS$
1c	58	183–185	$C_{10}H_{17}N_3OS$
1d	32	242	$C_5H_6ClN_3OS$
1e	85	232	$C_4H_6N_4OS$
1f	52	205–210	$C_5H_8N_4OS_2$
1g	92	192–194	$C_5H_5F_3N_4OS$
1h	82	257–259	$C_6H_7ClN_4O$

[a] Satisfactory analytical data (±0.3% for C and H) were reported for **1a**, **1b**, **1c**, **1g**, and **1h**; N analyses were reported for all except **1h**; S analyses were reported for **1e**, **1f**, and **1g**; Cl analyses were reported for **1d** and **1h**.

(10) For example, acetylation of 1-methyl-3-(3,4-dichlorophenyl)urea led to 1-acetyl-1-methyl-3-(3,4-dichlorophenyl)urea (**23**) as the only isolable reaction product. An authentic specimen of **23**[11] proved to be identical (melting point, mixture melting point, tlc, glc, and nmr and ir spectrum) with the above product.



23

(11) H. J. Gerjovich and R. S. Johnson, U. S. Patent 2,762,696 (1957) [*Chem. Abstr.*, **51**, 3911 (1957)].

(12) S. Petersen, "Die Methoden der organischen Chemie" (Houben-Weyl), Vol. 8, E. Müller, Ed., Georg Thieme Verlag, Stuttgart, Germany, 1952, p 157.

(13) E. Pedley, *J. Chem. Soc.*, 431 (1947).

(14) Solvent mixture (by volume): Tetrahydrofuran (2) and hexane (48).

chloride. This solution was haeted to reflux for 18 hr. Hydrogen chloride evolved during the first 3 hr. The reaction mixture was filtered while hot and cooled to give 9.0 g (98%) of **15**: an off-white solid; mp 258–261°; ir (KBr) 1790, 1760, and 1730 (C=O), 1340, 1160, and 1145 cm^{-1} (CF_3); nmr (DMSO-d_6) δ 3.2 ppm (s, NCH_3).

Anal. Calcd for $C_7H_3F_3N_4O_3S$: C, 30.0; H, 1.1; N, 20.0; S, 11.4. Found: C, 30.3; H, 1.0; N, 20.1; S, 11.1.

6-Chloro-2*H*-[1,2,4]thiadiazolo[2,3-*b*]pyridazin-2-one (16).—A mixture of 15.0 g (0.805 mol) of **1h** and 11.0 g (0.805 mol) of **2** in 100 ml of xylene was heated to reflux (18 hr), evaporated, and recrystallized from methanol (charcoal) to give 9.0 g (60%) of **16**, a light yellow crystalline solid, mp 162–165°, identical (mixture melting point, ir, nmr) with a product obtained by reaction of **2** with 3-amino-6-chloropyridazine.[1]

1,3-Bis(5-isobutyl-4-methylthiazol-2-yl)urea (20).—A slow stream of air was passed at 60° over a 1.0-g (3.5 mmol) sample of **9**. After 72 hr, the product was washed with acetone and then with ether to give 0.3 g (50%) of **20**: a tan solid; mp 180–215° dec; ir (KBr) 3400, 2400 (NH), 1700, 1625 (C=), 1540 cm^{-1} (amide II); mass spectrum (70 eV), 366 (M^+), 323, 197, 196, 171, 170, 153, 127, 100, 85, 76, 73, 69, 64, 59, 57, 44–41.

Anal. Calcd for $C_{17}H_{26}N_4OS_2$: C, 55.6; H, 7.1; N, 15.3. Found: C, 55.8; H, 7.1; N, 15.3.

***N*-(5-Methylthio-1,3,4-thiadiazol-2yl)acetamide (21). A. By Reaction of 1f with Acetyl Chloride.**—A mixture of 20.4 g (0.1 mol) of **1f**, 12.0 g (0.15 mol) of acetyl chloride, and 150 ml of xylene was refluxed with stirring for 24 hr. The product obtained after cooling and filtration was recrystallized from aqueous methanol to give 9.0 g (48%) of **21**: a tan solid; mp 209–212°; ir (KBr) 3160 (NH), 1709 (C=O), 1560 cm^{-1} (amide II); nmr (DMSO-d_6) δ 2.2 (s, 3, CH_3CO), 2.7 (s, 3, CH_3S), 12.45 ppm (s, 1, NH); mass spectrum (70 eV) 189 (M^+), 174 ($M - CH_3$), 147, 111, 97, 95, 85, 83, 71, 69, 57, 43, 27, 18.

Anal. Calcd for $C_5H_7N_3S_2O$: C, 31.8; H, 3.7; N, 22.2. Found: C, 31.8; H, 3.6; N, 22.4.

B. By Reaction of 1f with Acetyl Chloride in the Presence of Triethylamine.—To a solution of 20.4 g (0.1 mol) of **1f** and 10.1 g (0.1 mol) of triethylamine in 150 ml of *p*-dioxane was added with stirring 8.6 g (0.11 mol) of acetyl chloride. After 18 hr at ambient temperature, only starting material (**1f**) could be detected by tlc. The mixture was heated at 80° for 1.5 hr, evaporated to dryness, washed with water, and recrystallized from aqueous methanol (1:1) to give 8.5 g (46.3%) of **21**, mp 209–212°; a mixture melting point with the product obtained by method A was undepressed.

C. By Reaction of 2-Amino-5-methylthio-1,3,4-thiadiazole with Acetic Anhydride.—A solution of 2.7 g (18.5 mmol) of 2-amino-5-(methylthio)-1,3,4-thiadiazole[15] in 50 ml of acetic anhydride was heated to reflux for 2.5 hr, poured into 300 ml of water, and stirred for 3 hr. The solid was filtered, washed with water, and dried to give 3.0 g (86%) of **21**, a tan solid, mp 209–212°; a mixture melting point with the product obtained by method A was undepressed.

***N*-(5-Trifluoromethyl-1,2,4-thiadiazol-2-yl)acetamide (22).**—A solution of 5.05 g (22.1 mmol) of **1g** and 3.0 g (38.5 mmol) of acetyl chloride in 75 ml of xylene was refluxed for 2 hr. Cooling to 10° gave 2.5 g (58%) of **22**: a light tan crystalline solid; mp 235°; nmr (DMSO-d_6) δ 2.25 (s, 3, CH_3), 13.25 ppm (s, 1, NH).

Anal. Calcd for $C_5H_4F_3N_3SO$: C, 28.5; H, 1.9; N, 19.9. Found: C, 28.6; H, 2.0; N, 20.2.

1-Acetyl-3-(3,4-dichlorophenyl)-1-methylurea (23).—A mixture of 3-(3,4-dichlorophenyl)-1-methylurea (5.5 g, 25 mmol), triethylamine (2.5 g, 25 mmol), and acetyl chloride (2.0 g, 25 mmol) in 75 ml of xylene was heated in a sealed glass cylinder on a steam bath for 18 hr. The reaction mixture was evaporated and the residue was washed with water and recrystallized from benzene to give 1.5 g (23%) of colorless crystalline solid: mp 144–146°; nmr ($CDCl_3$) δ 2.35 (s, 3, CH_3CO), 3.55 (s, 3, CH_3N), 7.4–7.7 (m, 3, C_6H_3), 11.6 ppm (s, 1, NH); ir (KBr) 1715 (C=O), 1550 cm^{-1} (amide II); mixture melting point was authentic[11] **23** undepressed.

Anal. Calcd for $C_{10}H_{10}N_2O_2Cl_2$: C, 46.0; H, 3.8; N, 10.7; Cl, 27.2. Found: C, 46.1; H, 4.0; N, 10.4; Cl, 27.2.

Registry No.—**1a**, 34006-36-5; **1b**, 14934-65-7; **1c**, 38401-12-6; **1d**, 14953-32-6; **1e**, 26676-41-5; **1f**, 25958-19-4; **1g**, 25366-20-5; **1h**, 38401-17-1; **2**, 2757-23-5; **3**, 28924-68-7; **6**, 38401-20-6; **7**, 38401-21-7; **8**, 38401-22-8; **9**, 38401-23-9; **10**, 38401-24-0; **11**, 38401-25-1; **12**, 38401-26-2; **13**, 38400-58-7; **14**, 28924-66-5; **15**, 28924-65-4; **16**, 38400-66-7; **20**, 38401-31-9; **21**, 38583-51-6; **22**, 10444-99-2; **23**, 38401-33-1; oxalyl chloride, 79-37-8; 1-methyl-3-(5-methylsulfonyl-1,3,4-thiadiazol-2-yl)imidazolidinetrione, 28924-64-3; *m*-chloroperoxybenzoic acid, 937-14-4; acetyl chloride, 75-36-5; 2-amino-5-methylthio-1,3,4-thiadiazole, 5319-77-7; acetic anhydride, 108-24-7; 3-(3,4-dichlorophenyl)-1-methylurea, 3567-62-2.

Acknowledgment.—We thank Drs. B. C. Baker, W. J. McKinney, and G. E. Pollard for microanalyses and spectral measurements and Dr. S. B. Soloway for valuable suggestions.

(15) M. Busch and H. Biehler, *J. Prakt. Chem.*, [2] **93**, 339 (1916).

Reactions of Phosphorus Compounds. 33. Preparation of Heterocyclic Species from α-Substituted Vinyl Phosphonium Salts. Anomalous Products from Isopropenylphosphonium Halides[1]

EDWARD E. SCHWEIZER,* ANTHONY T. WEHMAN, AND DEBORAH MEEDER NYCZ

Department of Chemistry, University of Delaware, Newark, Delaware 19711

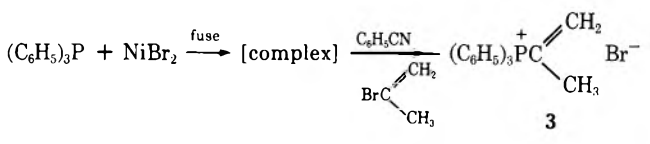
Received November 3, 1972

The synthetic utility of isopropenylmethyldiphenylphosphonium iodide (**2**), isopropenyltriphenylphosphonium bromide (**3**), and 1-phenylvinyltriphenylphosphonium bromide (**4**) is compared with that of the unsubstituted vinyltriphenylphosphonium salt, **1**, with respect to the preparation of heterocyclic and chain-extended species. An inner phosphonium zwitterion (**10**) can also be isolated from **2**. Under fusion conditions, 2-methyl-2*H*-1-benzopyran (**13**) is also formed from salts **2** and **3** with no inner zwitterion isolated in either case. A mechanism is proposed for the latter reaction.

Vinyltriphenylphosphonium bromide (**1**) has been shown to be a versatile reagent for the preparation of cyclic and chain-extended products.[2] This reaction has been postulated as one involving an initial conjugate addition followed by a Wittig reaction.[3] To date only one series of reactions, involving this Michael–Wittig sequence, has been reported using substituted vinyltriphenylphosphonium salts.[4]

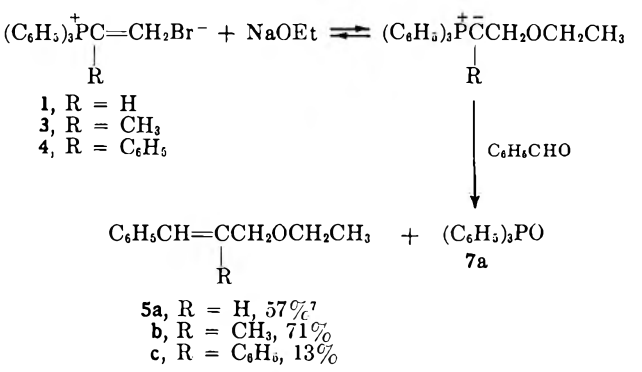
In order to expand the scope of this synthetic technique, we have prepared[5] a number of substituted vinylphosphonium salts and have investigated their reactivity *vis-a-vis* the unsubstituted vinyl salt **1** in the Michael–Wittig reaction sequence. Thus, isopropenylmethyldiphenylphosphonium iodide (**2**), isopropenyltriphenylphosphonium bromide (**3**), and 1-phenylvinyltriphenylphosphonium bromide (**4**) were subjected to a representative sampling of the previously demonstrated reactions of **1**, in order to compare the reactivity and synthetic utility of these new salts with the parent compound. Anomalous reactions are reported for salts **2** and **3**, and mechanisms are proposed.

It should be noted that, contrary to our previous report,[5] salt **3** may in fact be prepared readily utilizing a modification of the Horner[6] procedure. Fusion of triphenylphosphine with nickel bromide (anhydrous), followed by addition of dry benzonitrile solvent, 2-bromopropene, and heating of the resultant mixture, furnishes salt **3** in 50–60% yield.

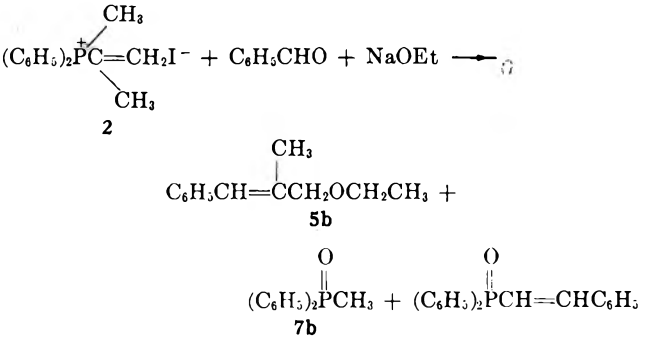


Vinylphosphonium salts **1**, **3**, and **4**, when treated with sodium ethoxide and benzaldehyde, produced the corresponding chain-extended cinnamyl ethyl ether and triphenylphosphine oxide (**7a**).

Salt **2**, when treated similarly, produced the expected 1-phenyl-2-methyl-4-oxa-1-hexene (**5b**) in 38% yield, as well as methyldiphenylphosphine oxide (**7b**)



(28%) and 2-phenylvinyldiphenylphosphine oxide (13%).



Salts **1–3** gave the expected products of Michael–Wittig cyclization reactions[8–10] when treated with bases containing a carbonyl moiety. The reactions are illustrated in eq 1–3.

In this reaction there are three expected steps: Michael addition, betaine formation, and betaine decomposition. Assuming that the betaine decomposition is the rate-determining step[11] for the reactions of salts **1**, **2**, and **3**, then one would expect the formation of olefinic species to be less favorable with salts containing a phosphonium moiety which is less electrophilic. Thus, the reactions of salt **2** were expected to be less favorable than the reactions of salt **1** and **3**, as found.

The high reactivity of the unsubstituted salt **1** in comparison to **2** and **3** may be due to the steric in-

(1) E. E. Schweizer, C. S. Kim, C. S. Labaw, and W. P. Murray, *Chem. Commun.*, 7 (1973), paper number 32 in this series.

(2) E. E. Schweizer and C. M. Kopay, *J. Org. Chem.*, **37**, 1561 (1972), and references cited therein.

(3) E. E. Schweizer, *J. Amer. Chem. Soc.*, **86**, 2744 (1964).

(4) E. E. Schweizer and W. S. Creasy, *J. Org. Chem.*, **36**, 2244 (1971).

(5) E. E. Schweizer and A. T. Wehman, *J. Chem. Soc. C*, 343 (1971).

(6) L. Horner, G. Mummenthey, H. Moser, and P. Beck, *Chem. Ber.*, **99**, 2782 (1966).

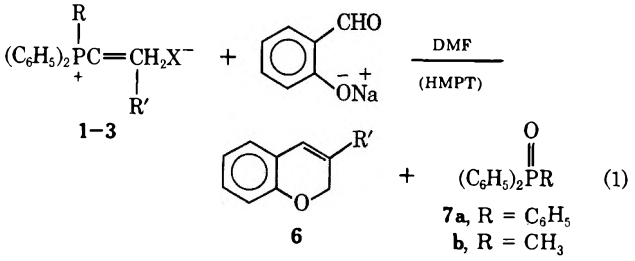
(7) E. E. Schweizer, L. D. Smucker, and R. J. Votral, *J. Org. Chem.*, **31**, 467 (1966).

(8) E. E. Schweizer and J. G. Liehr, *J. Org. Chem.*, **33**, 583 (1968).

(9) (a) E. E. Schweizer and K. K. Light, *J. Amer. Chem. Soc.*, **86**, 2963 (1964); (b) E. E. Schweizer and K. K. Light, *J. Org. Chem.*, **31**, 870 (1966).

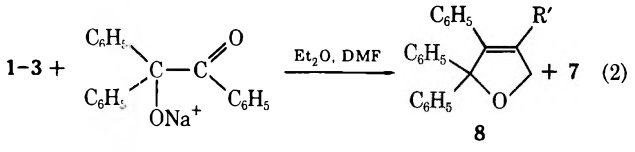
(10) E. E. Schweizer and J. G. Thompson, procedure submitted to *Org. Syn.*

(11) G. Wittig and U. Schoellkopf, *Chem. Ber.*, **87**, 1318 (1954).



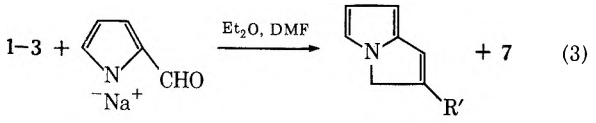
1-3 + 6 → 7a, R = C_6H_5; b, R = CH_3 (1)

From 1,6 (R′ = H); 54-58%[10]
From 2,6 (R′ = CH_3); 30%
From 3,6 (R′ = CH_3); 35%



1-3 + → 8 + 7 (2)

From 1,8 (R′ = H); 71%[8]
From 2,8 (R′ = CH_3); 36%
From 3,8 (R′ = CH_3); 47%



1-3 + → 9 + 7 (3)

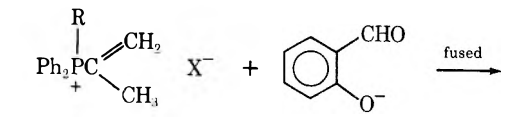
From 1,9 (R′ = H); 87%[9]
From 2,9 (R′ = CH_3); 25%
From 3,9 (R′ = CH_3); 67%

hibition, which would be expected[12] to slow down the initial conjugate addition step of the reaction.

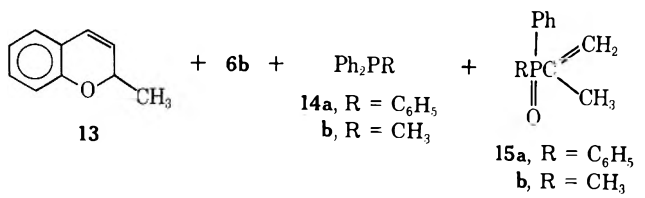
The first anomalous product was observed on allowing the phosphonium iodide (2) to react in solution; apart from the expected products it also yielded the isolable inner phosphonium zwitterion whose formation may be rationalized as shown in Scheme I.

The salicyloxide undergoes conjugate addition to the vinyl salt 2; proton transfer leads to the methylene ylide **11b**, which attacks the aldehyde group to give the betaine **12**. Protonation of the betaine oxygen with β elimination of the phenoxide and dehydration would give the zwitterion **10**.

Reactions of salts 2 and 3 under fusion conditions yielded the isomeric 2-methyl-2*H*-1-benzopyran (**13**) as the major product with only a small amount of the expected 3-methyl isomer, **6** (R′ = CH_3). The tertiary phosphine **14** and the phosphine oxide **15** were also formed.



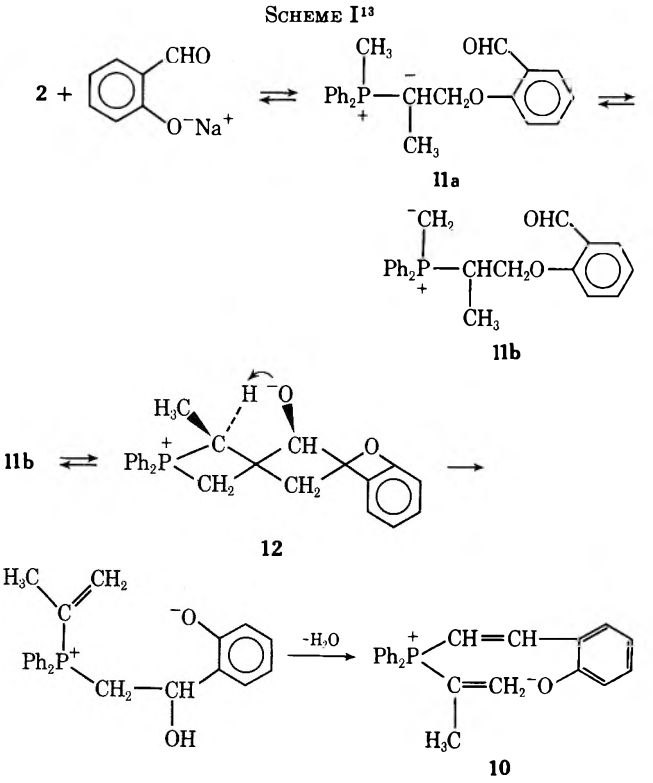
2, R = CH_3; X = I
3, R = C_6H_5; X = Br



13 + **6b** + Ph_2PR (**14a**, R = C_6H_5; **b**, R = CH_3) + **15a**, R = C_6H_5; **b**, R = CH_3

(12) E. D. Bergmann, D. Ginsburg, and R. Rappo in "Organic Reactions," Vol. 10, Wiley, New York, N. Y., 1959, pp 182–187.

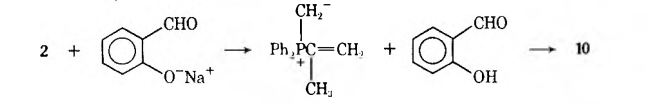
SCHEME I[13]



Attempts to isomerize **6** (R′ = CH_3) to **13** either thermally or by basic catalysis only resulted in the isolation of the starting material. Therefore, one is led to the proposition that rearrangement of the original phosphonium compound prior to the Wittig reaction must be the pathway to the isomeric product (Scheme II).

Under fusion conditions, the sodium salicyloxide, acting as a base, removes a proton from the isopropenyl group to produce the resonance-stabilized carbanion **16**, whose formation is demonstrated in an isolated experiment by the formation of equal amounts of deuterated sites at both the methyl and methylene groups. Reaction by path A would lead to the formation of allene (not isolated) and the isolated tertiary phosphine (**14a,b**) *via* an elimination reaction. Reaction by path B, involving an internal nucleophilic displacement on phosphorus, would result in the formation of a vinyl carbanion, which could give either the allylphosphorane **17** by proton transfer or allene and the tertiary phosphine **14a,b**. This allylic phosphorane is known[14] to react with sodium salicyloxide to produce 2-methyl-2*H*-1-benzopyran (**13**). Another possibility, the formation of a cyclopropylphosphorane, has been ruled out because it is known that this phosphorane reacts with sodium salicyloxide to produce 2,3-dihydro-1-benzoxepin[15] as well as the 2-methyl-2*H*-1-

(13) Both referees suggest the simpler pathway

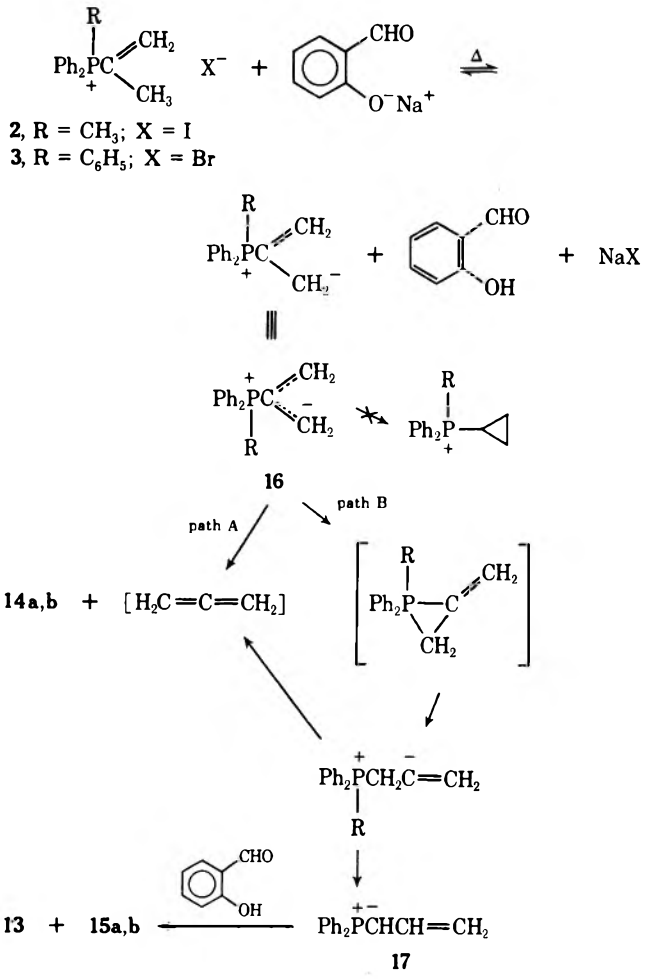


However, numerous attempts by Nycz to obtain a reaction between the sodium salicyloxide and ethyltriphenylphosphonium salts were shown to be unsuccessful (Nycz, unpublished results).

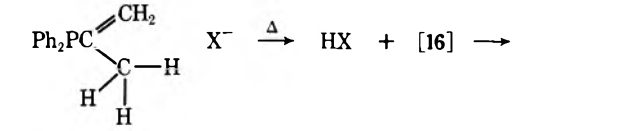
(14) E. E. Schweizer, E. T. Shaffer, C. T. Hughes, and C. J. Berninger, *J. Org. Chem.*, **31**, 2907 (1966).

(15) E. E. Schweizer, C. J. Berninger, and J. G. Thompson, *J. Org. Chem.*, **33**, 336 (1968).

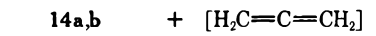
SCHEME II



benzopyran, and no benzoxepin has been observed in the reactions reported here. Furthermore, it was found that both of the isopropenylphosphonium halides, **2** and **3**, produced tertiary phosphines (**14a,b**) when



2, R = CH_3; X = I
3, R = C_6H_5; X = Br

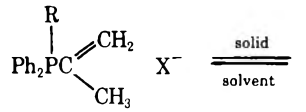


14a, R = C_6H_5
b, R = CH_3

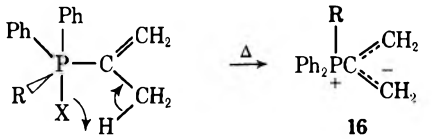
heated alone at 225° under vacuum. In this latter case, it is assumed that the halide ion must be acting as the base.

Since the 2-methyl isomer **13** was never isolated nor detected (nmr or vpc) in the reactions run in solution (DMF or HMPT over an 80–200° temperature range), one is led to the suggestion that the SNi rearrangement may be emanating from the pentavalent form of **2** (or **3**), **18a,b**, which would not be present in the highly polar solvents used otherwise.

1-Phenylvinyltriphenylphosphonium bromide (**4**), whose preparation has already been described,[5] was also subjected to ring synthesis reaction conditions with extremely limited success. The reaction of salt **4** with sodium salicyloxide in DMF solvent produced no

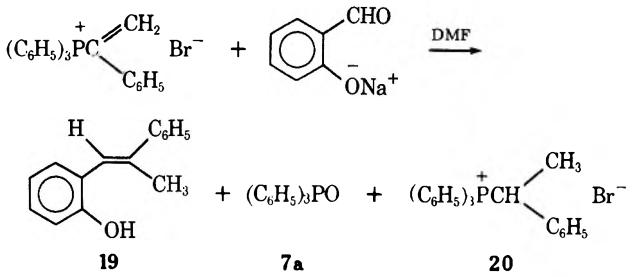


2, R = CH_3; X = I
R = C_6H_5; X = Br

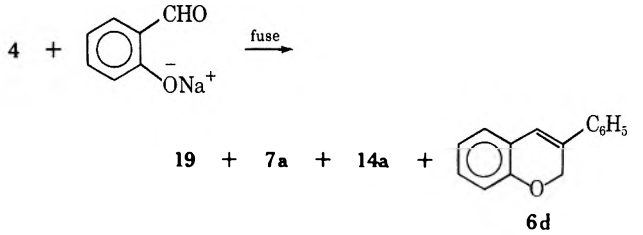


18a, R = C_6H_5; X = Br
b, R = CH_3; X = I

3-phenyl-2*H*-1-benzopyran. Instead, an open-chain compound (**19**) was formed in 40% yield, along with triphenylphosphine oxide (**7a**, R = C_6H_5, 50%), and the reduced 1-phenylethyltriphenylphosphonium bromide[5] (**20**) in 10% yield.



3-Phenyl-2*H*-1-benzopyran (**6d**, R′ = C_6H_5) could be produced in 8% yield only under fusion conditions; 21% **19**, 28% **7a**, and 23% triphenylphosphine (**14a**) were also formed.



Compound **19** is presumably formed *via* the reduced salt **20**, since it too leads to **19** (57% yield) when treated with sodium salicyloxide. Reactions involving **4** have invariably resulted in the isolation of salt **20**.[5]

The reason for the low yields of expected products from the reactions of **4** is unclear, but might be due to a combination of increased bulk at the carbon α to phorphorus as well as to the intermediacy of a semistabilized ylide formed by the initial Michael addition. The effect of the formation of the semistabilized ylide would be to decrease the rate of betaine formation, thus allowing side reactions to occur (*e.g.*, reduction).[5] The effect of bulk at the α carbon might be demonstrated by the reaction of **4** with the sodium salt of pyrrolaldehyde, wherein no **9** (R = C_6H_5) is formed,

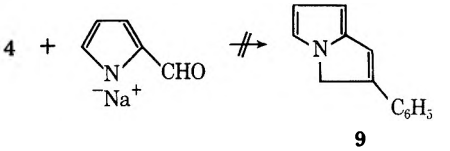


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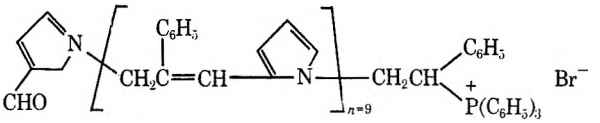
TABLE I

PREPARATION OF CINNAMYL ETHYL ETHERS 5

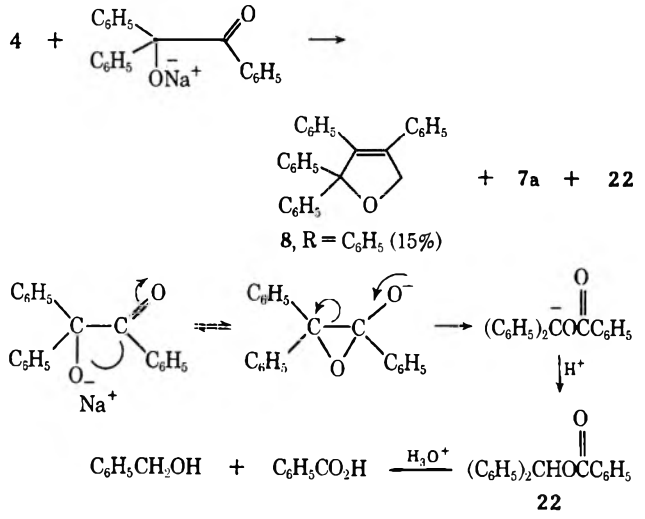
Salt (mol)	NaOEt, mol	C_6H_5CHO, mol	Yield, % 7	Yield, % 5	Isolation method	5 Analysis Calcd	5 Analysis Found
1 (0.08)	0.08	0.08		57	a	ref 6	
3 (0.03)	0.03	0.03	73	71	a	C 81.75	C 81.41
						H 9.15	H 9.14 (vpc)
4 (0.03)	0.03	0.03	48	12.5	b	C 85.72	C 85.40
						H 7.62	H 7.36 (vpc)



21

and thus an intermolecular reaction resulting in polymer 21 is more facile than ring formation.

When the anion of phenylbenzoin is employed, the excessive bulk both at the α carbon of the ylide and at the carbonyl does not permit reaction to any great extent, but the entropically more favored ring formation proceeds to a small degree. There is also produced a 48% yield of benzhydrylbenzoate (22), which can be rationalized by a rearrangement of the sodium salt of phenylbenzoin, facilitated by the lower reactivity of the phosphonium salt 4. Support for this rearrangement lies in the fact that when the sodium salt of phenylbenzoin is treated under the reaction conditions in the absence of 4, rearrangement proceeds to the extent of 80%. The utility of the Michael–Wittig reaction sequence is thus expanded through the use of substituted vinylphosphonium salts.



8, R = C_6H_5 (15%)

Experimental Section

General.—Infrared (ir) spectra were obtained on a Perkin-Elmer 137, ultraviolet (uv) spectra on a Perkin-Elmer 237 spectrophotometer, nuclear magnetic resonance (nmr) on a Varian A-60A or a Perkin-Elmer R-12b using tetramethylsilane as internal standard, and mass spectra on a CEC 21-110B double focusing spectrometer utilizing an ionizing potential of 70 eV.

Vapor phase chromatography (vpc) was accomplished on a Wilkens Aerograph A-90 P instrument employing a column of 10% UC-W98 on Chromosorb W (60–80 mesh, 10 ft × 0.25 in.), and thin layer chromatography (tlc) was accomplished by the ascending technique utilizing 2 × 8 in. plates coated with silica gel G of 0.25-mm thickness.

Melting points are corrected and were taken on a Fisher-Johns melting point apparatus. Analyses were performed by MHW Laboratories, Garden City, Mich., or Microanalysis, Inc., Wilmington, Del.

All reactions were run under an atmosphere of dry nitrogen. When products of known identity were obtained, their presence was proven by the use of two or more of the following methods: ir and nmr spectra, vpc retention time and coinjection with authentic material, and melting point and mixture melting point with an authentic sample. Purity of the compounds was determined by tlc, vpc, melting point, and nmr spectra.

Preparation of Isopropenyltriphenylphosphonium Bromide (3).—A mixture of 69 g (0.262 mol) of triphenylphosphine and 57.2 g (0.262 mol) of anhydrous nickel bromide was heated in a flask until fusion was complete and the deep green color was uniform. Benzonitrile (150 ml) was added and the solution was heated while water was removed with a Dean-Stark trap until the temperature had reached 200°. After cooling to *ca.* 50°, 36 g (0.30 mol) of 2-bromopropene was added dropwise. The reaction mixture was stirred at 50–80° overnight and then heated slowly, over a period of 2 days, until the temperature reached 200° once more. The flask and contents were cooled and steam distilled, and the distillate was discarded (benzonitrile–water). The residue was cooled and filtered to remove a black, insoluble material and the filtrate was extracted with CH_2Cl_2. The organic extract was dried over $MgSO_4$ and concentrated while EtOAc was added to precipitate a gummy solid which was recrystallized from CH_2Cl_2–EtOAc to furnish 55 g (55%) of **3**, mp 197–197.5° (lit.[16] mp 196.5–197.5°), ir and nmr in agreement with those reported.

Reaction of Vinylphosphonium Salts with Sodium Ethoxide and Benzaldehyde. Chain Extension Reaction.—Reaction was run as previously described.[7] Data are found in Table I.

1-Phenyl-2-methyl-4-oxa-1-hexene (5b) (*Z* isomer) had ir (neat) ν 2940, 2830 (CH), 1480, 1440 (CC), 1090 (COC), 745, 690 cm^{-1} (aromatic); nmr ($DCDl_3$) δ 1.23 (t, 3, J = 7 Hz, CH_3-CH_2), 1.88 (d, 3, J = 1.4 Hz, CH_3), 3.50 (q, 2, J = 7 Hz, CH_2CH_3), 3.99 (d, 2, J = 1.0 Hz, CH_2), 6.51 (qt, 1, J = 1.4 Hz, 1.0, vinyl), 7.28 (s, 5, C_6H_5).

The *E* isomer had ir (neat) ν 2950, 2840 (CH), 1485, 1435 (CC), 1110 (COC), 740, 700 cm^{-1} (aromatic); nmr ($CDCl_3$) δ 1.20 (t, 3, J = 7 Hz, CH_2CH_3), 1.98 (d, 3, J = 1.4 Hz, CH_3), 3.45 (q, 2, CH_2CH_3), 4.10 (d, 2, J = 0.8 Hz, CH_2), 6.51 (qt, 1, J = 1.4 Hz, 0.8, vinyl), 7.28 (s, 5, C_6H_5).

1,2-Diphenyl-4-oxa-1-hexene (5c) had ir (neat) ν 3010, 2940, 2820 (CH), 1600 (C=C), 1490, 1440 (CC), 1090 (COC), 760, 690 cm^{-1} (aromatic); nmr ($CDCl_3$) δ 1.22 (t, 3, J = 7 Hz, CH_2CH_3), 3.48 (q, 2, J = 7 Hz, CH_2CH_3), 4.62 (s, 2, CH_2), 7.11 (s, 1, vinyl), 7.1–7.6 (m, 10, C_6H_5).

Preparation of 2*H*-1-Benzopyrans (6) (Eq 1).—A mixture of 1 equiv of vinylphosphonium salt and 2 equiv of sodium salicyloxide[10] was weighed into a dry flask. Dry DMF was added, and the mixture was stirred and heated at reflux for 2 days. The reaction mixture was poured into water and extracted with ether and CH_2Cl_2. Both organic extracts were washed with dilute NaOH solution and water and then dried over $MgSO_4$. From the ether extract was obtained the 2*H*-1-benzopyran, phosphines, and phosphine oxides (Table II). The CH_2Cl_2 extracts provided phosphonium salts.

3-Methyl-2*H*-1-benzopyran had bp 64–65° (0.2 mm); ir (neat) ν 3020, 2950, 2900, 2810 (CH), 1570 (C=C), 1470, 1420 (CC), 1105 (COC), 835, 755 cm^{-1} (aromatic); nmr (CCl_4) δ 1.70 (dt, 3, J = 1.3, 1.3 Hz, CH_3), 4.57 (dq, 2, J = 1.2, 1.3 Hz, CH_2), 6.0 (qt, 1, J = 1.3, 1.2 Hz, vinyl), 6.5, 7.0 (m, 4, C_6H_4).

Reaction of Isopropenylphosphonium Salts with Sodium Salicyloxide. A. In DMF.—The reaction was run as previously described. When salt **2** was used, the phosphonium zwitterion **10** was isolated from the CH_2Cl_2 extraction by concentrating the

(16) D. Seyferth and J. Vogel, *J. Organometal. Chem.*, **6**, 205 (1966).

TABLE II

PREPARATION OF 2H-1-BENZOPYRANS (6) (EQ 1)

Salt (mol)	Sodium salicyloxide, mol	DMF, ml	Yield, % 6	Yield, % 7	6 Analysis Calcd	6 Analysis Found
1 (0.1)	0.2	125	54–58	55–72	ref 10	
2 (0.05)	0.10	150	30	29.5	C 82.71	C 82.52
					H 6.93	H 6.77 (vpc)
3 (0.025)	0.05	75	35	40		

solvent, leaving a viscous oil. This oil was then slowly poured into 500 ml of anhydrous ether and the solid was filtered off, giving a 10% yield of 10: mp 247–248°; ir (Nujol) 1570 (C=C), 1100 (*P*-phenyl), 1005 cm^{-1} (P salt); mass spectrum *m/e* 344, 303, 267, 226, 108, 77; nmr ($CDCl_3$) δ 2.17 (split d, 3, J = 13.5 Hz, CH_3), 5.91 (split d, 1, J = 22 Hz, isopropenyl vinyl cis to P), 6.74 (split d, 1, J = 46 Hz, isopropenyl (vinyl trans to P), 6.6–8.0 ppm (m, 16, vinyl and C_6H_5); uv max ($CHCl_3$) 246 nm (ϵ 70,801), 289 (17,000), 254 (8200). The zwitterion was then treated with HBr and formed the phosphonium bromide, mp 192–194°.

Anal. Calcd for $C_{23}H_{22}BrOP$: C, 64.92; H, 5.21. Found: C, 65.34; H, 5.26.

B. In HMPT.—The same procedure as A was followed. The only differences observed were in the yield of the 3-methyl-2*H*-1-benzopyran when the temperature was varied, and in the rate of development of the characteristic color change of the reaction mixture when the phosphorus ylide forms at the start of the reaction.[15] This color change occurs only after 30–40 min in DMF, but occurs after only 5 min in HMPT.

The yields of the 3 isomer were as follows: 80°, 14%; 160°, 30%; 200°, 0%.[17]

C. Fusion Method.—An intimate mixture of 1 equiv of either salt **2** or **3** and 2 equiv of sodium salicyloxide was placed in a dry flask equipped with a short path distilling head leading to a Dry Ice cooled receiver. Vacuum was applied to the system; the mixture was heated until fusion took place and distillation had ceased.

From salt **2**, fusion produced **6** (R′ = CH_3) (4%), **13** (11%), and diphenylmethylphosphine (12%).

From salt **3**, fusion resulted in the formation of **6** (R′ = CH_3) (9%), **13** (14%), and triphenylphosphine (15%).

Attempted Isomerization of 6 (R′ = CH_3) to 13.—A sample of redistilled **6** (R′ = CH_3), approximately 1.0 g, was heated in a flame-dried flask containing a small amount of sodium salicyloxide. The mixture was heated at 210° for 3 hr under nitrogen. A nmr spectrum of the mixture showed the presence of a small amount of some decomposition products, but no **13**. Further heating, followed by distillation, again showed no rearranged product by nmr or vpc.

Deuterium Exchange Studies.—Pure samples of both phosphonium halides **2** and **3** were placed into nmr tubes and dissolved in DMSO-d_6. An nmr spectrum was then taken of each (T' = 0) and ten integrations were run with the help of a Hewlett-Packard DC digital voltmeter, Model 405Br. A catalytic amount of potassium *tert*-butoxide was then added to each and another spectrum with ten integrations was run (T = 0). The nmr tubes were then placed in a sand bath at 160°. At various times, the nmr tubes were removed from the bath and additional spectra were run. With both salts, the phenyl protons were used as an internal standard for the integration. After 25 hr salt **3** showed a reduction of the methylene and methyl proton of 25 and 23%, respectively. Similarly the salt **2** showed a reduction of these protons of 20 and 17%, respectively.

Preparation of 2,5-Dihydrofurans (8) (Eq 2).—The procedure employed was essentially that of Schweizer and Liehr.[8] Pertinent data are reported in Table III.

2,2,3-Triphenyl-4-methyl-2,5-dihydrofuran had mp 149–150° (MeOH); ir (Nujol) 1605 (C=C), 1055 (COC), 760, 700 cm^{-1} (aromatic); nmr ($CDCl_3$) δ 1.78 (t, 3, J = 1.1 Hz, CH_3), 4.87 (q, 2, J = 1.1 Hz, CH_2), 6.7–7.4 (m, 15, C_6H_5); uv $\lambda_{max}^{CHCl_3}$ 263 mμ (ϵ 6820).

Preparation of 3*H*-Pyrrolizines (9) (eq 3).—Following the procedure of Schweizer and Light,[9] 3*H*-pyrrolizines **9** were prepared as indicated in Table IV.

(17) At this temperature, the HMPT decomposed and left an unseparable tar.

TABLE III

PREPARATION OF 2,5-DIHYDROFURANS (8) (EQ 2)

Salt (mol)	Yield, % 8	Yield, % 7	8 Analysis Calcd	8 Analysis Found
1 (0.04)	71		ref 8	
2 (0.03)	36	39	C 88.39	C 88.36
			H 6.45	H 6.56
3 (0.03)	47	52		

TABLE IV

PREPARATION OF 3H-PYRROLIZINES 9 (EQ 3)

Salt (mol)	Sodium pyrrolaldehyde, mol	Yield, % 9	Yield, % 7	9 Analysis Calcd	9 Analysis Found
1 (0.215)	0.183	87		ref 9	
2 (0.075)	0.075	25	27	C 80.61	C 80.90
				H 7.61	H 7.64 (vpc)
3 (0.075)	0.075	67	69		

3-Methyl-3*H*-pyrrolizine[18] had bp 66–67° (0.3 mm); mp 29–30°; ir (neat) 3020, 2860, 2810 (CH), 1605 (C=C), 940, 700 cm^{-1} (pyrrole ring); nmr (CCl_4) δ 1.95 (d, 3, J = 1.0 Hz, CH_3), 4.18 (d, 2, J = 0.8 Hz, CH_2), 5.50 (d, 1, J = 3.0 Hz, 6-H), 5.92 (t, 1, J = 3.0 Hz, 5-H), 6.0 (d, 1, J = 3.0 Hz, 4-H), 6.40 (dd, J = 1.0, 0.8 Hz, 1-H); uv λ_{max}^{EtOH} 219 mμ (ϵ 3660), 295 (7250).

Reaction of 1-Phenylvinyltriphenylphosphonium Bromide (4) with Sodium Salicyloxide. A. In DMF Solvent.—Into a dry flask equipped with mechanical stirrer and reflux condenser was placed 13.4 g (0.03 mol) of salt **4**, 8.65 g (0.06 mol) of sodium salicyloxide, and 125 ml of dry DMF. The mixture was stirred at room temperature for 1 day and then heated at 100° for 1 day. After cooling, the reaction mixture was worked up by pouring into water and extracting with ether and CH_2Cl_2. The extracts were dried over $MgSO_4$.

The ether extract provided, by column chromatography, 3.62 g (57.5%) yield of olefin **19** and 3.4 g (41% yield) of triphenylphosphine oxide (**7a**). The CH_2Cl_2 extract was poured into ether to yield 1.5 g (11%), of salt **20**.

B. Fusion Method.—A blended mixture of 13.4 g (0.03 mol) of salt **4** and 7.2 g (0.05 mol) of sodium salicyloxide was placed in a 250-ml one-necked flask equipped with magnetic stirrer and short-path distillation head leading to a Dry Ice–acetone cooled receiver. The flask was immersed in an oil bath and heating was begun, until fusion occurred (160–165°). Vacuum was applied and volatiles were distilled over a period of 1 hr. Vpc analysis of the volatiles showed the presence of salicylaldehyde (3.4 g for a 56% recovery) and styrene (0.4 g, 14% yield).

The residue from the fusion was taken up in DMF, poured into water, and extracted with ether. The ether extract was washed with water and dried ($MgSO_4$), and then chromatographed on silica gel to furnish, in order of elution (solvent), triphenylphosphine (hexane–15% benzene), 23%; 3-phenyl-2*H*-benzopyran (6) (R′ = C_6H_5) (hexane–20% benzene), 8%; **19** (benzene), 21%; triphenylphosphine oxide (**7a**) (EtOAc), 28%.

Compound 19 had mp 79–80° (MeOH); ir (KBr) 3400 (OH), 1600 (C=C), 1490, 1450 (CC), 760, 690 cm^{-1} (aromatic); nmr ($CDCl_3$) δ 2.07 (d, 3, J = 1.2 Hz, CH_3), 5.33 (br s, 1, OH), 6.74 (q, 1, J = 1.2 Hz, vinyl), 6.8–7.6 (m, 9, C_6H_5).

Anal. Calcd: C, 85.70; H, 6.71. Found: C, 85.93; H, 6.56.

Reaction of Salt 20 with Sodium Salicyloxide.—Into a flame-dried 250-ml flask equipped with reflux condenser and mechanical

(18) Material darkened very rapidly.

stirrer was placed 22.4 g (0.05 mol) of salt **20**, 14.4 g (0.10 mol) of sodium salicyloxide, and 150 ml of dry DMF, and the mixture was stirred at reflux for 2 days. It was worked up by pouring into water, acidifying, and extracting with ether. The dry ($MgSO_4$) organic extract was short path distilled; volatiles showed only solvents and salicylaldehyde. The distillation residue was column chromatographed to furnish 6.0 g (50% yield) of **19** and 9.3 g (67%) of triphenylphosphine oxide (**7a**).

Reaction of Salt 4 with the Sodium Salt of Pyrrolaldehyde.—To a flask containing 150 ml of dry ether and 3.16 g (0.075 mol) of 57% sodium hydride dispersion (Alfa) was added 7.15 g (0.075 mol) of pyrrolaldehyde. When hydrogen evolution had ceased (*ca.* 2 hr), 33.4 g (0.075 mol) of salt **4** was added and the mixture was refluxed for 10 hr. DMF (50 ml) was added, and the red-brown mixture was refluxed for an additional 12 hr. After cooling, the reaction mixture was poured into dilute aqueous acid and filtered, providing 18.2 g of purple solid **21**. The filtrate was extracted with ether and dried ($MgSO_4$). Evaporation of the ether left a mixture of **7a** and **21**, from which 12.5 g (60% yield) of triphenylphosphine oxide (**7a**) could be isolated by digestion with hot hexane. Compound **21** was dissolved in $CHCl_3$ and reprecipitated into ether for analysis, mp >300°.

Anal. Calcd for $C_{148}H_{126}BrN_{10}OP$, n = 9: C, 81.87; H, 5.95; N, 6.45. Found: C, 81.46; H, 6.07; N, 6.72.

Polymer **21** had ir (Nujol) 1600 (C=C), 920 (pyrrole), 760, 700 cm^{-1} (aromatic and pyrrole ring); nmr ($CDCl_3$) showed broad adsorptions at δ 1.8–4.2, 4.5–5.0, 5.8–6.3, 6.8–7.5; uv $\lambda_{max}^{CHCl_3}$ 242, 280, 350, 500 mμ; mol wt (osmometry) calcd 2171, found 2180.

Reaction of 4 with the Sodium Salt of Phenylbenzoin.—The sodium salt of phenylbenzoin was prepared by treating 8.65 g (0.03 mol) of phenylbenzoin dissolved in 100 ml of dry ether with 1.44 g (0.03 mol) of a 50% dispersion of sodium hydride. After stirring for 15 min, 13.4 g (0.03 mol) of salt **4**, dissolved in 100 ml of DMF, was added and the resultant mixture was stirred at ambient temperature for 2 days, then heated for 6 hr at 100°. The mixture was poured into water and extracted with ether. Chromatography of the dry ($MgSO_4$) ether extract on silica gel yielded (in order of elution) **22**, 4.1 g (47.5%); **8d**, 1.7 g (15%); **7a**, 4.4 g (52.8%).

2,2,3,4-Tetraphenyl-2,5-dihydrofuran (8d) had mp 109–110° (MeOH); ir (KBr) 1650, 1590 (C=C), 1480, 1330 (CC), 1230 (COC), 790, 770, 750, 690 cm^{-1} (aromatic); nmr ($CDCl_3$) δ 3.85 (s, 2, CH_2), 6.8–7.9 (m, 20, C_6H_5); uv $\lambda_{max}^{CHCl_3}$ 242 mμ (ε 10,000), 312 (9400).

Anal. Calcd: C, 89.78; H, 5.92. Found: C, 90.19; H, 6.11.

Rearrangement of the Sodium Salt of Phenylbenzoin.—A 5.76-g (0.02 mol) sample of phenylbenzoin in 100 ml of dry ether was treated with 0.96 g (0.02 mol) of a 50% dispersion of sodium hydride. When hydrogen evolution had ceased, 75 ml of dry DMF was added, and the mixture was heated at reflux for 2 hr, then stirred at room temperature for 24 hr. The mixture was poured into water and dilute acid was added until neutrality was reached. Extraction with ether resulted in the isolation of 4.7 g (81% yield) of benzhydryl benzoate (**22**), identical with an authentic sample. Hydrolysis in dilute acid furnished benzoic acid and benzhydrol (70% based on phenylbenzoin), identified by comparison of ir and nmr spectra and mixture melting point with authentic samples.

Registry No.—**2**, 30670-21-4; **3**, 7301-95-3; **4**, 30537-11-2; (*Z*)-**5b**, 38555-27-0; (*E*)-**5b**, 38555-28-1; **5c**, 38555-29-2; **6** (R′ = Me), 38555-30-5; **8** (R′ = Me), 38555-31-6; **8d**, 38555-32-7; **9** (R′ = Me), 38555-33-8; **10**, 38555-34-9; **10** bromide derivative, 33999-09-6; **19**, 38555-36-1; **20**, 30537-09-8; **21**, 38555-38-3; 2-bromopropene, 557-93-7.

Acknowldegment.—This work was supported by a U. S. Public Health Service Grant (CA 11000) for which we are most grateful.

The Preparation, Thermolysis, and Photolysis of Phenylmaleoyl Peroxide

MICHAEL M. MARTIN* AND JOHN M. KING

Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48104

Received November 28, 1972

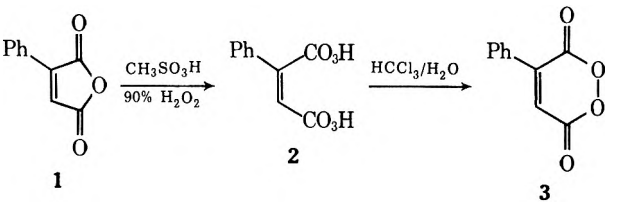
The decomposition of the cyclic monomeric peroxide derived from phenylmaleic acid generates carbon dioxide, phenylacetylene, and a carbonyl-containing polymeric substance. The yields of carbon dioxide and phenylacetylene are highest in a sensitized photolytic decomposition, and lowest in a thermolytic decomposition. These results are interpreted in terms of the nature of the likely intermediates in the decomposition sequence.

The chemistry of cyclic acyl peroxides has attracted the interest of organic chemists sporadically for many years. Phthaloyl peroxide was the first cyclic acyl peroxide to be investigated thoroughly.[1-5] More recently, cyclic malonyl peroxides have been the subject of several studies.[6,7] Cyclic acyl peroxides have also been implicated in the decomposition of dimeric and trimeric peroxides of cycloalkanones.[8] Cyclic diphenoyl peroxide has been prepared, but its chemistry has not been extensively explored.[9]

In this report, we wish to describe the synthesis, thermolysis and photolysis of phenylmaleoyl peroxide, **3**. This compound is the first monomeric cyclic maleoyl peroxide to be reported.

Results and Discussion

Synthesis.—Phenylmaleoyl peroxide (**3**) was generated in 38% yield when a heterogeneous mixture consisting of diperoxyphenylmaleic acid, **2**, chloroform, and water was agitated vigorously. The success of this



1 2 3

procedure depends upon the rapid cyclization of **2** to **3** in the polar aqueous phase, following which the less polar **3** is rapidly extracted into the inert chloroform phase, thereby preventing further hydrolysis to the monoperoxy acid.

(1) K. E. Russell, *J. Amer. Chem. Soc.*, **77**, 4814 (1955).
(2) F. D. Greene, *ibid.*, **78**, 2246 (1956).
(3) G. Wittig and H. F. Ebel, *Justus Liebigs Ann. Chem.*, **650**, 20 (1961).
(4) M. Jones, Jr., and M. R. DeCamp, *J. Org. Chem.*, **36**, 1536 (1971).
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(7) O. L. Chapman, P. W. Wojtkowski, W. Adam, O. Rodriquez, and R. Rucktäschel, *ibid.*, **94**, 1365 (1972).
(8) P. R. Story, D. D. Denson, C. E. Bishop, B. C. Clark, Jr., and J. C. Farine, *ibid.*, **90**, 817 (1968).
(9) F. Ramirez, S. B. Bhatia, R. B. Mitra, Z. Hamlet, and N. B. Desai, *ibid.*, **86**, 4394 (1964).

Decompositions.—The decomposition of **3** proceeds smoothly under conditions of thermolysis, direct photolysis, and photolysis in the presence of a triplet sensitizer. Three products, carbon dioxide, phenylacetylene and a carbonyl-containing polymer which was not fully characterized, together account for all of the peroxide decomposed. The relative yields of these three substances are dependent upon the mode of decomposition. The yields of carbon dioxide and phenylacetylene are summarized in Table I. Clearly, the yields of

$$3 \longrightarrow CO_2 + PhC{\equiv}CH + \text{polymer}$$

TABLE I

YIELDS OF CARBON DIOXIDE AND PHENYLACETYLENE FROM THE DECOMPOSITION OF PHENYLMALEOYL PEROXIDE

Conditions	Yield, mol/mol 3 CO_2	Yield, mol/mol 3 PhC_2H
Thermolysis (refluxing CCl_4)	1.10	0.13
Direct photolysis (CCl_4, 22–25°)	1.62	0.63
Sensitized photolysis (CCl_4, 22–25°, benzil)	1.88	0.82

these two products are higher in a photolysis than in a thermolysis, and higher when the photolysis is sensitized than when it is not.

Before advancing an interpretation of these findings based upon the properties of the expected intermediates, it is necessary to consider the possible intervention of a side reaction which would influence these product yields. Phthaloyl peroxide is known to add to acetylenes by a nondecarboxylative process.[10] If an analogous reaction were to occur between **3** and the phenylacetylene being produced during the decomposition, the yields of both carbon dioxide and phenylacetylene would be affected. To test for the possible intervention of this reaction, the thermolysis of **3** was carried out in the presence of several equivalents of added phenylacetylene. If the addition of **3** to phenylacetylene occurs with sufficient facility to compete with the decomposition of **3**, it would be expected that the yield of carbon dioxide would be significantly below the yield obtained in the absence of added phenylacetylene. In fact, in the presence of 2 equiv of phenylacetylene, 1.04 equiv of carbon dioxide was evolved, an amount only slightly less than the value of 1.10 obtained in the absence of added phenylacetylene. Thus, it can be concluded that a competing reaction between **3** and phenylacetylene formed during the decomposition is not occurring to any significant extent.

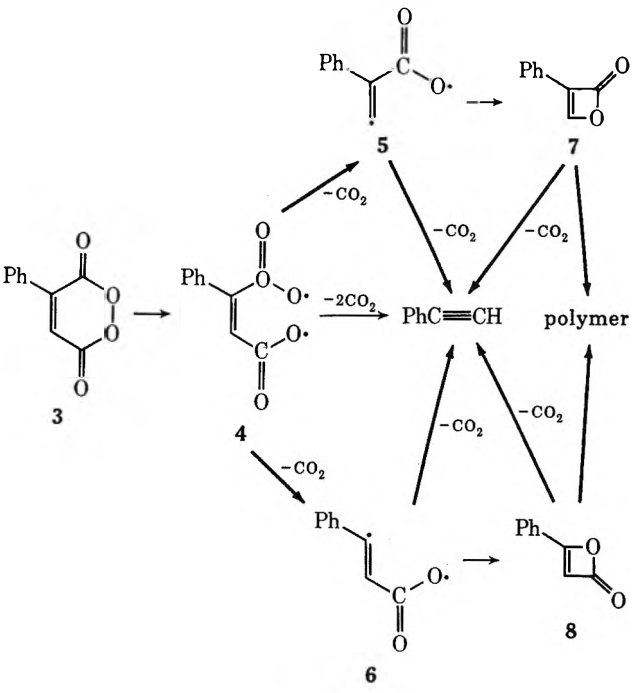
Although additional studies will be required to establish rigorously the mechanism for the decomposition of phenylmaleoyl peroxide, the results obtained herein may be discussed within the framework of Scheme I.

Thermolysis of the oxygen–oxygen bond of **3** would generate a short-lived diacyloxy radical **4**, which could produce phenylacetylene directly, or *via* the monoacyloxy diradicals **5** and **6** formed by monodecarboxylation of **4**, or from unstable lactonic intermediates such as **7** and **8**. Polymeric materials could also arise from **7** and **8**, or from ketene intermediates derived from **7** and **8** by a process analogous to one observed in the decomposition of phthaloyl peroxide.[5]

(10) F. D. Greene and W. W. Rees, *J. Amer. Chem. Soc.*, **82**, 893 (1960).

SCHEME I

THE DECOMPOSITION OF PHENYLMALEOYL PEROXIDE



The photosensitized decomposition of **3** must be interpreted in terms of triplet states of the intermediates. If the monoacyloxy diradicals **5** and **6** are triplets, spin inversion would be required before nonradical species **7** and **8** could be formed. The sequence leading to polymer would thereby be disfavored relative to the competing decarboxylation reaction, which would produce phenylacetylene. The possibility of a photosensitized decarboxylation of nonradical intermediates **7** and **8** to phenylacetylene cannot be excluded.

The results of the direct photolysis of **3** can be interpreted in several ways. The relatively high yields of carbon dioxide and phenylacetylene may suggest that the direct photolysis is also occurring primarily *via* triplet intermediates. On the other hand, direct photolysis may generate singlet intermediates similar to those produced during thermolysis, in which case the higher yields of phenylacetylene and carbon dioxide observed during photolysis may reflect a different partition of the intermediates **7** and **8** between decarboxylation and polymerization at the lower temperature of the photolysis (25° *vs.* 76°). Or, direct photolysis might produce higher energy singlet species **5** and **6** than thermolysis. Higher energy singlet intermediates might be more prone to decarboxylation than cyclization. Finally, photolytic decarboxylation of the nonradical intermediates **7** and **8** may account for the higher yields of carbon dioxide and phenylacetylete under photolytic than thermolytic conditions.

Experimental Section

Caution. Although we experienced no problems in handling any of the materials described in this paper, we urge that all of these peroxidic compounds be treated as potentially hazardous substances.

Diperoxyphenylmaleic Acid (2).—Phenylmaleic anhydride,[11,12] methanesulfonic acid, and 90% hydrogen peroxide in molar ra-

(11) L. E. Miller, H. B. Staley, and D. J. Mann, *ibid.*, **71**, 374 (1949).
(12) C. S. Rondesvedt and A. H. Filbey, *J. Org. Chem.*, **19**, 119 (1954).

tios of 1:5:6 were stirred at room temperature for 90 min. An equal volume of cold, saturated ammonium sulfate solution was added, and the mixture was extracted four times with equal volumes of ether. The ether solution was washed twice with cold, saturated ammonium sulfate, dried over magnesium sulfate, filtered, and concentrated at reduced pressure and room temperature, leaving a viscous oil. Crystallization was induced by adding sufficient chloroform, containing a little ether, to produce a clear solution, then removing solvent at reduced pressure. The solid obtained was triturated with several portions of chloroform and dried *in vacuo* to give a 57% yield of crude diperoxy acid containing greater than 98% of the theoretical active oxygen. Recrystallization from chloroform–ether gave pure diperoxyphenylmaleic acid: mp 92.5–93.5°; ir (Nujol) 3270, 1760, 1625, 1600, 1580, 680 cm^{-1}.

Anal. Calcd for $C_{10}H_8O_6$: C, 53.58; H, 3.60; active oxygen,[13] 14.27. Found: C, 53.43; H, 3.59; active oxygen, 14.00.

Phenylmaleoyl Peroxide (3).—A mixture of diperoxyphenylmaleic acid (0.50 g, 2.1 mmol) of 96% purity, 5 ml of water, and 50 ml of chloroform was agitated at room temperature for 60 min with a Vibromixer. The aqueous phase was washed with 5 ml of chloroform, and the combined chloroform layers were washed twice with 5 ml of cold, 10% sodium bicarbonate, dried over magnesium sulfate, filtered, and evaporated, giving a 38% yield of phenylmaleoyl peroxide of 94–96% purity. One recrystallization from chloroform–hexane gave 0.13 g (33%) of pure product: mp 105.5–106°; ir ($HCCl_3$) 3070, 4040, 1765 (shoulder), 1750, 1630, 1605, 1580, 700 cm^{-1}; uv (CCl_4) broad λ_{max} 312 nm (log ϵ 4.06); nmr ($CDCl_3$) δ 7.23 (s, 1 H), 7.3–7.9 (b m, 5 H). Phenylmaleoyl peroxide is very soluble in methylene chloride and chloroform, soluble in benzene, slightly soluble in carbon tetrachloride, and practically insoluble in hexane.

Anal. Calcd for $C_{10}H_6O_4$: C, 63.16; H, 3.18; active oxygen, 8.41; mol wt, 190.15. Found: C, 63.25; H, 3.21; active oxygen, 8.25; mol wt, 190 (cryoscopic, benzene).

Hydrolysis of phenylmaleoyl peroxide in aqueous acetone, followed by dehydration with trifluoroacetic anhydride, gave phenylmaleic anhydride, mp 117–119° (lit.[11] mp 119–120°).

Decomposition Studies.—A 0.02–0.1 *M* solution of phenylmaleoyl peroxide in carbon tetrachloride was placed in a flask equipped with a reflux condenser. A stream of dried, prepurified nitrogen was passed into the reaction flask through a tube which ended a few centimeters above the surface of the refluxing solvent for the thermal decompositions, or through a fritted gas dispersion tube submerged in the medium for the photodecompositions. The nitrogen stream leaving the top of the reflux condenser was passed through a trap cooled in Dry Ice–acetone, then two U tubes filled with Ascarite, and finally through a bubbler containing sulfuric acid. The weight of carbon dioxide evolved was obtained from the increase in weight of the first Ascarite U tube.

In a typical thermal decomposition, the system was flushed with nitrogen at room temperature until the first Ascarite U tube came to constant weight. The reaction flask was then immersed in an oil bath 5–10° above the boiling point of the solvent while the nitrogen continued to flow. At intervals, the flow was stopped, and the first Ascarite U tube was removed and weighed. Refluxing was continued until the Ascarite trap came to constant weight.

In a typical photodecomposition, the Pyrex reaction flask was immersed in a bath maintained at 22–25°. The system was flushed with nitrogen and a constant weight for the first Ascarite tube was obtained. The reaction mixture was then irradiated with a 275-W sun lamp mounted over the reaction flask at a distance of 4 in. until the Ascarite U tube reached constant weight.

The direct photolysis of 40 mg of phenylmaleoyl peroxide in 12 ml of carbon tetrachloride was 80% complete in 5 hr. In the presence of 8 mg of benzophenone, 98% decomposition occurred in 5 hr. In the presence of 80 mg of benzophenone decomposition was 90% complete in 2 hr, 99% in 4 hr. Finally, in the presence of 40 mg of benzil, decomposition was 99% complete in 2 hr. In the absence of light no decomposition was observed over 10–12 hr in the presence or absence of sensitizer.

The yield of phenylacetylene was obtained by diluting the reaction mixture to 100 ml and determining the concentration of phenylacetylene by glc on a silicone gum rubber column, using solutions of phenylacetylene of known concentration as reference standards.

At the completion of thermolysis, the reaction mixture contained a floating precipitate. The mixture was concentrated to about one-fourth its original volume, and the precipitate was filtered, washed with a little carbon tetrachloride, and dried, giving a yellow powder amounting to about 50% of the weight of initial peroxide. This substance exhibited a broad absorption band between 1800 and 1670 cm^{-1}. The average molecular weight (vapor pressure osmometry in chloroform) was 3400. The filtrate obtained after removal of the insoluble material was then distilled at reduced pressure until all solvent and phenylacetylene had been removed. The residue consisted of a brown, sticky solid amounting to about 25% of the weight of the initial peroxide. This material exhibited broad absorption between 1860 and 1675 cm^{-1}, and had an average molecular weight of 435.

Photolytic decompositions produced only the soluble residues. No insoluble polymer was generated. Yields of residues were determined simply by weighing the material remaining after solvent and phenylacetylene had been removed by distillation. In the case of the sensitized decompositions, the weight of sensitizer had to be subtracted from the observed weight of the residue.

In all cases the residue was examined by glc on a silicone column for the presence of hexachloroethane. None was ever detected.

Registry No.—1, 36122-35-7; 2, 38605-60-6; 3, 38606-11-0.

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Routes to Functionalized Guanidines. The Synthesis of Guanidino Diesters[1a]

TALMAGE R. BOSIN,[1b] ROBERT N. HANSON,[1c] JOSEPH V. RODRICKS,[1d]
RICHARD A. SIMPSON, AND HENRY RAPOPORT*

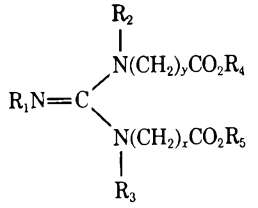
Department of Chemistry, University of California, Berkeley, California 94720

Received December 5, 1972

Six general methods for the synthesis of acyclic and cyclic guanidines, of structures 1 and 2 and bearing a variety of substituents, are described. These guanidines may be symmetrical or unsymmetrical, and the substituents they bear provide the basis for further chemical manipulation. The acyclic guanidines are derived from single carbon intermediates, such as **3**, **9**, **13**, and **14**, and the appropriately substituted amine. The cyclic guanidines result from the functionalization of a 2-*p*-toluenesulfonamidopyrimidine which is subsequently hydrogenated. Use of the tosyl as a protecting group reduces the effects of the strongly alkaline guanidine moiety, and its facile removal is achieved with hydrogen fluoride. Detosylation of the tosyl-protected guanidino diester **12** resulted in formation of the imidazolin-4-one **51**; this reaction proved to be general for the guanidines **1**, $x = 1$, and **2**, $z = 1, 2$. These imidazolinones underwent deuterium exchange for which a mechanism involving the formation of a mesoionic intermediate is proposed.

Increasingly among the functional groups found in natural products, there are instances of the occurrence of the guanidine moiety. In addition to the well-known and obvious examples of arginine, creatinine, and creatine (the latter two are classed as glycocyamidines[2]), the guanidino group recently has been found in the puffer fish poison, tetrodotoxin,[3] in the paralytic shellfish poison, saxitoxin,[4] in the peptide antibiotics capreomycin,[5] viomycin,[6] and tuberactinomycin,[7] in the antifungal agent, stendomycin,[8] and in the alkaloids of *Alchornea javanensis*.[9] Interestingly, all of these compounds contain the guanidine moiety as part of a cyclic system.

Thus it is of interest to prepare guanidines which are suitably functionalized to permit a variety of synthetic manipulations, the most important of which is probably the conversion to cyclic guanidines, retaining some functionality in addition to the guanidino group. This paper describes routes to acyclic and cyclic guanidino diesters, namely, **1** and **2**; the routes are general and



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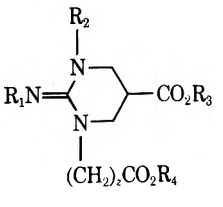


2

flexible in design so that such intermediates may find wide synthetic use. Two groups of such esters are described: (1) tosyl-protected guanidino diesters (**1**, R_1 = Ts; **2**, R_1 = Ts) and (2) unprotected guanidino diesters. The tosyl protecting group is very useful in these syntheses, since the possible interference of the strongly alkaline guanidine function is largely eliminated. Also, the facile deprotection of tosylguanidines with anhydrous HF[10,11] makes this an especially suitable protecting group.

Tosyl-Protected Guanidino Diesters.—Any of the six reaction paths a–f can be used to prepare tosyl-protected guanidino diesters.

The first four synthetic routes are based on a variation of the classical Rathke[12] guanidine synthesis, the reaction of an *S*-methylisothiourea with an amine. In our approach the *S*-methylisothiourea is first converted to the more reactive amidinium chloride (*e.g.*, **11**) or carbodiimide (*e.g.*, **7**), since the conditions required for direct conversion of an isothiourea to a guanidine are too drastic for use with sensitive amino esters.

The entire scheme hinges on the availability of the appropriate *S*-methylisothioureas (*e.g.*, **4**, **10**, **16**,) and we have found that such compounds can be generated with ease from *S*,*S*-dimethyl-*N*-*p*-toluenesulfonyliminodithiocarbonimidate (**3**) or from *p*-toluenesulfonylisothiocyanate (**14**). The thiomethyl groups of the former compound were shown[13] to undergo nucleophilic displacement. This displacement reaction was then extended[14] to include the sodium salts of various β-amino acids as in **3** → **4**. The preparation of various sulfonyl isothiocyanates (*e.g.*, **14**) has also been described.[13,15,16]

Reaction path a is useful for the preparation of guanidines of type **8** (**1** in which either R_2 or R_3, or both are H). The intermediate *S*-methylisothiourea **4** can be obtained by direct displacement of a methylthio group of **3** with the sodium salt of an amino acid,[14] a process which requires boiling in ethanol. Such conditions are untenable if an amino acid ester is to be used directly because of competing diketopiperazine formation. Under these conditions *N*-methylamino acids do not displace the methylthio group of **3** and, as a result, path a is limited to the production of guanidines such as **8**.

(1) (a) Supported in part by the U. S. Army Research Office, Durham, N. C.; (b) National Institutes of Mental Health Postdoctoral Fellow; (c) National Science Foundation Predoctoral Fellow; (d) on special assignment from the U. S. Food and Drug Administration.

(2) C. Lempert, *Chem. Rev.*, **59**, 667 (1959).

(3) A. Furusaki, Y. Tomije, and I. Nitta, *Bull. Chem. Soc. Jap.*, **43**, 3332 (1970), and references cited therein.

(4) J. Wong and H. Rapoport, *J. Amer. Chem. Soc.*, **93**, 7344 (1971).

(5) B. W. Bycroft, D. Cameron, and A. W. Johnson, *J. Chem. Soc. C*, 3040 (1971).

(6) B. W. Bycroft, L. R. Croft, A. W. Johnson, and T. Webb, *J. Chem. Soc., Perkin Trans. 1*, 820 (1972).

(7) H. Yoshioka, T. Aoki, H. Goko, K. Nakatsu, T. Noda, H. Sakakibara, T. Take, A. Nagata, J. Abe, T. Wakamiya, T. Shiba, and T. Kaneko, *Tetrahedron Lett.*, **No. 23**, 2043 (1971).

(8) M. Bodanszki, J. Izdebski, and I. Myramatsu, *J. Amer. Chem. Soc.*, **91**, 2351 (1969).

(9) N. K. Hart, S. R. Johns, J. A. Lamberton, and R. I. Willing, *Aust. J. Chem.*, **23**, 1679 (1970).

(10) R. H. Mazur and G. Plume, *Experientia*, **24**, 661 (1968).

(11) J. V. Rodricks and H. Rapoport, *J. Org. Chem.*, **36**, 46 (1971).

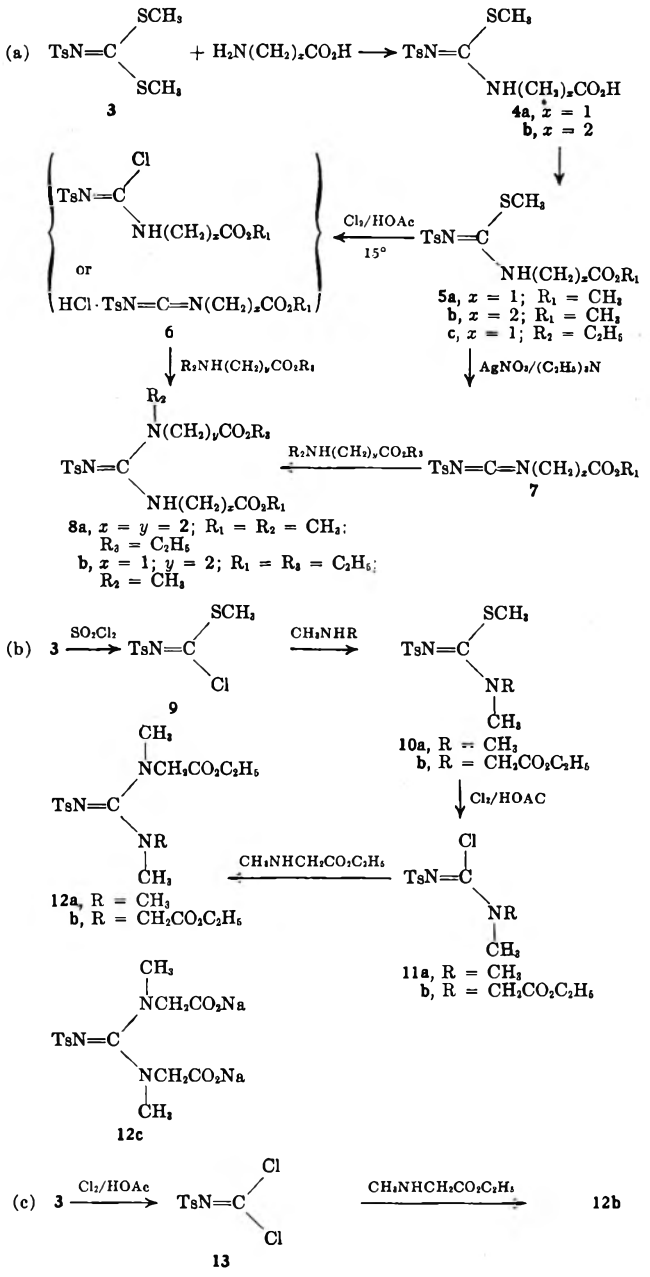
(12) B. Rathke, *Ber.*, **17**, 297 (1884).

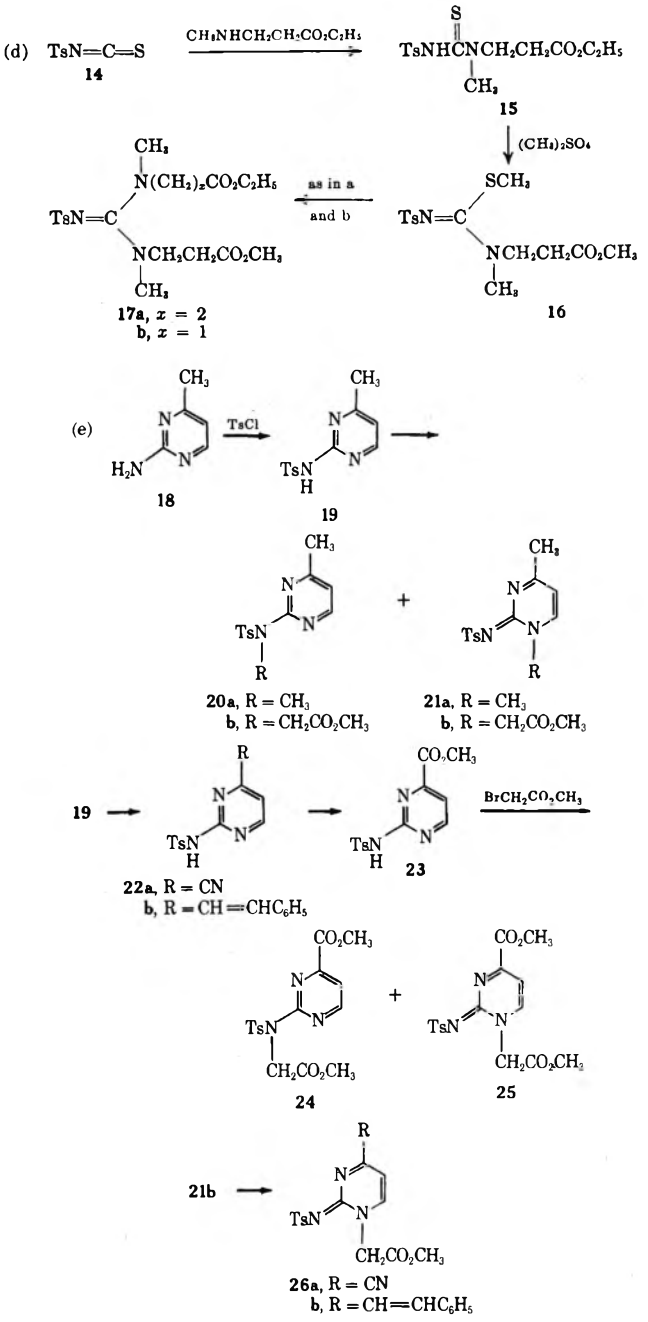
(13) R. Gompper and W. Hagele, *Chem. Ber.*, **99**, 2885 (1966).

(14) J. Gante, *Angew. Chem.*, **19**, 858 (1967).

(15) K. Hartke, *Arch. Pharm. (Weinheim)*, **299**, 174 (1966).

(16) K. Dickore and E. Kuhle, *Angew. Chem., Int. Ed. Engl.*, **4**, 430 (1965)





Esterification of the acid **4** can be effected with either methyl iodide or dimethyl sulfate; if other than a methyl ester is desired, Fischer esterification is successful. Use of the alkylating agents does not cause alkylation of the isothiourea nitrogen. The *S*-methylisothiourea **5**, when treated with $AgNO_3/Et_3N$,[17] is converted to the intermediate sulfonylcarbodiimide **7**; the latter is not isolated but is immediately trapped by the appropriate amino ester to yield the guanidino diester. Alternatively, the sulfonylcarbodiimide salt or chloro amidine **6** can be generated by chlorination of the isothiourea **4**.

Pathway b is based on the conversion of **3** to the monochlorinated compound **9** using sulfuryl chloride as the chlorinating agent.[18] The monochloro compound **9** then undergoes nucleophilic displacement at room temperature with the appropriate amino ester to produce the corresponding *S*-methylisothiourea **10**, which is converted to the guanidino diester using the procedure of path a. Use of the $AgNO_3/Et_3N$ reagent is prohibited in this sequence, and the chloro amidine **11** will be the reactive intermediate.

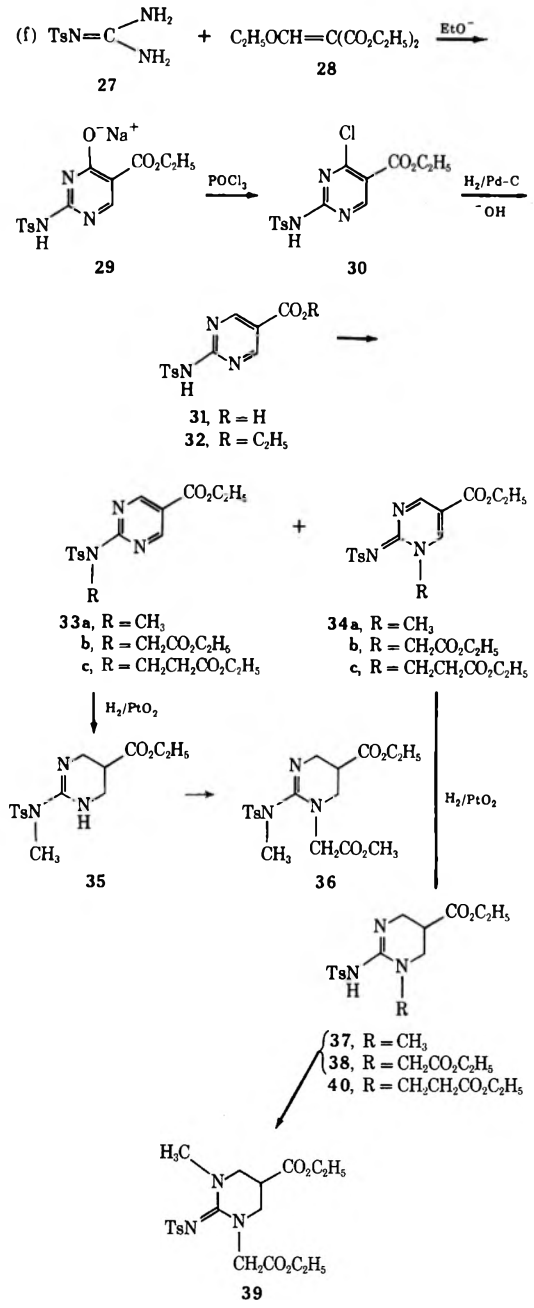
Path c is useful because it is a one-step reaction, although it is limited to the introduction of identical amino ester fragments. *S,S*-Dimethyl-*N*-*p*-toluenesulfonyliminodithiocarbonimidate (**3**) is smoothly converted to *N*-*p*-toluenesulfonylimidocarbonyl chloride (**13**) upon treatment of a glacial acetic acid solution of **3** with Cl_2.[19] The dichloro compound readily reacts with 2 equiv of an amino ester at room temperature or below.

Path d is as flexible as path b; *p*-toluenesulfonylisothiocyanate (**14**) reacts readily with amino esters to afford *N*-tosylthioureas **15**. The thiourea can be converted to an *S*-methylisothiourea by action of an alkyl-

(17) A. F. Ferris and B. A. Schutz, *J. Org. Chem.*, **28**, 71 (1963).

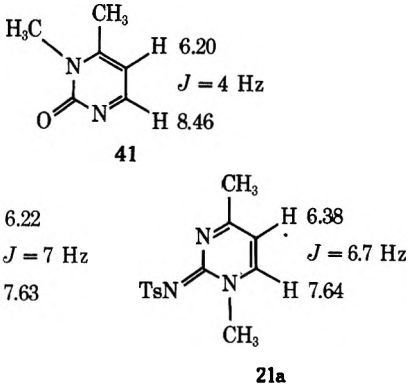
(18) R. Neidlein and W Haussmann, *Angew. Chem., Int. Ed. Engl.*, **4**, 521 (1965).

(19) R. Neidlein and W. Haussmann, *Tetrahedron Lett.*, **No. 22**, 1753 (1965); R. Gompper and R. Kunz, *Chem. Ber.*, **99**, 2900 (1966).



ating agent, although the alkylation process results in transesterification as well (**15** → **16**). Generally path d results in somewhat better yields of *S*-methylisothiourea than can be achieved by path b.

Path e is applicable for the synthesis of tosylguanidines from 2-aminopyrimidines on which exocyclic tosylation with *p*-toluenesulfonyl chloride in pyridine proceeds easily.[20] However, alkylation, contrary to the literature regarding *N*-sulfonylaminopyrimidines,[20] results in both exo (**20**) and endo (**21**) isomers, with no apparent alkylation at N-3. The exo isomer was identified by comparison to an authentic sample prepared unambiguously *via* the Ullman reaction[21] with *N*-methyl-*p*-toluenesulfonamide and 2-chloro-4-methylpyrimidine. Structural assignment of the endo isomer was based upon the nmr comparison of the pyrimidine ring protons with those of the 3,4- and 1,4-dimethyl-2-oxopyrimidines,[22,23] **41** and **42**, respectively. The 2-tosylamidopyrimidines could be further substituted by



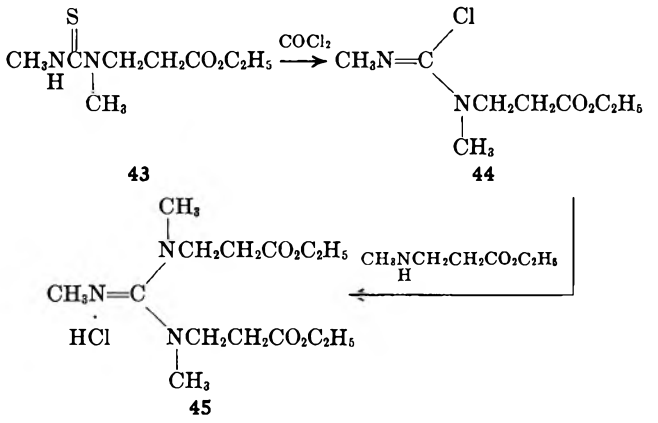
alkylation with various alkyl halides and by oxidation of the C-4 methyl either before or after alkylation.[24,25] Reduction of the pyrimidines would then proceed to yield the desired functionalized tosyl-protected guanidines.[26]

Path f extends the synthesis to 2-aminopyrimidines which cannot be directly tosylated with tosyl chloride. It was found that tosylguanidine readily condenses with diethyl ethoxymethylenemalonate in sodium ethoxide–ethanol to give the salt of the pyrimidin-4-one **29**.[27] This salt, when heated with phosphorus oxychloride, gives the 4-chloropyrimidine **30** in high yield without the presence of the usual tertiary amine.[27c] Reductive dehalogenation[28] followed by esterification yields 2-tosylamido-5-ethoxycarbonylpyrimidine (**32**). Alkylation and ring reductions as described in path e result in various functionalized tosyl-protected cyclic guanidines in which one ester function is at C-5 rather than at C-4. It should be noted that the alkylation of the trialkyl guanidines **37** and **38** occurs predominantly on the endocyclic nitrogen with very little alkylation on the exocyclic tosylated nitrogen.

Unprotected Guanidine Diesters.—The synthesis of unprotected guanidines carrying a diester function is modeled after path d of the tosyl-protected guanidino diester synthesis. Thus, the synthesis depends upon the availability of alkyl isothiocyanates. As an example, methyl isothiocyanate was treated with ethyl 3-*N*-methylaminopropionate to afford the thiourea **43**, which was converted by phosgene[29] to the chloro formamidinium chloride **44**. In this case the base-weakening effect of the sulfonyl group is eliminated, and the

(20) J. P. English, J. H. Clark, R. G. Shephard, H. W. Marson, J. Krapcho, and R. O. Roblin, Jr., *J. Amer. Chem. Soc.*, **68**, 1039 (1946).
(21) M. A. Phillips, *J. Chem. Soc.*, 9 (1941).
(22) D. J. Brown and T. C. Lee, *Aust. J. Chem.*, **19**, 2321 (1966).
(23) D. J. Brown and T. C. Lee, *Aust. J. Chem.*, **21**, 243 (1968).
(24) T. Matsukawa and K. Shirakawa, *J. Pharm. Soc. Jap.*, **72**, 909 (1952).
(25) G. Daves, P. O'Brien, L. Lewis, and C. Cheng., *J. Heterocycl. Chem.*, **1**, 130 (1964).
(26) (a) H. Aft and B. E. Christensen, *J. Org. Chem.*, **27**, 2170 (1962); (b) R. F. Evans, *J. Chem. Soc.*, 2450 (1964); (c) R. F. Evans and J. S. Shannon, *J. Chem. Soc.*, 1406 (1965); (d) B. W. Bycroft, D. Cameron, L. R. Croft, and A. W. Johnson, *Chem. Commun.*, 1301 (1968).
(27) For analogous reactions with diethyl ethoxymethylenemalonate see (a) H. C. Koppel, R. H. Springer, R. K. Robins, and C. Cheng, *J. Org. Chem.*, **27**, 3614 (1962); (b) J. H. Chesterfield, D. T. Hurst, J. W. F. McOmie, and M. S. Tute, *J. Chem. Soc.*, 1001 (1964); (c) E. Peters, J. F. Holland, B. Bryant, H. J. Minnemeyer, C. Hohenstein, and H. Tieckelmann, *Cancer Res.*, **19**, 729 (1959).
(28) R. G. Shepherd, W. E. Taft, and H. M. Krazinski, *J. Org. Chem.*, **26**, 2764 (1961).
(29) For similar reactions see H. Eilingsfeld, G. Naubauer, M. Seefelder, and H. Weidinger, *Chem. Ber.*, **97**, 1232 (1964).

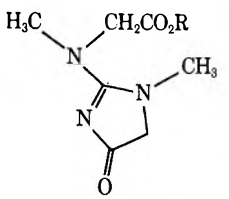
product forms a salt with the HCl released during the reaction. The intermediate **44** was taken to the guanidino diester hydrochloride **45**; also resulting from the



reaction was 1 equiv of amino ester hydrochloride, giving a mixture of water-soluble salts. Advantage can be taken of the great difference in basicity between amino ester salt and guanidino diester salt, and the pair can be separated by ion-exchange chromatography on an acid resin. The 4 *N* acid required to remove the guanidine salt effects ester hydrolysis; however, reesterification of the diacid, using ethanolic HCl, proceeds with ease. The overall yield of final diester **45**, based on thiourea **43** and including ion-exchange chromatography and reesterification, is 52%. Although our work on unprotected guanidino diesters is limited to this single case, it is presumably widely applicable and is based on the availability of alkyl isothiocyanate.

Deprotection of Tosyl-Protected Guanidino Diesters. —The tosyl-protected guanidino diesters are potential intermediates for the synthesis of a variety of functionalized guanidines, the *N*-tosyl group providing protection from the intervention of the strongly alkaline guanidine group in any further chemical manipulations of the diesters. However, attempts to remove the tosyl group by exposure to anhydrous HF, a procedure which has been demonstrated to remove tosyl groups from guanidines quantitatively,[11] yielded the corresponding acylguanidines.

When *N*-tosyl-*N'*,*N''*-dimethyl-*N'*,*N''*-di(ethoxycarbonylmethyl)guanidine (**12b**) was stirred at room temperature for 2 hr in anhydrous HF, detosylation was effected, but in addition the detosylated intermediate underwent cyclization to form the imidazolin-4-one **46a** in very good yield. Likewise, **12a** and the cyclic guanidino diesters **36** and **38–40** gave their respective analogs **47–51** under the same conditions in 30–90% yield. The detosylation of the disodium salt **12c** in HF resulted in the isolation in a 20% yield of the acid **46b**



46a, R = C_2H_5
b, R = H

after ion-exchange chromatography. The ethyl ester **46a** was obtained by Fisher esterification, indicating that both acids and esters experienced cyclization under these conditions. Fisher esterification of **12c** gave only tosylamide and sarcosine ethyl ester. Thus in all examples where the N substituents are either acetate or propionate residues, the use of HF as a detosylating agent leads to imidazolinones or their homologs.

To verify that the cyclization resulted from the detosylation conditions and not during the isolation procedure, *N*-*p*-toluenesulfonyl-*N'*,*N''*,*N'''*-trimethyl-*N'*-ethoxycarbonylmethylguanidine (**12a**) and **41** were subjected to the detosylation conditions and, after removal of the HF, the residues were immediately examined by nmr. The spectra indicated that cyclization had occurred to give **52** and **55**, as was evidenced by the absence of the ethyl ester absorption for **52** and the presence of a single ethyl ester for **55**, identical with the spectrum of **55** prepared independently.

The bicyclic series contains both acylamino (**48**) and acylimino (**49–51**) forms of the imidazolinones, thereby permitting a comparison of their properties. The uv absorption maxima (λ_{max} 222–229 nm) and extinction coefficients (ϵ 16,000–20,000) for the obligatory acylimino compounds **46**, **47**, and **50** and the values for the acylamino isomer **48** (λ_{max} 210 nm ϵ 9750) correlate well with the reported values and substantiate the use of uv spectroscopy as a means of differentiating between the two tautomeric forms.[30,31] These data also established the acylimino structure as the preferred tautomer for the labile imidazolinone **49** and tetrahydropyrimidinone **51**.

Although the C-5 hydrogens of the imidazolin-4-ones are potentially exchangeable, little work has been reported other than a single study involving deuterium exchange at pD 9 in which the acylamino tautomers underwent exchange much more rapidly than their acylimino counterparts.[31] The variety of compounds (**46–51**) which we prepared permitted a more detailed study, and their exchange behavior was examined in phosphate buffer solutions at pD's 3, 7, and 10. In addition, compound **50** was examined at pD 1 (D_2SO_4–D_2O) and at pD 13 (NaOD–D_2O).

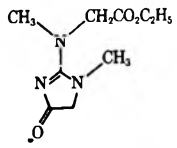
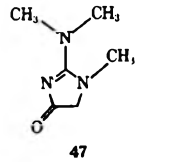
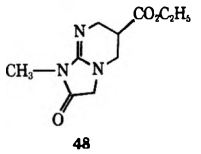
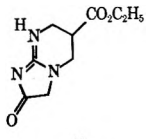
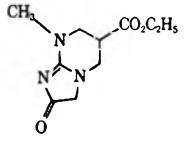
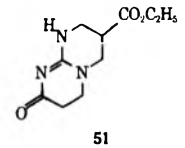
From Table I it is apparent that the tetrahydropyrimidinone **51** undergoes negligible exchange over the pD range observed relative to the imidazolinones. Within the imidazolinone series, exchange for the acylamino compound **48** was more sensitive to pD than were those compounds containing the acylimino group. Generally the rate of exchange increases as one goes to a more acidic pD; indeed, at pD 1, **49** undergoes complete exchange within 5 min. For compound **47**, however, the rate increased upon raising the pD from 7 to 10, which was paralleled by the behavior of **49**; **49** underwent complete deuterium exchange at pD 13 within 5 min. Apparently two mechanisms are involved; however, the one in the lower pD range is of greater interest.

A simple "enolic" mechanism for the acid-catalyzed exchange can be eliminated because it implies comparable rates of exchange for the pyrimidinone **51** as well as for the imidazolinones. That the exchange in-

(30) K. Matsumoto and H. Rapoport, *J. Org. Chem.*, **33**, 552 (1968).
(31) G. L. Kenyon and G. L. Rowley, *J. Amer. Chem. Soc.*, **93**, 5552 (1971).

TABLE I

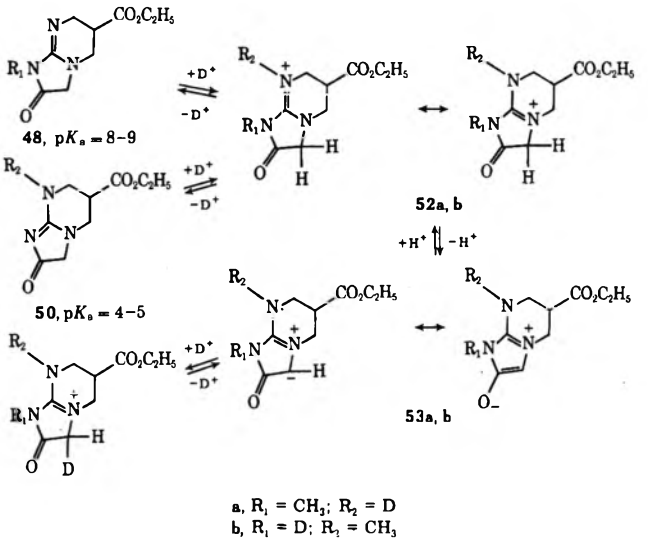
DEUTERIUM EXCHANGES[a] OF SOME IMIDAZOLINONES AND TETRAHYDROPYRIMIDINONES

Compd	Half-life, min		
	pD 3[b]	pD 7[b]	pD 10[b]
 46a	5–10	60	*c*
 47	10–15	90	45
 48	5	20	*d*
 49	115	150	1000
 50	140	1250	2000
 51	1300[e]	1300[e]	1300[e]

[a] Exchange performed in aqueous phosphate buffer solutions. [b] ±0.5 pD. [c] Ester hydrolysis interfered with exchange measurements. [d] Hydrolysis of the imidazoline ring was more rapid than exchange. [e] Less than 5% exchange (detectability limit) had occurred when the experiment was terminated; therefore, this is a lower limit.

creases with decreasing pD indicates the necessity of a protonated intermediate. Such a protonated species **52** is structurally analogous to and isoelectronic with the oxazolin-4-one salts.[32] As with the oxazolinonium compounds, it is not difficult to envision the loss of a proton from C-5 to give a mesoionic intermediate **53** which is analogous to munchnones,[33] sydnones,[34] and other mesoionic compounds.[35] Such an intermediate is not possible with the pyrimidinone because of the additional methylene, and what exchange does occur proceeds *via* a different mechanism.

The difference in exchange behavior between the acylamino and acylimino imidazolinones is readily explained by their pK_a differences. Compound **48** possesses a pK_a of approximately 8–9, whereas the values of the other imidazolinones are in the 4–5 region.[30,31] Therefore, at pD 7, **48** would be greater than 90% protonated while the acylimino imidazolinones are less than 1% protonated. Because exchange requires the protonated species **52**, only **52a** (R_1 = CH_3; R_2 = D) exists in a concentration large enough to yield rapid exchange. As one progresses to pD 3, the rate of exchange for the acylimino imidazolinones increases to a rate comparable to that of the acylamino compound at pD 7, as expected, since the necessary intermediate **52b** (R_1 = D; R_2 = CH_3) now represents approximately 90% of the total concentration. The rate of exchange for **53** at pD **3** is very rapid and is matched by **50** only when the pD is lowered to 1.



a, R_1 = CH_3; R_2 = D
b, R_1 = D; R_2 = CH_3

In the higher pD region, the exchange mechanism probably involves simply proton removal from C-5 followed by deuteration. Such polar abstraction is reported to be accomplished with triethylamine in the oxazolinone series[33,36,37] and it would seem unlikely that the mechanism would differ significantly with the imidazolinones.

Experimental Section[38]

***N*-(Methylmercapto-*N*-*p*-toluenesulfonylcarbonimidoyl)-β-alanine (4b).**—A solution of 0.445 g (5 mmol) of β-alanine, 12.5 ml of ethanol, 5 ml of 1 *N* NaOH solution, and 1.38 g (5 mmol) of *S*,*S*-dimethyl-*N*-*p*-toluenesulfonyliminodithiocarboimidate (**3**)[13] was heated at reflux for 5.5 hr. Upon cooling in an ice bath, acidification with 5 ml of 1 *N* HCl solution, and standing for 2 days, 1.12 g (71%) of crystals of **4b** formed: mp 114–116°; nmr

(32) E. Brunn, E. Funke, H. Gotthardt, and R. Huisgen, *Chem. Ber.*, **104**, 1562 (1971), and references cited therein.

(33) G. V. Boyd and P. H. Wright, *J. Chem. Soc., Perkin Trans. 1*, 914 (1972).

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(CF_3COOH) δ 7.40–8.08 (AB q, 4 H), 3.95 (m, 2 H), 2.97 (t, 2 H), 2.68 (s, 3 H), and 2.48 (s, 3 H).

Anal. Calcd for $C_{12}H_{16}N_2O_4S_2$: C, 45.6; H, 5.1; N, 8.9; S, 20.3. Found: C, 45.4; H, 5.3; N, 8.7; S, 20.2.

N-(**Methylmercapto-*N*-*p*-toluenesulfonylcarbonimidoyl)-β-alanine Methyl Ester (5b).**—Stirring a solution of 0.250 g (0.79 mmol) of 4b, 1.12 g (7.90 mmol) of methyl iodide, and 10 ml of methanol overnight at room temperature followed by heating at reflux for 3 hr and removal of methanol yielded 0.16 g (60%) of ester **5b**: mp 125–126°; nmr (CF_3COOH) δ 7.38–7.98 (AB q, 4 H), 3.97 (m, 2 H), 3.85 (s, 3 H), 2.92 (t, 2 H), 2.67 (s, 3 H), and 2.47 (s, 3 H); uv (90% EtOH) λ_{max} 239 nm (ε 19,820).

Anal. Calcd for $C_{13}H_{18}N_2O_4S_2$: C, 47.3; H, 5.5; N, 8.5; S, 19.4. Found: C, 47.3; H, 5.4; N, 8.7; S, 19.3.

N-(**Methylmercapto-*N*-*p*-toluenesulfonylcarbonimidoyl)glycine Methyl Ester (5a).**—A solution of 0.453 g (1.5 mmol) of *N*-(methylmercapto-*N*-*p*-toluenesulfonylcarbonimidoyl)glycine (**4a**),[14] 0.315 g (1.65 mmol) of tris(2-hydroxypropyl)amine, 0.227 g (1.80 mmol) of dimethyl sulfate, and 20 ml of methanol was boiled for 1 hr. Cooling gave crystals which were recrystallized from methanol to yield 0.44 g (93%) of ester **5a**, mp 119–120°.

Anal. Calcd for $C_{12}H_{16}N_2O_4S_2$: C, 45.6; H, 5.1; N, 8.9; S, 20.3. Found: C, 45.3; H, 5.2; N, 9.0; S, 20.0.

N-(**Methylmercapto-*N*-*p*-toluenesulfonylcarbonimidoyl)glycine Ethyl Ester (5c).**—The ethyl ester was prepared by boiling a solution of 3.15 g of **4a**[14] in 30 ml of absolute ethanol containing 2 ml of concentrated sulfuric acid. Water (50 ml) was added, the aqueous phase was extracted with benzene, and the benzene layer was washed with aqueous Na_2CO_3 and water, and then dried. Evaporation and crystallization of the residue from ethanol gave ethyl ester **5c**: 2.94 g (87%); mp 119–120°; nmr δ 7.90–7-25 (q, 4 H), 4.18 (d, 2 H), 4.15 (q, 2 H), 2.44 (s, 3 H), 2.40 (s, 3 H), and 1.04 (t, 3 H); mass spectrum *m/e* 330 (M^+), 285 ($M^+ - OC_2H_5$).

Anal. Calcd for $C_{13}H_{18}N_2O_4S_2$: C, 47.3; H, 5.5; N, 8.5; S, 19.4. Found: C, 47.1; H, 5.6; N, 8.6; S, 19.2.

N-*p*-**Toluenesulfonyl-*N*′-methyl-*N*′-(2-ethoxycarbonylethyl)-*N*″-(2-methoxycarbonylethyl)guanidine (8a).**—To a solution of 0.66 g (2 mmol) of **5b**, 1.05 g (8.0 mmol) of ethyl 3-*N*-methylaminopropionate,[39] and 0.20 g (2 mmol) of Et_3N in 30 ml of acetonitrile, cooled in an ice bath, was added dropwise a solution containing 0.34 g (2 mmol) of $AgNO_3$ in 3 ml of acetonitrile. An immediate yellow precipitate of $AgSCH_3$ formed. The mixture was allowed to warm to room temperature and was stirred overnight. The $AgSCH_3$ was removed by centrifugation, sonicated three times with acetonitrile, and recentrifuged three times. Removal of the acetonitrile gave a red oil, which was placed on a column containing 80 g of silica gel and eluted with 2% CH_3OH–$CHCl_3$. Three 50-ml fractions were initially taken followed by 15 25-ml fractions. Combining fractions 11–16 gave 0.57 g (68%) of the guanidine **8a**: R_f 0.51 with 2% CH_2OH–$CHCl_3$ and 0.65 with 5% CH_3OH–$CHCl_3$ on silica gel; uv λ_{max} 230 nm (ε 15,320); nmr (CF_3COOH) δ 7.95–7.39 (AB q, 4 H), 4.29 (q, 2 H), 3.79 (s, 3 H), 3.74 (m, 4 H), 3.15 (s, 3 H), 2.83 (broad s, 4 H), 2.48 (s, 3 H), 1.28 (t, 3 H).

Anal. Calcd for $C_{18}H_{27}N_3O_6S$: C, 52.3; H, 6.6; N, 10.2; S, 7.8. Found: C, 52.0; H, 6.6; N, 10.1; S, 8.0.

N-*p*-**Toluenesulfonyl-*N*′-methyl-*N*′-(2-ethoxycarbonylethyl)-*N*″-ethoxycarbonylmethylguanidine (8b).**—To 15 ml of glacial acetic acid cooled in an ice bath and saturated with Cl_2 gas was added 330 mg (1 mmol) of **5c** and the solution was allowed to stir at 14° for 3 hr. The excess Cl_2 was removed *in vacuo* at room temperature and the acetic acid was removed by lyophilization to yield **6** ($x = 1$; $R_1 = C_2H_5$) as a crystalline, colorless solid. This solid was dissolved in 5 ml of acetonitrile, cooled in an ice bath, and treated dropwise with a solution of ethyl 3-*N*-methylaminopropionate (262 mg, 2.0 mmol)[39] in 3 ml of acetonitrile. The solution was allowed to stir for 3 hr at ice-bath temperature and then overnight at room temperature. Removal of the solvent gave a pale yellow oil which was purified by chromatography on a 30-g silica gel column, eluting with 5% CH_3OH–$CHCl_3$. The product, guanidine **8b**, was obtained crystalline from ethanol–ether: 380 mg (92%); mp 104–105°; nmr δ 7.8–7.0 (AB q, 4 H), 4.2–3.8 (q plus d, 6 H, 2-OCH_2– and NCH_2C=O) 3.50 (t, 2 H, NCH_2–), 2.82 (s, 3 H, NCH_3), 2.43 (t, 2 H, –CH_2–C=O), 2.28 (s, 3 H, CH_3), 1.08 (t, 6 H, CH_3C); mass spectrum *m/e* 413 (M^+), 368 ($M^+ - OC_2H_5$).

Anal. Calcd for $C_{15}H_{27}N_3O_6S$: C, 52.3; H, 6.6. Found: C, 51.9; H, 6.7.

N-(**Methylmercaptochloromethylene)-*p*-toluenesulfonimide (9).**—The dithiocarbonimidate **3**, 1.38 g (5.0 mmol), in 20 ml of CCl_4 containing 0.40 ml (5.0 mmol) of SO_2Cl_2 was heated at reflux for 9 hr and then stirred at room temperature overnight. Removal of the solvent and chromatography on silica gel, eluting with $CHCl_3$, gave 0.98 g (68%) of **9**: mp 84–87° (lit.[19] mp 89–90°); nmr δ 7.90–7.25 (AB q, 4 H), 2.48 (s, 6 H).

N-*p*-**Toluenesulfonyl-*N*′-methyl-*N*′-ethoxycarbonylmethyl-*S*-methylisothiourea (10b).**—*N*-(Methylmercaptochloromethylene)-*p*-toluenesulfonimide (**9**) (0.33 g, 1.2 mmol) was dissolved in 8 ml of acetonitrile, and after cooling in an ice bath, a solution of sarcosine ethyl ester (0.336 g, 2.87 mmol)[40] in 2 ml of acetonitrile was added dropwise. The solution was allowed to stir for 1 hr at 0°, then 40 hr at room temperature. Removal of the solvent and chromatography on 50 g of silica gel, eluting with 2% CH_3OH–$CHCl_3$, gave the isothiourea **10b**: 0.344 g (87%); mg 99–100°; nmr (CF_3COOH), δ 7.91–7.30 (AB q, 4 H), 4.57 (s 2 H), 4.28 (q, 2 H), 3.43 (s, 3 H), 2.54 (s, 3 H), 2.43 (s, 3 H), 1.29 (t, 3 H).

Anal. Calcd for $C_{14}H_{20}N_2O_4S_2$: C, 48.8; H, 5.9; N, 8.1; S, 18.6. Found: C, 48.7; H, 5.8; N, 8.0; S, 18.6.

N′,*N*′,*S*-**Trimethyl-*N*-*p*-toluenesulfonylcarbonimidate (10a).**—To 6.5 g (25 mmol) of **9** dissolved in 100 ml of acetonitrile and cooled to 0° was added 50 ml of an acetonitrile solution containing 4 ml of dimethylamine. The temperature was maintained at 0° for 3 hr and then allowed to warm to room temperature. After being stirred overnight, the solution was stripped to dryness and the residue was purified by chromatography on silica gel using 2% CH_3OH–$CHCl_3$ as the eluent. The imidate **10a** was obtained in 84% yield (5.6 g): mp 55–57°; nmr δ 7.52 (AB q, 4 H), 3.20 (s, 6 H), 2.42 (s, 3 H), 2.38 (s, 3 H).

Anal. Calcd for $C_{11}H_{16}N_2O_2S_2$: C, 48.5; H, 5.9; S, 23.5. Found: C, 48.5; H, 5.8; S, 23.8.

N-*p*-**Toluenesulfonyl-*N*′,*N*′,*N*″-trimethyl-*N*‴-ethoxycarbonylmethylguanidine (12a).**—Glacial acetic acid (100 ml) saturated with Cl_2 at 0° was treated dropwise with stirring with 6.36 g (18.6 mmol) of **10a** in 50 ml of glacial acetic acid. The solution was stirred at 5–10° for 2 hr and the solvent and Cl_2 were removed by aspiration. To the residue of **11a** dissolved in 100 ml of acetonitrile and cooled to 0° was added over 10 min, with rapid stirring, 4.40 g (37.6 mmol) of sarcosine ethyl ester dissolved in 25 ml of acetonitrile. After being allowed to warm to room temperature, the reaction mixture was stirred overnight. The solvent was removed by aspiration and the residue was chromatographed on silica gel to yield the product **12a**: 3.8 g (11.2 mmol, 60%); mp 121–122°; nmr δ 7.50 (AB q, 4 H), 4.12 (s, 2 H), 4.03 (q, 2 H), 3.04 (s, 6 H), 2.94 (s, 3 H), 2.36 (s, 3 H), 1.23 (t, 3 H); uv λ_{max} 237 nm.

Anal. Calcd for $C_{15}H_{23}N_3O_4S$: C, 52.8; H, 6.8; N, 12.3. Found: C, 52.6; H, 6.8; N, 12.2.

N-*p*-**Toluenesulfonyl-*N*′,*N*″-dimethyl-*N*′,*N*″-di(ethoxycarbonylmethyl)guanidine (12b).** **A.**—To 12 ml of glacial acetic acid, cooled in an ice bath and saturated with Cl_2, was added dropwise a solution containing 0.27 g (0.78 mmol) of isothiourea **10b** dissolved in 3 ml of glacial acetic acid. The slush was stirred for 2 hr at 14°, the excess Cl_2 was removed by aspiration, and the acetic acid was removed by lyophilization. The resulting yellow oil **11b** was sonicated with three 5-ml portions of petroleum ether (bp 30–60°), dissolved in 5 ml of acetonitrile, and cooled in an ice bath. A solution containing 0.227 g (1.94 mmol) of sarcosine ethyl ester was added dropwise to the cold solution, which was then allowed to stir for 3 hr at 0° and overnight at room temperature. Removal of the solvent gave an oil which was chromatographed on silica gel (30 g), eluting with 2% CH_3OH–$CHCl_3$. A 0.181-g (56.5%) yield of guanidine **14b** was obtained: mp 82–83°; nmr δ 7.92–7.08 (AB q, 4 H), 4.25 (s, 4 H), 4.09 (q, 4 H), 3.06 (s, 6 H), 2.37 (s, 3 H), 1.20 (t, 6 H).

Anal. Calcd for $C_{18}H_{27}N_3O_6S$: C, 52.3; H, 6.6; N, 10.2; S, 7.8. Found: C, 52.5; H, 6.6; N, 10.0; S, 7.7.

B.—To an ice-cooled solution of 1.76 g (7 mmol) of *N*-*p*-toluenesulfonylimidocarbonyl chloride (**13**)[19] in 25 ml of acetonitrile was added dropwise over 40 min a solution of 3.44 g (29.4 mmol) of sarcosine ethyl ester in 5 ml of acetonitrile. The reaction solution was allowed to stir at 0° for 2 hr, then overnight at room temperature. Removal of the solvent *in vacuo* and chro-

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matography of the residue on silica gel, eluting with 2% CH_3OH–$CHCl_3$, gave **12b** in 75% yield.

N-*p*-**Toluenesulfonyl**-*N'*,*N''*-**dimethyl**-*N'N''*-**di(carboxymethyl)guanidine Disodium Salt (12c).**—A suspension of 2.2 g of **12b** and 235 ml of 0.05 *N* NaOH (dioxane–water) was heated at 70° and stirred overnight. Removal of the solvent by lyophilization gave 2.8 g of a crude product which was digested in hot ethanol, cooled, and filtered to give the purified disodium salt **12c**: nmr (D_2O) δ 7.50 (AB q, 4 H), 3.88 (s, 4 H), 3.00 (s, 6 H), 2.40 (s, 3 H); uv λ_{max} 240 nm.

Anal. Calcd for $C_{14}H_{17}N_3O_6SNa_2$: N, 10.4. Found: N, 10.1.

N-*p*-**Toluenesulfonyl**-*N'*-**methyl**-*N'*-**(2-ethoxycarbonylethyl)thiourea (15).**—*p*-Toluenesulfonyl isothiocyanate (**14**)[16] (2.13 g, 10 mmol), dissolved in 3.5 ml of ether and cooled in an ice bath, was treated dropwise with a solution containing 1.31 g (10 mmol) of ethyl β-*N*-methylaminopropionate dissolved in 4 ml of ether. The mixture was stirred for 2 hr at 0° and 3 hr at room temperature, then filtered to give a quantitative yield of thiourea **15**: mp 122–123° after recrystallization from benzene–ether; nmr (CF_3COOH) δ 7.94–7.28 (AB q, 4 H), 4.24 (q, 2 H), 4.02 (t, 2 H), 3.30 (s, 3 H), 2.88 (t, 2 H), 2.43 (s, 3 H), 1.30 (t, 3 H).

Anal. Calcd for $C_{14}H_{20}N_2O_4S_2$: C, 48.8; H, 5.9; N, 8.1; S, 18.6. Found: C, 48.6; H, 5.8; N, 8.3; S, 18.8.

N-*p*-**Toluenesulfonyl**-*N'*-**methyl**-*N'*-**(2-methoxycarbonylethyl)**-*S*-**methylisothiourea (16).**—The thiourea **15**, 0.67 g (2 mmol), 0.42 g (2.2 mmol) of tris(2-hydroxypropyl)amine, 0.3 g (2.4 mmol) of dimethyl sulfate, and 4 ml of methanol were heated at reflux for 1 hr. Evaporation of the methanol and chromatography of the residue on silica gel, eluting with 2% CH_3OH–$CHCl_3$, gave the *S*-methylisothiourea **16**: mp 47–48°; R_f 0.59 on silica gel, eluting with 2% MeOH–$CHCl_3$; nmr (CF_3COOH) δ 7.98–7.38 (AB q, 4 H), 3.94 (m, 2 H), 3.83 (s, 3 H), 3.49 (s, 3 H), 2.96 (t, 2 H), 2.71 (s, 3 H), 2.48 (s, 3 H).

Anal. Calcd for $C_{14}H_{20}N_2O_4S_2$: C, 48.8; H, 5.9; N, 8.1; S, 18.6. Found: C, 49.0; H, 6.0; N, 8.2; S, 18.8.

N-*p*-**Toluenesulfonyl**-*N'*,*N''*-**dimethyl**-*N'*-**(2-ethoxycarbonylethyl)**-*N''*-**(2-methoxycarbonylethyl)guanidine (17a).**—The *S*-methylisothiourea **16** (1.0 g, 2.9 mmol) dissolved in 2 ml of glacial acetic acid was added dropwise to 15 ml of glacial acetic acid saturated with Cl_2. Following the addition, Cl_2 was again passed into the slush until saturation was achieved. The solution was allowed to stir at 14° for 2 hr, the excess Cl_2 was removed *in vacuo*, and the glacial acetic acid was removed by lyophilization. The residual oil was sonicated with three 5-ml portions of petroleum ether (bp 30–75°), dissolved in 5 ml of acetonitrile, and cooled in an ice bath. To this cold solution was added dropwise an acetonitrile solution containing 0.76 g (5.80 mmol) of ethyl β-*N*-methylaminopropionate. The clear solution was allowed to stir for 3 hr in an ice bath and then overnight at room temperature. Removal of the solvent and purification of the residue *via* a silica gel column, eluting with 4% CH_3OH–$CHCl_3$, gave 0.472 g (38%) of guanidine **17a** as an oil: R_f 0.56 on silica gel with 4% CH_3OH–$CHCl_3$; nmr (CF_3COOH) δ 8.02–7.43 (AB q, 4 H), 4.28 (q, 2 H), 3.82 (s, 3 H), 3.60–3.92 (m, 4 H), 3.18 (s, 6 H), 2.89 (t, 4 H), 2.49 (s, 3 H), 1.30 (t, 3 H).

Anal. Calcd for $C_{19}H_{29}N_3O_6S$: C, 53.4; H, 6.8; N, 9.8; S, 7.5. Found: C, 53.0; H, 6.6; N, 9.8; S, 7.3.

N-*p*-**Toluenesulfonyl**-*N'*,*N''*-**dimethyl**-*N'*-**(ethoxycarbonylmethyl)**-*N''*-**(2-methoxycarbonylethyl)guanidine (17b).**—The experimental procedure described above was followed in detail employing the following quantities: *N*-*p*-toluenesulfonyl-*N'*-methyl-*N'*-(2-methoxycarbonylethyl)-*S*-methylisothiourea (**16**), 0.82 g (2.39 mmol); sarcosine ethyl ester, 0.56 g (4.8 mmol). The yield was 0.76 g (77%) of guanidine **17b** as an oil: nmr (CF_3COOH) δ 7.99–7.48 (AB q, 4 H), 4.39 (s, 2 H), 4.33 (q, 2 H), 3.84 (s, 3 H), 3.80–3.60 (m, 2 H), 3.29 (s, 3 H), 3.25 (s, 3 H), 3.08–2.08 (m, 2 H), 2.52 (s, 3 H), 1.33 (t, 3 H).

Anal. Calcd for $C_{18}H_{27}N_3O_6S$: C, 52.3; H, 6.6; N, 10.2; S, 7.8. Found: C, 51.9; H, 6.4; N, 10.0: S, 7.5.

2-*p*-Toluenesulfonamido-4-methylpyrimidine (19).—*p*-Toluenesulfonyl chloride (3.80 g, 20 mmol) was added gradually to a solution of 2-amino-4-methylpyrimidine (**18**, 1.08 g, 10 mmol)[41] in 5 ml of pyridine. After stirring at 60° for 2.5 hr, 4 ml of 5 *N* sodium hydroxide was added, the mixture was evaporated to dryness, and the residue was digested in water, cooled, and filtered. Washing with water and crystallization from ethanol gave 1.98 g (76%) of 2-*p*-toluenesulfonamido-4-methylpyrimidine: mp 230–232°; nmr δ 8.41 (d, 1 H), 8.01 (d, 2 H), 7.08 (d, 2 H), 6.66 (d, 1 H), 2.35 (s, 6 H); ir (KBr) 6.28, 6.39 μ; uv λ_{max} 264 nm (ε 4080), 232 (15,600), 218 (15,400).

Anal. Calcd for $C_{12}H_{13}N_3O_2S$: C, 54.8; H, 5.0; N, 16.0. Found: C, 54.8; H, 5.0; N, 15.8.

Alkylation of 2-*p*-Toluenesulfonamido-4-methylpyrimidine (19).—The sodium salt of **19** was generated by the addition of an ethanolic solution of the pyrimidine (1 mol) to a sodium ethoxide (1.05 mol)–ethanol solution, and the cooled suspension was evaporated to dryness. The residue was dissolved in DMSO, a 10% excess of the alkylating agent was added, and the reaction mixture was stirred at room temperature for 2–10 hr, followed by removal of the DMSO at reduced pressure. The residue was partitioned between water and chloroform, and the organic phase was chromatographed employing $CHCl_3$ and 5% C_2H_5OH–$CHCl_3$ as eluents to achieve exo and endo isomer separation. The exo isomers were eluted with chloroform, after which the endo isomers could be quickly eluted with 5% C_2H_5OH–$CHCl_3$, the overall yield of the isomers ranging from 70 to 80%.

2-(*N*-Methyl-*p*-toluenesulfonamido)-4-methylpyrimidine (20a) (yield 52%) had mp 62–63°; nmr δ 8.24 (d, 1 H, J = 4.9 Hz), 7.93 (d, 2 H), 7.23 (d, 2 H), 6.68 (d, 1 H, J = 4.9 Hz), 3.66 (s, 3 H), 2.35 (s, 6 H); ir ($CHCl_3$) 6.34, 6.43 μ; uv λ_{max} 264 nm (ε 4860), 223 (19,800).

Anal. Calcd for $C_{13}H_{15}N_3O_2S$: C, 56.3; H, 5.5; N, 15.2. Found: C, 56.3; H, 5.4; N, 15.2.

1,4-Dimethyl-2-*p*-toluenesulfonimidopyrimidine (21a) (yield 18%) had mp 178–181°; nmr δ 7.89 (d, 2 H), 7.88 (d, 1 H, J = 6.6 Hz), 7.16 (d, 2 H), 6.37 (d, 1 H, J = 6.6 Hz), 3.63 (s, 3 H), 2.40 (s, 3 H), 2.34 (s, 3 H); ir (KBr) 6.15, 6.50 μ; uv λ_{max} 318 nm (ε 4330), 252 (20,900), 223 (12,700).

Anal. Calcd for $C_{13}H_{15}N_3O_2S$: C, 56.3; N, 5.5; N, 15.2. Found: C, 53.4; H, 5.5; N, 14.9.

2-(*N*-Methoxycarbonylmethyl-*p*-toluenesulfonamido)-4-methylpyrimidine (20b) (yield 28%) had mp 120–122°; nmr δ 8.15 (d, 1 H, J = 5.3 Hz), 8.07 (d, 2 H), 7.23 (d, 2 H), 6.65 (d, 1 H, J = 5.3 Hz), 4.98 (s, 2 H), 3.72 (s, 3 H), 2.35 (s, 6 H); ir ($CHCl_3$) 5.67, 6.31, 6.42 μ; uv λ_{max} 265 (s), 222 nm.

Anal. Calcd for $C_{15}H_{17}N_3O_4S$: C, 53.7; H, 5.1; N, 12.5. Found: C, 53.6; H, 5.0; N, 12.4.

1-Methoxycarbonylmethyl-2-*p*-toluenesulfonimido-4-methyl-1,2-dihydropyrimidine (21b) (yield 52%) had mp 163–164°; nmr (DMSO-d_6) δ 8.15 (d, 1 H, J = 6.7 Hz), 7.68 (d, 2 H), 7.27 (d, 2 H), 6.68 (d, 1 H, J = 6.7 Hz), 4.83 (s, 2 H), 3.67 (s, 3 H), 2.30 (s, 6 H); ir (KBr) 5.72, 6.15, 6.49 μ; λ_{max} 316, 245, 216 nm.

Anal. Calcd for $C_{15}H_{17}N_3O_4S$: C, 53.7; H, 5.1; N, 12.5. Found: C, 53.7; H, 5.2; N, 12.5.

Oxidation of 4-Methylpyrimidines 19 and 21b. 2-*p*-Toluenesulfonamido-4-cyanopyrimidine (22a).—To a stirring solution of 8.10 g (31 mmol) of 2-tosylamido-4-methylpyrimidine (**19**) in concentrated hydrochloric–acetic acid (1:9) was added rapidly sodium nitrite (3.7 g, 55 mmol). The reaction mixture was stirred at room temperature for 2 hr and the solid which formed was removed by filtration, washed with water, and dried *in vacuo* to yield 6.95 g (25.4 mmol, 82%) of **22a**: mp 201–203°; nmr (DMSO-d_6) δ 8.58 (d, 1 H, J = 5 Hz), 7.98 (d, 2 H), 7.43 (d, 1 H, J = 5 Hz), 7.38 (d, 2 H), 2.35 (s, 3 H); ir (KBr) 6.38 μ.

2-*p*-Toluenesulfonamido-4-methoxycarbonylpyrimidine (23).—Concentrated sulfuric acid (1.8 ml, 32 mmol) was added to a mixture of **22a** (274 mg, 1.00 mmol) and 10 ml of methanol. After the mixture was heated at reflux for 72 hr, the solid which remained was removed by filtration, washed with methanol, and dried to yield 142 mg (0.46 mmol, 46%) of the ester **23**: mp 236–238°; nmr (DMSO-d_6) δ 8.70 (d, 1 H, J = 5.0 Hz), 7.95 (d, 2 H), 7.51 (d, 1 H, J = 5 Hz), 7.33 (d, 2 H), 3.92 (s, 3 H), 2.37 (s, 3 H); ir (KBr) 5.37, 6.37 μ; uv λ_{max} 297 nm (ε 2930), 275 (2090), 235 (17,600), 222 (15,600).

Anal. Calcd for $C_{13}H_{13}N_3O_4S$: C, 50.8; H, 4.3. Found: C, 50.6; H, 4.1.

2-*p*-Toluenesulfonamido-4-β-styrylpyrimidine (22b).—2-Tosylamido-4-methylpyrimidine (**19**, 1.33 g, 5 mmol), benzaldehyde (1 ml), glacial acetic acid (3 ml), and concentrated hydrochloric acid (1 ml) were heated at reflux for 12 hr. The reaction solution was concentrated and the brown gum which remained was triturated with acetone to give 1.19 g (3.4 mmol, 68%) of pure **22b**, mp 263–265°.

Anal. Calcd for $C_{19}H_{17}N_3O_2S$: C, 64.9; N, 4.9; N, 12.0. Found: C, 64.8; H, 4.7; N, 12.1.

(41) D. M. Burness, *J. Org. Chem.*, **21**, 97 (1956).

1-Methoxycarbonylmethyl-2-*p*-toluenesulfonimido-4-cyano-1,2-dihydropyrimidine (26a).—To 671 mg (2.0 mmol) of 1-methoxycarbonylmethyl-2-tosylimido-4-methylpyrimidine (**21b**) in glacial acetic acid were added sequentially with stirring concentrated hydrochloric acid (0.5 ml) and sodium nitrite (221 mg, 3.2 mmol). The solution was stirred at room temperature for 1.5 hr and the solid which formed was removed by filtration, washed with water, and dried to give 550 mg (1.6 mmol, 80%) of **26a**: mp 199–199.5°; nmr (DMSO-d_6) δ 8.57 (d, 1 H, J = 6.8 Hz), 7.80 (d, 2 H), 7.27 (d, 1 H, J = 6.8 Hz), 7.21 (d, 2 H), 4.94 (s, 2 H), 3.70 (s, 3 H), 2.33 (s, 3 H); ir (KBr) 5.72, 6.18, 6.48 μ; uv λ_{max} 365 nm (ϵ 3200), 253 (19,700), 224 (18,800); mass spectrum m/e 282 ($M^+ - 64$), 281 ($M^+ - 65$).

1-Methoxycarbonylmethyl-2-*p*-toluenesulfonimido-4-β-styryl-1,2-dihydropyrimidine (26b).—A solution consisting of **21b** (6.68 g, 20 mmol), benzaldehyde (15 ml), and acetic acid (60 ml) was heated at reflux for 18 hr. The solvent was removed by distillation, the residue was triturated with ethyl acetate, and the precipitate was collected by filtration, washed with ethyl acetate, and recrystallized from ethyl acetate–methanol to give 5.95 g (14 mmol, 70%) of **26b**: mp 180–182°; nmr (DMSO-d_6) δ 8.28 (d, 1 H, J = 7 Hz), 7.18–7.82 (11 H), 6.97 (d, 1 H, J = 7 Hz), 4.90 (s, 2 H), 3.73 (s, 3 H), 2.30 (s, 3 H); ir (KBr) 5.72, 6.22, 6.55 μ; uv λ_{max} 343 nm (ϵ 23,800), 246 (16,700), 225 (17,100).

Anal. Calcd for $C_{22}H_{21}N_3O_4S$: C, 62.4; H, 5.0; N, 9.9. Found: C, 62.2; H, 5.0; N, 10.1.

Alkylation of 2-*p*-Toluenesulfonamido-4-methoxycarbonylpyrimidine (23).—To a hot solution of 0.90 g (2.9 mmol) of **23** in methanol was added a solution of sodium methoxide (69 mg of sodium dissolved in methanol). The resulting solution was evaporated and the residue was dissolved in DMSO. Methyl bromoacetate (2.9 mmol) was added and the reaction mixture was stirred at room temperature for 5 hr. The solvent was removed *in vacuo*, the residue was partitioned between $CHCl_3$ and H_2O, the organic layer was washed twice with H_2O, dried, and concentrated, and the concentrate was chromatographed on silica gel. Elution with $CHCl_3$ gave the exo and endo isomers in 40 and 30% yields, respectively. The exo isomer **24** had mp 118–120°; nmr δ 8.56 (d, 1 H), 8.5 (d, 2 H), 7.48 (d, 1 H), 7.23 (d, 2 H), 5.03 (s, 2 H), 3.99 (s, 3 H), 3.75 (s, 3 H), 2.40 (s, 3 H); ir ($CHCl_3$) 5.73, 6.38 μ; uv λ_{max} 295, 276, 231 (s), 222 nm. The endo isomer **25** had mp 145–148°; nmr δ 8.05 (d, 1 H), 8.00 (d, 2 H), 7.21 (d, 2 H), 7.13 (d, 1 H), 4.90 (s, 2 H), 3.98 (s, 3 H), 3.74 (s, 3 H), 2.38 (s, 3 H); ir (KBr) 5.78, 6.18, 6.49 μ; uv λ_{max} 360, 252.5, 222 nm.

Anal. Calcd for $C_{16}H_{17}N_3O_6S$: C, 50.7; H, 4.5; N, 11.1. Found: C, 50.4; H, 4.8; N, 10.9.

Sodium 2-*p*-Toluenesulfonamido-4-oxo-5-ethoxycarbonylpyrimidinate (29).—Tosylguanidine (**27**, 118.0 g, 0.56 mol) was added to 700 ml of 0.97 N sodium ethoxide in ethanol; the mixture was brought to reflux and diethyl ethoxymethylenemalonate (**28**, 142.5 g, 0.66 mol) was added over a 20-min period. After heating at reflux for 12 hr, the mixture was cooled and filtered. The precipitate was washed with ethanol and dried to give 192.1 g (0.54 mol, 96.4%) of the pale yellow salt **29**: mp 347–349° dec; nmr (DMSO-d_6) δ 8.25 (s, 1 H), 7.70 (d, 2 H), 7.20 (d, 2 H), 4.10 (q, 2 H), 2.32 (s, 3 H), 1.20 (t, 3 H); ir (KBr) 5.80, 6.43, 6.53 μ.

2-*p*-Toluenesulfonamido-4-chloro-5-ethoxycarbonylpyrimidine (30).—To 100 g (0.28 mol) of the sodium salt **29** was added slowly 1 l. of phosphorus oxychloride. The mixture was gradually warmed and maintained at 110° for 5 hr. The solvent was removed *in vacuo*, the residue was partitioned between ice water and chloroform, and the organic layer was washed twice with water, dried, and evaporated to yield 95.0 g (0.27 mol, 96%) of the chloropyrimidine **30**, recrystallized from 2-propanol: mp 183–185°; nmr δ 8.85 (s, 1 H), 7.98 (d, 2 H), 7.25 (d, 2 H), 4.35 (q, 2 H), 2.42 (s, 3 H), 1.37 (t, 3 H); ir (KBr) 5.75, 5.80, 6.32 μ; uv λ_{max} 254, 230 nm.

Anal. Calcd for $C_{14}H_{14}N_3O_4SCl$: C, 47.3; H, 4.0; N, 11.8. Found: C, 47.2; H, 3.9; N, 11.8.

2-*p*-Toluenesulfonamido-5-carboxypyrimidine (31).—To 30 ml of 0.67 N sodium hydroxide were added 2.47 g (7.0 mmol) of **30** and 0.43 g of 10% palladium on carbon. The mixture was shaken for 2 hr on a Parr hydrogenator, by which time hydrogen uptake had ceased. The catalyst was removed by filtration, the carboxylic acid was precipitated by acidification with hydrochloric acid, and the white precipitate was collected and crystallized from 2-propanol to give 2.0 g (6.8 mmol, 97%) of **31**: mp 300–303° dec; nmr (DMSO-d_6) δ 8.85 (s, 2 H), 7.88 (d, 2 H), 7.32 (d, 2 H), 2.37 (s, 3 H); ir (KBr) 5.68, 6.26 μ; uv λ_{max} 248, 228 nm.

Anal. Calcd for $C_{12}H_{11}N_3O_4S$: C, 49.1; H, 3.8; N, 14.3. Found: C, 48.9; H, 3.9; N, 14.3.

2-*p*-Toluenesulfonamido-5-ethoxycarbonylpyrimidine (32).—2-Tosylamido-5-carboxypyrimidine (**31**, 27.7 g, 95 mmol) was heated at reflux in 100 g of thionyl chloride until hydrogen chloride evolution ceased. The solvent was removed by distillation, absolute ethanol was added, and the mixture was heated at reflux for 4 hr. The precipitate which formed upon cooling was collected, a second crop which formed in the filtrate was added, and the combined ethyl ester **32**, 25.4 g (79 mmol, 83%), one spot by tlc, was recrystallized from 2-propanol: mp 186–187°; nmr δ 9.13 (s, 2 H), 7.98 (d, 2 H), 7.27 (d, 2 H), 4.38 (q, 2 H), 2.40 (s, 3 H), 1.37 (t, 3 H); ir (KBr) 5.78, 6.25 μ; uv λ_{max} 252, 228 nm.

Anal. Calcd for $C_{14}H_{15}N_3O_4S$: C, 52.3; H, 4.7; N, 13.1. Found: C, 52.3; H, 4.7; N, 12.8.

Exo and Endo *N*-Methyl Isomers 33a and 34a.—To a hot suspension of 2-tosylamido-5-ethoxycarbonylpyrimidine (**32**, 22.8 g, 7 mmol) in absolute ethanol (500 ml) was added 100 ml of 0.8 N sodium ethoxide–ethanol. After heating for 15 min, the suspension was evaporated to dryness, the sodium salt was dissolved in 250 ml of DMSO, methyl iodide (7 ml) was added, and the solution was stirred at room temperature for 10 hr. The solvent was removed *in vacuo*, the residue was partitioned between water and chloroform, and the organic phase was washed twice with water, dried, evaporated, and chromatographed, the exo isomer **33a** being eluted with $CHCl_3$ (11.3 g, 34.5 mmol, 49%) and the endo isomer **34a** with 3% C_2H_5OH–$CHCl_3$ (10.6 g, 31.8 mmol, 45%).

Exo isomer 33a had mp 100–101; nmr δ 8.97 (s, 2 H), 7.93 (d, H), 7.25 (d, 2 H), 4.35 (q, 2 H), 3.72 (s, 3 H), 2.38 (s, 3 H), 1.35 (t, 3 H); ir ($CHCl_2$) 5.82, 6.28 μ; uv λ_{max} 260 nm (ϵ 21,800), 231.5 (14,800).

Anal. Calcd for $C_{15}H_{17}N_3O_4S$: C, 53.7; H, 5.1; N, 12.5. Found: C, 53.5; H, 5.0; N, 12.5.

Endo isomer 34a had mp 223–225°; nmr δ 8.83 (d, 1 H, 1.3 Hz), 8.50 (d, 1 H, 1.3 Hz), 7.80 (d, 2 H), 4.27 (q, 2 H), 3.68 (s, 3 H), 2.33 (s, 3 H), 1.30 (t, 3 H); ir ($CHCl_3$) 5.82, 6.11 μ; uv λ_{max} 323 nm (ϵ 3100), 275 (33,700), 223 (17,200).

Anal. Calcd for $C_{15}H_{17}N_3O_4S$: C, 53.7; H, 5.1; N, 12.5. Found: C, 53.6; H, 5.2; N, 12.7.

Exo and Endo Ethoxycarbonylmethyl Isomers 33b and 34b.—The same procedure as above, substituting ethyl bromoacetate for methyl iodide, was used on a 2.0-mmol scale to give 30 mg (0.08 mmol, 4%) of the exo isomer **33b** and 69 mg (1.7 mmol, 85%) of the endo isomer **34b**.

Exo isomer 33b had mp 122–124° from 2-propanol; nmr δ 8.85 (s, 2 H), 7.98 (d, 2 H), 7.18 (d, 2 H), 4.97 (s, 2 H), 4.32 (q, 2 H), 4.20 (q, 2 H), 2.38 (s, 3 H), 1.35 (t, 3 H), 1.27 (t, 3 H); ir ($CHCl_3$) 5.69, 5.79, 6.24 μ; uv λ_{max} 253, 234 nm.

Anal. Calcd for $C_{18}H_{21}N_3O_6S$: C, 53.1; H, 5.2; N, 10.3. Found: C, 53.0; H, 5.1; N, 10.3.

Endo Isomer 34b was an oil: nmr δ 8.93 (d, 1 H, J = 3 Hz), 8.38 (d, 1 H, J = 3 Hz), 7.77 (d, 2 H), 4.77 (s, 2 H), 4.32 (q, 2 H), 4.20 (q, 2 H), 2.37 (s, 3 H), 1.33 (t, 3 H), 1.23 (t, 3 H); ir ($CHCl_3$) 5.70, 5.79, 6.08, 6.41 μ; uv λ_{max} 325, 273, 224 nm.

Anal. Calcd for $C_{18}H_{21}N_3O_6S$: C, 53.1; H, 5.2; N, 10.3. Found: C, 53.0; H, 5.1; N, 10.3.

Exo and Endo 2-Ethoxycarbonylethyl Isomers 33c and 34c.—To 90 ml of DMSO was added 30.0 g (87.5 mmol) of sodium 2-tosylimido-5-ethoxycarbonylpyrimidinate, prepared as above and collecting only the salt which precipitated, and 17.5 g (97 mmol) of ethyl β-bromopropionate, and the reaction mixture was stirred at room temperature for 6 hr. The solvent was evaporated, leaving a residue which was digested with chloroform. The filtered chloroform digest was extracted twice with 50-ml portions of 2 N sodium hydroxide and once with water. Acidification of the combined alkaline and aqueous extracts gave 20.8 g (71 mmol, 81%) of recovered starting pyrimidine as its carboxylic acid. Drying and evaporating the chloroform layer and chromatography of the residue was previously described yielded 0.35 g (0.8 mmol, 1%) of the exo isomer **33c** and 3.88 g (9.0 mmol, 10.5%) of the endo isomer **34c**.

Exo isomer 33c was an oil: nmr δ 8.87 (s, 2 H), 7.92 (d, 2 H), 7.20 (d, 2 H), 5.92–4.67 (6 H), 2.93 (t, 2 H), 2.33 (s, 3 H), 1.33 (t, 3 H), 1.23 (t, 3 H); uv λ_{max} 256, 231 nm.

Endo isomer 34c had mp 147–150° from 2-propanol; nmr δ 8.87 (d, 1 H, 3 Hz), 8.57 (d, 1 H, 3 Hz), 7.82 (d, 2 H), 7.13 (d, 2 H), 3.87–4.47 (6 H), 2.97 (t, 2 H), 2.35 (s, 3 H), 1.33 (t, 3 H), 1.22 (t, 3 H); ir ($CHCl_3$) 5.80, 6.10, 6.45 μv; uv λ_{max} 315, 273, 225 nm.

Anal. Calcd for $C_{19}H_{23}N_3O_6S$: C, 54.1; H, 5.5; N, 10.0. Found: C, 54.0; H, 5.5; N, 9.8.

1-Methyl-2-*p*-toluenesulfonamido-5-ethoxycarbonyl-1,4,5,6-tetrahydropyrimidine (37).—To 10.4 g (31 mmol) of **36a** dissolved in 150 ml of glacial acetic acid were added 3.0 ml of 12 *N* hydrochloric acid and 0.7 g of platinum oxide. The mixture was shaken at 50 psi for 3 hr, at which time hydrogen uptake had ceased. Filtration, evaporation, and re-solution in chloroform was followed by washing twice with saturated sodium bicarbonate, drying, and evaporating. The residue was recrystallized from benzene–hexane to give 9.8 g (29 mmol, 93%) of tetrahydropyrimidine **37**: mp 114–116; nmr δ 7.70 (d, 2 H), 7.15 (d, 2 H), 4.10 (quartet, 2 H), 3.45 (d, 4 H), 2.98 (s, 3 H), 1.20 (t, 3 H); ir ($CHCl_3$) 5.79, 6.30, 6.40 μ; uv λ_{max} 232 nm (ε 17,100).

Anal. Calcd for $C_{15}H_{21}N_3O_4S$: C, 53.1; H, 6.2; N, 12.4. Found: C, 52.8; H, 6.1; N, 12.3.

The identical procedure was satisfactory for the reduction of all the other 2-tosylamido- and 2-tosylimidopyrimidines.

2-(*N*-methyl-*p*-toluenesulfonamido)-5-ethoxycarbonyl-1,4,5,6-tetrahydropyrimidine (35) (yield 76%) was a colorless oil: nmr δ 8.25 (s, 1 H), 7.58 (d, 2 H), 7.23 (d, 2 H), 4.10 (q, 2 H), 3.43–3.63 (m, 4 H), 3.00 (s, 3 H), 2.50–2.82 (m, 1 H), 2.37 (s, 3 H), 1.22 (t, 3 H); ir ($CHCl_3$) 5.80, 6.06 μ; uv λ_{max} 228 nm (ε 16,400).

1-Ethoxycarbonylmethyl-2-*p*-toluenesulfonamido-5-ethoxycarbonyl-1,4,5,6-tetrahydropyrimidine (38) (yield 86%) was crystallized from benzene–hexane: mp 108–110°; nmr δ 7.70 (s, 1 H), 7.62 (d, 2 H), 7.10 (d, 2 H), 4.12 (q, 2 H), 4.07 (s, 2 H), 4.00 (q, 2 H), 3.53 (d, 4 H), 2.97 (quintet, 1 H), 2.33 (s, 3 H), 1.57 (t, 3 H), 1.52 (t, 3 H); ir ($CHCl_3$) 5.74, 6.25, 6.45 μ; uv λ_{max} 230 nm.

Anal. Calcd for $C_{18}H_{25}N_3O_6S$: C, 52.6; H, 6.1; N, 10.2. Found: C, 52.6; H, 6.1; N, 10.3.

1-(2-Ethoxycarbonylethyl)-2-*p*-toluenesulfonamido-5-ethoxycarbonyl-1,4,5,6-tetrahydropyrimidine (40) (yield 91%) was crystallized from benzene–hexane: mp 93–95°; nmr δ 7.73 (d, 2 H), 7.20 (d, 2 H), 4.08, 4.05 (overlapping doublets, 4 H), 3.63, 3.57 (overlapping triplet and doublet, 6 H), 2.97 (quintet, 1 H), 2.53 (t, 2 H), 2.37 (s, 3 H), 1.22, 1.18 (overlapping triplets, 6 H); ir ($CHCl_3$) 5.80, 6.30, 6.46 μ; uv λ_{max} 232 nm.

Anal. Calcd for $C_{19}H_{27}N_3O_6S$: C, 53.6; H, 6.4; N, 9.9. Found: C, 53.7; H, 6.2; N, 10.2.

1-Ethoxycarbonylmethyl-2-*p*-toluenesulfonimido-3-methyl-5-ethoxycarbonylhexahydropyrimidine (39). Method A.—A hot solution of **38** (4.98 g, 12.1 mmol) in 100 ml of absolute ethanol was added to 30 ml of 0.42 *N* sodium ethoxide–ethanol. The resulting solution was evaporated to dryness, the residue was dissolved in DMSO, excess methyl iodide was added, and the reaction mixture was stirred at room temperature for 10 hr. After the solvent was removed by distillation, the residue was dissolved in chloroform, washed with water, and chromatographed, employing 1% C_2H_5OH–$CHCl_3$ as the eluent. The only two products isolated were recovered starting material **43** (2.26 g, 5.5 mmol, 45%) and the 3-methyl isomer **39** (1.95 g, 4.6 mmol, 38%).

Method B.—To 1.3 g (38 mmol) of **37** dissolved in 55 ml of dry benzene was added 0.18 g of sodium hydride as a 56% oil dispersion. After 15 min, when the evolution of hydrogen had ceased, ethyl bromoacetate (50% excess) was added. After the reaction had been warmed at 60–70° for 12 hr, hydrogen chloride was bubbled through the solution. The mixture was filtered to remove sodium chloride and bromide, and evaporated to dryness. Chromatography of the resulting oil yielded 0.53 g (1.6 mmol, 42%) of starting material **37** and 0.84 g (2.0 mmol, 52%) of the alkylated product **39**, identical with that from method A: mp 152–163°; nmr δ 7.62 (d, 2 H), 7.07 (d, 2 H), 4.12 (q, 2 H), 3.98 (q, 2 H), 3.55 (d, 4 H), 3.17 (s, 3 H), 2.97 (quintet, 1 H), 2.33 (s, 3 H), 1.23, 1.17 (overlapping triplets, 6 H); ir ($CHCl_3$) 5.76, 6.37, 6.61 μ; uv λ_{max} 224 nm.

Anal. Calcd for $C_{19}H_{27}N_3O_6S$: C, 53.6; H, 6.4; N, 9.9. Found: C, 53.6; H, 6.1; N, 9.8.

1-Ethoxycarbonylmethyl-2-(*N*-methyl-*p*-toluenesulfonamido)-5-ethoxycarbonyl-1,4,5,6-tetrahydropyrimidine (36).—To 25 ml of benzene containing 0.39 g (1.1 mmol) of **35** was added 0.06 g (1.5 mmol) of sodium hydride as a 56% oil dispersion. The mixture was heated to reflux and 0.44 g (2.7 mmol) of ethyl bromoacetate was added. After 24 hr the reaction mixture was cooled, flushed with hydrogen chloride, filtered, and evaporated to dryness. Chromatography gave 0.20 g (0.57 mmol, 51%) of recovered starting material **35** and 0.13 g (0.31 mmol, 30%) of the alkylated product **36** as a clear, colorless oil: nmr δ 7.65 (d, 2 H), 7.20 (d, 2 H), 4.17, 4.13 (overlapping quintets, 4 H), 3.54 (d, 4 H), 3.13 (m, 1 H), 2.77 (s, 3 H), 2.38 (s, 3 H), 1.28, 1.26 (overlapping triplets, 6 H); ir ($CHCl_3$) 5.69, 6.09 μ; uv λ_{max} 228 nm.

Anal. Calcd for $C_{19}H_{27}N_3O_6S$: C, 53.6; H, 6.4; N, 9.9. Found: C, 53.6; H, 5.8; N, 9.8.

***N,N'*-Dimethyl-*N*-(2-ethoxycarbonylethyl)thiourea (43).**—Methyl isothiocyanate (1.0 g, 13.7 mmol) was dissolved in 10 ml of ether and cooled to 0°. Ethyl β-*N*-methylaminopropionate (1.80 g, 13.7 mmol) dissolved in 5 ml of ether was then added dropwise over a 15-min period. The reaction mixture was allowed to stir for 1 hr at 0° and then to warm to room temperature over the next 2 hr. Removal of the solvent *in vacuo* gave **43** as a clear oil in 92% yield, 2.58 g: tlc R_f 0.57, eluting with 5% CH_3OH–$CHCl_3$; nmr δ 6.71 (broad d, 1 H, –NH–), 4.13 (q, 2 H), 4.08 (t, 2 H), 3.18 (s, 3 H), 3.06 (d, 3 H), 2.70 (t, 2 H), 1.25 (t, 3 H).

Anal. Calcd for $C_8H_{16}N_2O_2S$: C, 47.0; H, 7.9; N, 13.7; S, 15.7. Found: C 47.1; H, 8.2; N, 13.6; S, 15.9.

***N,N'*-Dimethyl-*N*-(2-ethoxycarbonylethyl)chloroformamidinium Chloride (44).**—A solution of 1.0 g (4.9 mmol) of thiourea **43** dissolved in 8 ml of THF was treated at room temperature with 0.6 g (6.1 mmol) of $COCl_2$ dissolved in 5 ml of THF and the reaction mixture was allowed to stir overnight. Addition of ether precipitated the product as an orange oil: ir showed the reported characteristic C=N absorption at 6.05 μ;[32] nmr ($CDCl_3$–DMSO-d_6) δ 4.17 (t, 2 H), 4.13 (q, 2 H), 3.57 (s, 3 H), 3.32 (s, 3 H), 2.87 (m, 2 H), 1.25 (t, 3 H).

***N,N',N''*-Trimethyl-*N,N'*-di(2-ethoxycarbonylethyl)guanidine Hydrochloride (45).**—Phosgene (1 g) was dissolved in 50 ml of THF at 0° and a solution of *N,N'*-dimethyl-*N*-(2-ethoxycarbonylethyl)thiourea (**43**) (450 mg, 2.20 mmol) was added dropwise over a period of 45 min. The reaction was allowed to warm to room tenperature, where it was maintained for 3 hr. The phosgene was removed with a stream of dry N_2 (3 hr), the remaining THF was removed *in vacuo*, the residue was dissolved in 25 ml of THF, and the solvent was evaporated again. The residual oil was dissolved in 20 ml of acetonitrile and a solution of ethyl β-*N*-methylpropionate (576 mg, 4.40 mmol) in 10 ml of acetonitrile was added dropwise at 0°, where the solution was kept for 1 hr and then allowed to stir at room temperature overnight.

The acetonitrile was removed *in vacuo* and the residue was dissolved in 25 ml of water and applied to a 400-ml column of Bio-Rad AG 50W-X4 (50–100 mesh) ion-exchange resin. The column was eluted with 4.2 l. of 0.2 *N* HCl to remove ethyl β-*N*-methylpropionate hydrochloride and then with 3.6 l. of 4 *N* HCl to remove the product guanidine hydrochloride as its diacid. The water was removed *in vacuo*, the residue was dissolved in 100 ml of 2-propanol, and the 2-propanol was evaporated to a residue which was dissolved in 50 ml of ethanol and the solution was saturated with HCl at 0°, then stirred for 3 hr, during which the temperatue rose to 20°. Removal of the ethanol and application of the residue to a silica column eluting with 20% CH_3OH–$CHCl_3$ followed by evaporation left the pentasubstituted guanidine hydrochloride **45** as a colorless oil (386 mg, 52% yield): nmr (CD_3OD) δ 4.15 (q, 4 H), 3.60 (m, 4 H), 3.00 (s, 6 H), 2.92 (s, 3 H), 2.77 (t, 4 H), 1.25 (t, 6 H); mass spectrum *m/e* 301 (M^+), 256 ($M^+ - OCH_2CH_3$).

Procedure for the Cyclization to the Imidazolinones. $\Delta^{1,8a}$-2-Oxoimidazolino[1,2-*a*]-8-methyl-6-ethoxycarbonylhexahydropyrimidine (50).—To 1.4 g (3.3 mmol) of **39** in a Kel-F reaction vessel[11] was added 5 ml of anhydrous HF. The vessel was sealed and stirred at room temperature for 2 hr, the HF was removed, the residue was partitioned between water and CH_2Cl_2, and the CH_2Cl_2 was evaporated to give 0.53 g (90%) of *p*-toluenesulfonyl fluoride. The aqoeous phase was adjusted to pH 9 with 5% potassium carbonate and lyophilized, the residue was digested with 1:1 C_2H_5OH–$CHCl_3$ and filtered, and the filtrate was evaporated to dryness. Chromatography of the residue on neutral alumina, activity III, employing 1:1 C_2H_5OH–$CHCl_3$ as the eluent and crystallization from benzene–hexane gave 0.67 g (3.0 mmol, 90%) of pure imidazolinone **50**: mp 121–123°; nmr δ 4.20 (q, 2, H), 3.93 (s, 2 H), 3.62 (d, 4 H), 3.17 (quintet,

1 H), 3.17 (s, 3 H), 1.27 (t, 3 H); ir ($CHCl_3$) 5.80, 5.90, 6.26 μ; uv (pH 12) λ_{max} 223 nm (ϵ 19,800).

Anal. Calcd for $C_{10}H_{15}N_3O_3$: C, 53.3; H, 6.7; N, 18.7. Found: C, 53.1; H, 6.8; N, 18.8.

The identical procedure was satisfactory for the synthesis of the other imidazolinones. The monocyclic imidazolinones were converted to hydrogen chloride salts for characterization by passing hydrogen chloride through a THF solution of the imidazolinone.

1-Methyl-2-(*N*-methyl-*N*-ethoxycarbonylmethyl)aminoimidazolin-4-one (46a) (yield 88%) was crystallized from 2-propanol–ether: mp 171–172°; nmr (D_2O) δ 4.60 (s, 4 H), 0.00 (q, 2 H), 3.35 (s, 6 H), 1.30 (t, 3 H); uv (pH 12) λ_{max} 229 nm (ϵ 21,500).

Anal. Calcd for $C_9H_{16}N_3O_3Cl$: C, 43.3; H, 6.5; N, 16.8. Found: C, 43.0; H, 6.4; N, 17.0.

1-Methyl-2-(*N*-methyl-*N*-carboxymethyl)aminomidazolin-4-one (46b) (yield 19%) had nmr (D_2O) δ 4.38 (s, 4 H), 3.32 (s, 6 H); uv (pH 12) λ_{max} 229 nm (ϵ 22,000).

46b HCl had mp 197–199° dec; nmr (D_2O) δ 4.33 (s, 2 H), 3.25 (s, 9 H); uv (pH 12) λ_{max} 227 nm (ϵ 17,600).

Anal. Calcd for $C_7H_{12}N_3O_3Cl$: C, 40.6; H, 6.8; N, 23.7. Found: C, 40.6; H, 6.8; N, 23.7.

1-Methylimidazolin-2-oxo[1,2-*a*]-$\Delta^{8,8a}$-6-ethoxycarbonyltetrahydropyrimidine (48) (yield 45%) was an oil: nmr δ (4.05 (q, 2 H), 3.74 (s, 2 H), 3.55 (2 H), 2.88 (s, 3 H), 2.86 (m, 1 H), 1.16 (t, 3 H); ir ($CHCl_3$) 5.76, 6.02 μ; uv (0.01 *N* NaOH–absolute EtOH) λ_{max} 210 nm (ϵ 9750); mass spectrum *m/e* 225 (M^+).

$\Delta^{1,9a}$-Tetrahydropyrimidin-2-oxo[1,2-*a*]-7-ethoxycarbonylhexahydropyrimidine (51) (yield 33% from benzene–hexane) had mp 227–230; nmr δ 4.10 (q, 2 H), 3.40 (d, 4 H), 3.33 (t, 2 H), 3.0 (m, 1 H), 2.45 (t, 2 H), 1.17 (t, 3 H); ir ($CHCl_3$) 5.79, 6.20 μ; uv (0.01 *N* NaOH–absolute EtOH) λ_{max} 227 nm (ϵ 21,500).

Anal. Calcd for $C_{10}H_{15}N_3O_3$: C, 53.3; H, 6.7; N, 18.7. Found: C, 53.1; H, 6.5; N, 18.5.

$\Delta^{1,8a}$-2-Oxoimidazolino[1,2-*a*]-6-ethoxycarbonylhexahydropyrimidine (49) (yield 32% from benzene–hexane) had mp 202–204°; nmr (DMSO-d_6) δ 8.35 (s, 1 H), 4.10 (q, 2 H), 3.67 (s, 2 H), 3.42 (d, 4 H), 3.12 (quintet, 1 H), 1.18 (t, 3 H); ir (KBr) 5.82, 6.10, 6.39 μ; uv (0.01 NaOH–absolute EtOH) λ_{max} 229 nm (ϵ 16,400).

Anal. Calcd for $C_9H_{13}N_3O_3$: C, 51.2; H, 6.2; N, 19.9. Found: C, 51.0; H, 6.2; N, 20.0.

Deuterium Exchange.—For each of the deuterium-exchange reactions, 20–30 mg of sample was dissolved in *ca.* 0.5 ml of a deuterated phosphate buffer of the desired pD. The phosphate buffers were prepared by dissolving phosphorus pentoxide in deuterium oxide and adjusting the pD with a previously prepared sodium deuteroxide solution. The three buffers utilized were of pD's 3, 7, and 10 ($\pm$0.5). The amount of exchange was determined from the nmr spectra, taken at intervals. This was determined by measuring the total integral of the ethyl ester methylene, the imidazolinone methylene, and the –OH spinning side band which coincided with the absorptions of interest. Subtracting the –OH spinning side band, determined by integrating the spinning side band downfield from the –OH peak, and the ethyl methylene, which was equal to two-thirds of the ethyl ester methyl integral, from the total integral gave the value of the integral of the imidazolinone signal. This divided by two-thirds of the ester methyl integral which was widely separated from other absorptions and easily integrated, give the per cent protium remaining. The difference was the amount of exchange.

Registry No.—**3**, 2651-15-2; **4a**, 16817-16-6; **4b**, 38653-55-3; **5a**, 38653-56-4; **5b**, 38653-57-5; **5c**, 38653-58-6; **6** (x = 1; R = Et), 38653-59-7; **8a**, 38653-60-0; **8b**, 38653-61-1; **9**, 2973-83-3; **10a**, 20979-72-0; **10b**, 38653-64-4; **11a**, 27703-15-7; **11b**, 38653-66-6; **12a**, 38653-67-7; **12b**, 38653-68-8; **12c**, 38653-69-9; **14**, 1424-52-8; **15**, 38653-71-3; **16**, 38653-72-4; **17a**, 38653-73-5; **17b**, 38653-74-6; **18**, 108-52-1; **19**, 38653-76-8; **20a**, 38652-87-8; **20b**, 38652-88-9; **21a**, 38652-89-0; **21b**, 38652-90-3; **22a**, 38652-91-4; **22b**, 28858-47-1; **23**, 38652-93-6; **24**, 38652-94-7; **25**, 38652-95-8; **26a**, 38652-96-9; **26b**, 38652-97-0; **27**, 6584-12-9; **28**, 87-13-8; **29**, 38653-00-8; **30**, 38653-01-9; **31**, 38653-02-0; **32**, 38653-03-1; **33a**, 38653-04-2; **33b**, 38653-05-3; **33c**, 38653-06-4; **34a**, 38653-07-5; **34b**, 38653-08-6; **34c**, 38653-09-7; **35**, 38653-10-0; **36**, 38653-11-1; **37**, 38653-12-2; **38**, 38653-13-3; **39**, 38653-14-4; **40**, 38653-15-5; **43**, 38653-16-6; **45**, 38653-17-7; **46a**, 38653-18-8; **46b**, 38653-19-9; **46b** HCl, 38653-20-2; **48**, 38653-21-3; **49**, 38653-22-4; **50**, 38653-23-5; **51**, 38653-24-6; β-alanine, 107-95-9; ethyl 3-*N*-methylaminopropionate, 2213-08-3; sarcosine ethyl ester, 13200-60-7; *p*-toluenesulfonyl chloride, 98-59-9; phosgene, 75-44-5; *p*-toluenesulfonyl fluoride, 455-16-3.

Notes

Nuclear Magnetic Resonance Spectra of Cyclic Amines. Shielding of α Protons Trans to a Lone Pair and Cis to an *N*-Methyl Group in Pyrrolidines

ELI BREUER* AND DAVID MELUMAD

Department of Pharmaceutical Chemistry, The Hebrew University School of Pharmacy, Jerusalem, Israel

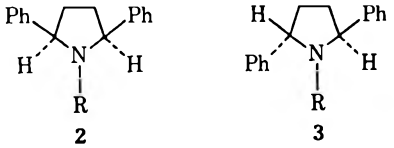
Received October 16, 1972

The shielding of axial α protons in saturated six-membered nitrogen heterocycles is well documented.[1-4] This shielding is presumably caused by the anisotropy of the trans axial lone pair and that of the C–N bond of the equatorial alkyl substituent on the nitrogen, the former being the dominant factor.[4]

In N-substituted pyrrolidines no such observation, concerning differentiation between α protons cis and trans to the lone pair, has been reported by nmr measurements at room temperature. It was, however, found recently that upon cooling the α protons of *N*-methylpyrrolidine separate into two peaks with $\Delta\delta$ of 1.08 ppm that coalesce at about −100°.[5]

In this communication we assess the contributions of a trans lone electron pair and of a cis-*N*-methyl group to the shielding of α protons in pyrrolidines. Our observations also provide a method to assign the stereochemistry of *N*-alkyl-α,α′-disubstituted pyrrolidines.

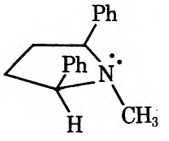
In the course of our studies concerning the Leuckart reaction of cyclopropyl ketones that produce derivatives of pyrrolidine,[6,7] we have prepared *cis*- and *trans*-2,5-diphenylpyrrolidine[8] (**2a** and **3a**) and their *N*-methyl derivatives[9] (**2b** and **3b**).



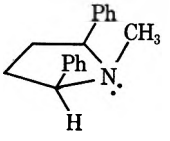
2 **3**

a, R = H; **b**, R = Me

Considering the possibility of nitrogen inversion in these pyrrolidines,[10] it is evident that in the cases of **3a** and **3b** the two pairs of invertomers are identical, and that the two possible invertomers of **2a** should not differ much in energies. In contrast, **2b** should exist predominantly or even perhaps exclusively in the transoid conformation **2b**-I, due to increased nonbonded interactions in conformation **2b**-II. In conformation **2b**-I both α protons are trans to the lone pair and cis to the *N*-methyl group.



2b-I



2b-II

Examination of the nmr data ($CDCl_3$) listed in Table I reveals that the benzylic methine protons of the cis compounds (**2a** and **2b**) appear at higher field than those of the trans isomers (**3a** and **3b**), respectively. It can also be seen that N-methylation causes a considerably larger shift in the cis series (0.91 ppm) than it does for pyrrolidine and *trans*-2,5-diphenylpyrrolidine (0.33 ppm).

TABLE I
CHEMICAL SHIFTS OF α PROTONS OF PYRROLIDINE AND SOME OF ITS DERIVATIVES[a]

	δ, ppm	
	$CDCl_3$	$CDCl_3$ + TFA
Pyrrolidine (**1a**)	2.78	3.40
cis-2,5-Diphenylpyrrolidine (**2a**)	4.25	5.00
trans-2,5-Diphenylpyrrolidine (**3a**)	4.43	5.00
N-Methylpyrrolidine (**1b**)	2.45	3.76, 3.00
cis-1-Methyl-2,5-diphenylpyrrolidine (**2b**)	3.34	4.45
trans-1-Methyl-2,5-diphenylpyrrolidine (**3b**)	4.10	5.20, 4.37

[a] Measured by a Jeol C-60H instrument with TMS as internal standard.

Assuming that **2a**, **3a**, and **3b** exist as 1:1 mixtures of their invertomers and that **2b** exist entirely as the transoid ivertomer **2b**-I it follows that (1) the α protons of **2a**, **3a**, and **3b** are shielded to the extent of 50% by the trans lone pair, (2) the α protons of **3b** are shielded to the extent of 50% also by the *cis*-*N*-methyl group, and (3) the α protons of **2b** are 100% shielded both by the *cis*-*N*-methyl group and by the trans lone pair.

Consequently, the difference of 0.33 ppm between the chemical shifts of **3a** and **3b** represents 50% of the shielding by the *cis*-*N*-methyl group (compare **1a** and **1b**). The difference of 0.91 ppm between the chemical shifts of **2a** and **2b** should be due to 100% shielding of the α protons by a *cis*-*N*-methyl group (0.66 ppm), plus 50% shielding by the trans lone pair: 0.25 ppm (= 0.91 − 0.66). The chemical shift difference of 0.18 ppm between **2a** and **3a** may be due to deshielding of the α protons of **3a** by the *cis*-phenyl groups.[11] On

(1) H. P. Hamlow, S. Okuda, and N. Nakagawa, *Tetrahedron Lett.*, 2553 (1964).
(2) H. Booth and J. H. Little, *Tetrahedron*, **23**, 291 (1967).
(3) R. O. Hutchins, L. D. Kopp, and E. L. Eliel, *J. Amer. Chem. Soc.*, **90**, 7174 (1968).
(4) J. B. Lambert and R. G. Keske, *Tetrahedron Lett.*, 2023 (1969).
(5) J. B. Lambert and W. L. Oliver, *J. Amer. Chem. Soc.*, **91**, 7774 (1969).
(6) E. Breuer and Y. Stein, *Israel J. Chem.*, **6**, 901 (1968).
(7) E. Breuer and D. Melumad, *Tetrahedron Lett.*, 3595 (1969).
(9) C. G. Overberger, M. Valentine, and J. P. Anselme, *J. Amer. Chem. Soc.*, **91**, 687 (1969).
(9) E. Breuer and D. Melumad, *J. Org. Chem.*, **37**, 3949 (1972).
(10) The other conceivable process for pyrrolidines is pseudorotation, which is of such low energy that it has not been observed by nmr;[5] therefore the pyrrolidines are assumed to be planar for the purpose of this discussion.
(11) This difference may also indicate that the two possible conformations of **2a** are not equally populated and that the invertomer with the N–H trans to the phenyl groups predominates. This seems to be supported by the identity of the δ values of **2a** and **3a** in acidic medium. If this view is accepted the value for 50% shielding by a trans lone pair should be corrected from 0.25 to 0.43 ppm.

the basis of these data we can estimate the chemical shift difference between the α protons of *N*-methylpyrrolidine in the absence of nitrogen inversion. In this case two of the α protons should be fully shielded both by the trans lone pair (0.50 ppm) and by the *cis*-*N*-methyl group (0.66 ppm); therefore the shift should amount to 1.16 ppm, which is in good agreement with the observed value of 1.08 ppm.[5]

The present conclusions are borne out by the results from the protonation experiments (Table I, column 2). In the presence of excess trifluoroacetic acid (TFA) the α protons of **2b** appear as one signal indicating a single protonated species. The α protons of **1b** and **3b** are split into two signals of equal areas with a chemical shift difference of 0.76–0.83 ppm, which presumably results from full-scale shielding of half of the α protons in **1b** and **3b** by a *cis*-*N*-methyl group. It is worthy of note that the high field signal of **3b** corresponds well with the chemical shift of the α protons of **2b**, both of which are fully shielded by a *cis*-*N*-methyl group.

From the data presented the following conclusions can be drawn. (1) The α protons of a pyrrolidine are shielded when situated trans to an electron pair and cis to an *N*-methyl group. (2) The chemical shift difference of 1.08 ppm observed at $-100°$ between the α protons of *N*-methylpyrrolidine[5] is caused predominantly (0.66–0.83 ppm) by the *cis*-*N*-methyl group and to a lesser degree by the trans lone pair. (3) The stereochemistry of a symmetrically N,α,α'-trisubstituted pyrrolidine (and presumably any symmetrical nitrogen heterocycle) can be established by examination of the nmr spectrum of the protonated form. In the cis isomer the α protons should appear together, while in the trans isomer they should appear separately. (4) The treatment presented can easily be applied to assess the contribution of a trans lone pair and that of a *cis*-*N*-alkyl group to the shielding of α protons in any saturated symmetrical nitrogen heterocycle.

The shielding of α protons in azacycloalkanes by a trans lone pair[12] and by a *cis*-*N*-alkyl group seems to be a general phenomenon. A consequence of this is that in pairs of cis,trans isomers of *N*-alkyl-α,α' symmetrically disubstituted azacycloalkanes the α protons of the cis isomer should always appear in the nmr at higher field than those of the trans isomer. No exception to this was found in an extensive literature survey of nmr data of appropriate three-, five-, and six-membered azacycloalkanes.[13]

Further study of this problem in other ring systems is in progress.

Registry No.—**1a**, 123-75-1; **1b**, 120-94-5; **2a**, 22147-83-7; **2b**, 35657-63-7; **3a**, 22147-84-8; **3b**, 35657-66-0.

Acknowledgment.—We wish to thank Professor S. Sarel for his comments concerning this work.

(12) Although this phenomenon is usually viewed as shielding of α protons trans to a lone pair,[1-4] it may also be viewed as deshielding by a skew or cis related lone pair: C. C. Price, *Tetrahedron Lett.*, 4527 (1971). We thank Dr. C. C. Price for directing our attention to his results.

(13) No data were found for appropriate azetidines and hexahydroazepines.

The Reactivity of Diazo Ketones. IV.[1] Reaction of α-Diazo Ketones with Molecular Oxygen

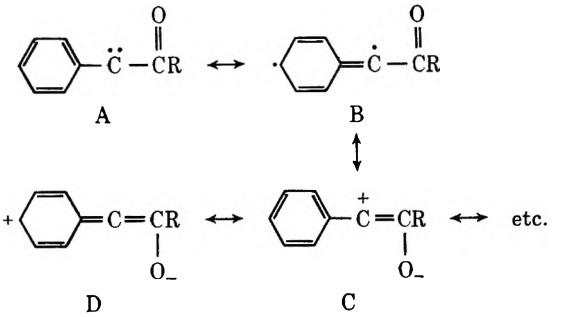
MASANOBU TANAKA, TOSHIKAZU NAGAI, AND NIICHIRO TOKURA*

Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka, Japan

Received March 17, 1972

It was reported[1a] that PhC̈COR (R = Ph, Me) type ketocarbenes react with sulfur dioxide to give the ketosulfenes in competition with the Wolff rearrangement, while RC̈COPh (R = Me, H) type ketocarbenes do not react, but yield the products resulting from 1,2-hydrogen shift and a 1,3-dipolar addition reaction. In this case, it was suggested[1a] that the resonance form A or B of the PhC̈COR type ketocarbene as shown in Scheme I reacts with sulfur dioxide, for

SCHEME I



sulfur dioxide is known to react electrophilically and radically, but no nucleophilically.

In order to obtain further information on the reactivity of the ketocarbene, thermal or photochemical reactions of several α-diazo ketones with molecular oxygen were investigated.

A number of reports[2] on the photochemical reactions of diaryldiazomethane and the thermal reactions of tetraarylethylenes with molecular oxygen have been published. These reactions are explained by the addition of diarylcarbenes to molecular oxygen[2-4] (Scheme II).

A "carbonyl oxide" (E) has been suggested[4] as the primary product[4b] in the formation of cyclic peroxide[4a] from the photooxidation of diphenyldiazomethane. Also, the formation of benzophenone from the "carbonyl oxide" (E) on irradiation of diphenyldiazomethane in solid air matrix at 20°K has been reported.[4c]

(1) (a) M. Tanaka, T. Nagai, and N. Tokura, *J. Org. Chem.*, **37**, 4106 (1972); (b) T. Nagai, M. Tanaka, and N. Tokura, *Tetrahedron Lett.*, 6293 (1968); (c) M. Tanaka, T. Nagai, and N. Tokura, *ibid.*, 4979 (1972).

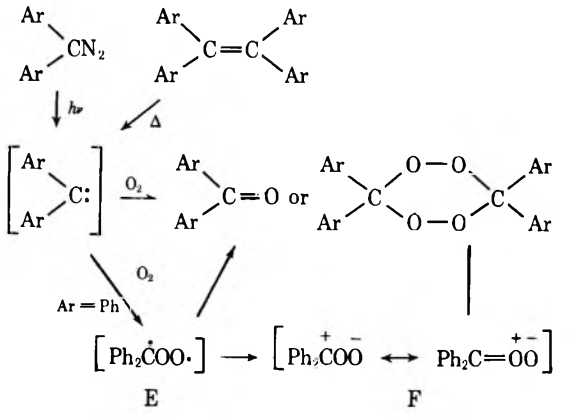
(2) (a) H. Staudinger, E. Anthes, and F. Pfenninger, *Ber. Deut. Chem. Ges.*, **49**, 1928 (1916); (b) W. Kirmse, L. Horner, and H. Hoffman, *Justus Liebigs Ann. Chem.*, **619**, 19 (1958); (c) P. D. Bartlett and T. G. Traylor, *J. Amer. Chem. Soc.*, **84**, 3408 (1962); (d) R. W. Murray and A. M. Trozzolo, *J. Org. Chem.*, **26**, 3109 (1961).

(3) V. Franzen and H. I. Joschek, *Justus Liebigs Ann. Chem.*, **633**, 7 (1960).

(4) (a) P. D. Bartlett and T. G. Traylor, *J. Amer. Chem. Soc.*, **84**, 3408 (1962). (b) Peroxidic zwitterion F is suggested to be formed from the radical structure E as shown in Scheme II: R. W. Murray and A. Suzui, *ibid.*, **93**, 4963 (1971). (c) Benzophenone is suggested to be obtained from the related carbonyl oxide, but the mechanism of the deoxygenation from the carbonyl oxide is not determined.[2c]

SCHEME II

REACTION OF DIARYLDIAZOMETHANE OR TETRAARYLETHYLENE WITH MOLECULAR OXYGEN

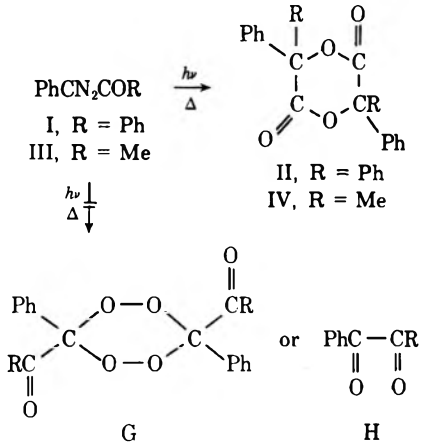


On the other hand, only indirect information[5,6] on the reaction of ketocarbene with molecular oxygen has been obtained from the photolysis of azibenzil in organic glass around 77°K. The photolysis gave a very small amount of benzil[6] besides ketene and a high yield of solvent-substituted deoxybenzoin.

In the present study, α-diazo ketones as described in Scheme IV were used.

Reactions of α-diazo ketones with molecular oxygen did not proceed at ordinary temperature, but did readily by the thermal or photochemical decomposition of α-diazo ketones in aromatic solvents. The thermal or photochemical reactions of $PhCN_2COR$ (R = Ph, Me) type diazo ketones with molecular oxygen gave tetraphenylglycolide (II) and 3,6-dimethyl-3,6-diphenylglycolide (IV), respectively, instead of the peroxides (G) or ketones (H) (Scheme III).

SCHEME III



Thermal reactions were carried out around the decomposition point of diazo ketones (Scheme IV and Table I). However, from only Table I, it is too difficult to discuss the substituent effect of these reactions, for the reaction conditions are different in temperature and solvent. Keeping in mind this point, under similar conditions, the photochemical reactions were achieved (Scheme IV and Table II).

(5) A. M. Trozzolo, *Accounts Chem. Res.*, **1**, 329 (1968).

(6) The deoxygenation process in the formation of benzil is not made clear, but the reaction of phenyl benzoyl carbene with molecular oxygen is suggested.[5]

SCHEME IV

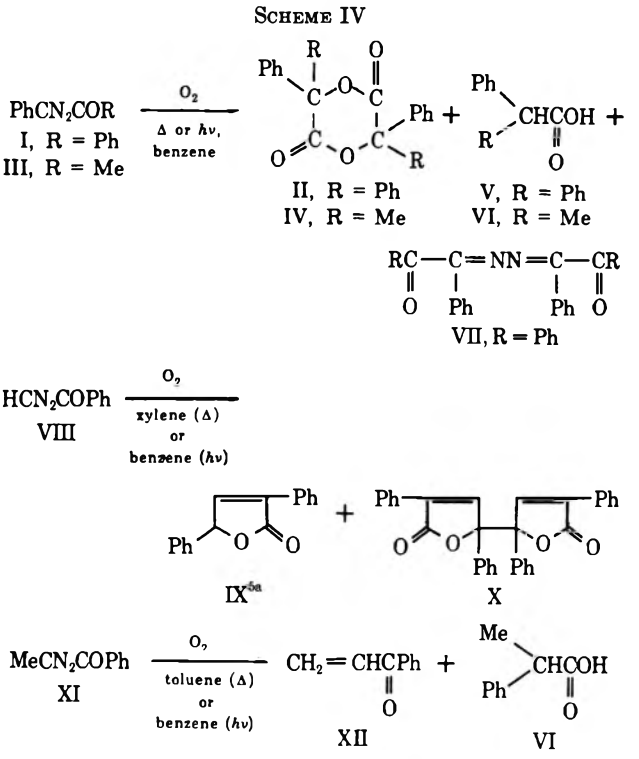


TABLE I

THERMAL REACTION[a] OF $R_1CN_2COR_2$ WITH O_2

R_1	R_2	Solvent	Temp, °C	Products (yield, mol %)[b]
Ph	Ph	Benzene	70–80	II (40), V (21), VII (15)
H	Ph	Xylene	130–140	IX (6), X (37)
Me	Ph	Toluene	110–115	XII (54), VI (2)
Ph	Me	Benzene	60–70	IV (43), VI (8)

[a] Reaction time 4.5 hr. [b] The yields are in mole per cent based on unrecovered starting material for V, VI, and XII, based on a 0.5 mol of unrecovered starting material for II, IV, VII, and IX, and based on a 0.25 mol of unrecovered starting material for X.

TABLE II

PHOTOCHEMICAL REACTION[a] OF $R_1CN_2COR_2$ WITH O_2 IN BENZENE AT 15–20°

R_1	R_2	Time, hr	Products (yield, mol %)
Ph	Ph	6	II (41), V (17), VII (trace)
H	Ph	8	IX (26), X (18)
Me	Ph	9	XII (58), VI (trace)
Ph	Me	4	IV (49), VI (2)

[a] The irradiation was undertaken by using a 300-W high-pressure mercury lamp in a Pyrex tube at 15–20°.

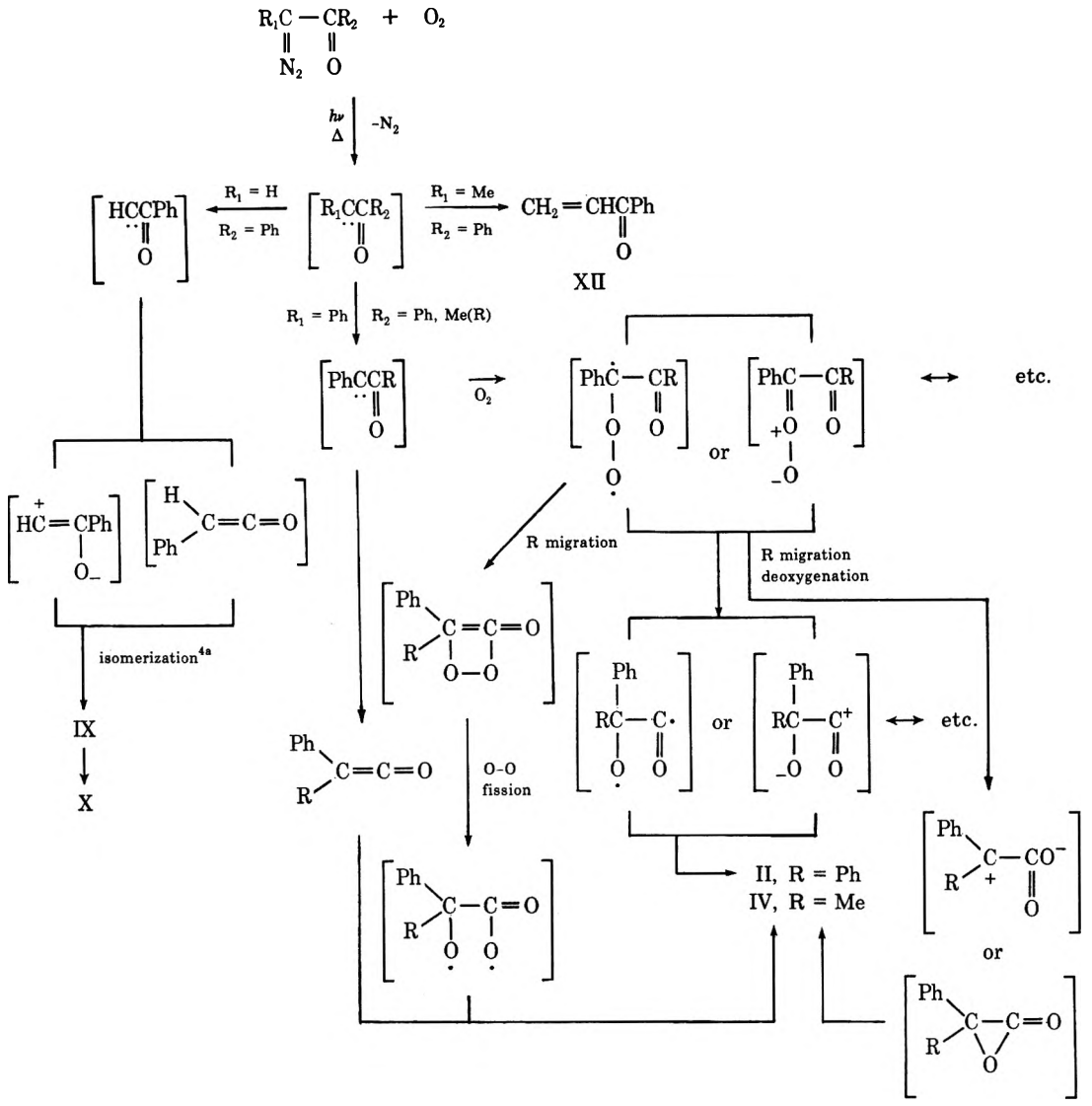
The results of photochemical reactions resembled those of thermal reactions.

Confirmation of the structure of II or IV was made, as will be described in the Experimental Section, from elemental analysis, molecular weight determination, ir, ^1H nmr, ^{13}C nmr spectra, and the reaction. Moreover, II was identified by the mixture melting point method with the authentic sample.[7a]

In these reactions of $R_1CN_2COR_2$ type diazo ketones (R_1 = Ph, Me, H; R_2 = Ph, Me) with molecular oxygen, a remarkable substituent effect was observed,

(7) (a) C. S. Marrel, F. D. Hager, and E. C. Caudle, *Org. Syn.*, **3**, 45 (1923); (b) G. Baddeley, G. Holt, and J. Kenner, *Nature (London)*, **163**, 776 (1949); (c) V. Franzen, *Justus Liebigs Ann. Chem.*, **602**, 199 (1957).

SCHEME V



namely, $PhCN_2COR$ (R = Ph, Me) type diazo ketones gave cyclic diesters (II, IV). By contrast, RCN_2COPh (R = H, Me) type diazo ketones afforded the products resulting from 1,2-hydrogen shift[7b,c] and 1,3-dipolar[8] addition reaction of the ketocarbene intermediate.

Tetraphenylglycolide (II) was not obtained from the reaction of diphenylketene or bisbenzilketazine (VII) with molecular oxygen under the same conditions as the thermal reaction of azibenzil (I) with molecular oxygen.

Thus, the interaction of the $PhC\ddot{C}COR$ type ketocarbene generated from the corresponding diazo ketones with molecular oxygen followed by R migration may be postulated for the formation of the cyclic diesters. The possible intermediates are described in Scheme V.

The reactivity of $R_1C\ddot{C}COR_2$ type ketocarbenes with molecular oxygen resembles that[1a] with sulfur dioxide (Table III).

Then, it is proposed that the radical reactivity of

TABLE III

REACTIVITY OF $R_1C\ddot{C}COR_2$ WITH O_2 OR SO_2

R_1	R_2	O_2	SO_2
Ph	Ph	+ (Carbonyl oxide)	+ (Ketosulfene)
H	Ph	− (1,3-Dipolar addition)	− (1,3-Dipolar addition)
Me	Ph	− (1,2-Hydrogen shift)	− (1,2-Hydrogen shift)
Ph	Me	+ (Carbonyl oxide)	+ (Ketosulfene)

$PhC\ddot{C}COR$ type ketocarbenes may be due to the resonance[9] form B as shown in Scheme I.

Experimental Section

Materials.—Azibenzil (I), mp 78° (lit.[10] mp 78°), and phenyl acetyl diazomethane (III), mp 59–60° (lit.[10] mp 59–60°), were prepared by diazo transfer reactions from the related ketones.

Diazoacetophenone (VIII), mp 48–50° (lit.[11] mp 49–50°), and methyl benzoyl diazomethane (XI),[11] which is the liquid diazo compound recrystallized[12] from ether at −70°, were obtained by the reaction of benzoyl chloride with related diazoalkanes.

(8) (a) D. Yates and T. J. Clark, *Tetrahedron Lett.*, 435 (1961); (b) R. Huisgen, G. Binsch, H. Konig, and H. J. Sturm, *Angew. Chem.*, **73**, 368 (1961); (c) G. Binoch, *ibid.*, **75**, 634 (1963); (d) W. Kirmse and L. Horner, *Justus Liebigs Ann. Chem.*, **625**, 34 (1959).

(9) (a) The resonance of divalent carbon with the phenyl ring has been proposed; see W. Kirmse, "Carbene Chemistry," Academic Press, New York, N. Y., 1964, p 214; (b) R. W. Murray and A. M. Trozzolo, *J. Org. Chem.*, **26**, 3109 (1961).

(10) M. Regitz, *Chem. Ber.*, **98**, 1210 (1965).

(11) F. Arndt and B. Eistert, *ibid.*, **68**, 200 (1935).

(12) M. Regitz, *Angew. Chem.*, **79**, 733 (1967).

Thermal Reactions of α-Diazo Ketones with Molecular Oxygen. A. Reaction of Azibenzil (I) with Molecular Oxygen.—Molecular oxygen gas (280 l.) was introduced to a benzene solution (85 ml of benzene) of azibenzil (8.5 g, 0.038 mol) for 4.5 hr at refluxing temperature. Into the reaction mixture, water (40 ml) and ether (40 ml) were added. From the organic layer, benzene and ether were removed under reduced pressure. Methanol (100 ml) was added to the residue. After the methanol solution was cooled, white powders precipitated. The benzene (20 ml) solution of the white powders was subjected to chromatography on silica gel. Elution with benzene gave tetraphenylglycolide (II), which was recrystallized from ethyl acetate. From the filtered solution, methanol was distilled and ether (10 ml) was added. The ether solution was cooled to give a yellow solid (VII). The filtered ether solution gave V. The yields are shown in Table I.

The water layer offered no product. Tetraphenylglycolide (II) had mp 190–193°; ir 1750 cm^{-1} ($\nu_{C=O}$ of ester group); ^1H nmr ($CDCl_3$) τ 2.5–3.4 (Ph).

^{13}C nmr ($CHCl_3$) exhibited peaks at 166 corresponding to the ester group along with the peak at 129 ppm (Ph), from TMS over the range of 126–235 ppm.

The uv spectra of II have no absorption corresponding to *cis*-stilbene [292 mμ (ε 1.01 × 10^4) in THF] type over the range of 280–310 mμ, indicating no double bond in the structure of II.

Anal. Calcd for $C_{28}H_{20}O_4$: C, 79.98; H, 4.79; mol wt, 420. Found: C, 79.85; H, 4.85; mol wt, 432.

Moreover, II was identified by mixture melting point with the authentic sample,[13] mmp 189–192°. Bisbenzilketazine (VII) and diphenylacetic acid (V) were identified respectively by infrared spectral comparison and the mixture melting point with authentic samples: VII, mmp 200–201° (lit.[14] mp 202°), and VII, mmp 148° (lit.[7a] mp 148°).

B. Reaction of Diazoacetophenone (VIII) with Molecular Oxygen.—Into a xylene solution (80 ml of xylene) of diazoacetophenone (7.3 g, 0.05 mol), molecular oxygen gas (280 l.) was passed for 4.5 hr at 130–140°. The products were separated by chromatography using silica gel as the adsorbent. The products, corresponding butenolide (IX), mp 107–108°, and the dimer X, mp 288–289°, were obtained in the yields shown in Table I. These products were identified by infrared spectral comparison and the mixture melting point, 107–108 and 288–289°, respectively, with the samples (lit.[8a] mp of IX 107–108°; mp of X 288–289°).

C. Reaction of Methylbenzoyldiazomethane (XI) with Molecular Oxygen.—Molecular oxygen gas (280 l.) was passed into a toluene solution (toluene 100 ml) of methylbenzoyldiazomethane (6.4 g, 0.04 mol) for 4.5 hr at 110–115°. Absorption of a cyclic ester group (1750 cm^{-1}) was absent in the ir spectrum of the reaction mixture. The products, vinyl phenyl ketone (XII) and phenyl methylacetic acid (VI), were obtained by using silica gel chromatography. The yields are shown in Table I. Vinyl phenyl ketone was identified by infrared spectral and boiling point comparison with the authentic sample, bp 115° (18 mm) [lit.[7c] bp 115° (18 mm)]. Phenylmethylacetic acid, obtained after hydrolysis, was identified by the sample (lit.[15] mp 265–268°).

D. Reaction of Phenylacetyldiazomethane (III) with Molecular Oxygen.—To a benzene solution (benzene 70 ml) of phenylacetyldiazomethane (3.2 g, 0.02 mol), molecular oxygen gas (280 l.) was added for 4.5 hr at 60–70°. Water (20 ml) and ether (20 ml) were added into the reaction mixture. The organic layer was separated, from which benzene and ether were evaporated under reduced pressure. To the residue, methanol (100 ml) was added. The methanol solution was cooled to give the white powders. The benzene (20 ml) solution of the white powders was subjected to chromatography on silica gel. Elution with benzene gave 3,6-dimethyl-3,6-diphenylglycolide (IV), which was recrystallized from ethyl acetate. From the filtered solution, methanol was evaporated to offer phenylmethylacetic acid (VI), which was identified by infrared spectral comparison and mixture melting point with authentic sample, mmp 286–288° (lit.[15] mp 288–289°). The yields are shown in Table I.

3,6-Dimethyl-3,6-diphenylglycolide (IV) had mp 164–165°; ir 1750 cm^{-1} ($\nu_{C=O}$ of ester group); ^1H nmr ($CDCl_3$) τ 2.5–3.5 (10 H, phenyl), 8.0–8.6 (6 H, *S*-methyl).

^{13}C nmr ($CHCl_3$) showed peaks at 169 corresponding to the ester group along with the peak at 129 ppm (Ph) from TMS over the range of 126–235 ppm.

Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44; mol wt, 296. Found: C, 52.63; H, 5.37; mol wt, 285.

Photochemical Reactions of α-Diazo Ketones with Molecular Oxygen in Benzene.—Four α-diazo ketones as described in thermal reactions were used. Molecular oxygen (280 l.) was introduced into the benzene (300 ml) solution of α-diazo ketone (0.01 mol), which was irradiated by a high-pressure mercury lamp at 15–20°. The irradiation was stopped with disappearance of the absorption in ir caused by the diazo group. The products were separated in the manner as done in thermal reactions, respectively. The products and the yields are shown in Table II. These products were identified by infrared spectral comparison and mixture melting point with samples previously prepared.

Apparatus.—Ir spectra were taken on a Hitachi EPI-S2 type infrared spectrometer. Nmr spectra were obtained with a JNM3H-60 spectrometer. Mass spectra and uv spectra were run on a Hitachi VD-10001-A spectrometer and Hitachi EPS-3 spectrophotometer. Molecular weight was determined by a Hitachi Perkin-Elmer 115 apparatus.

Registry No.—I, 3469-17-8; II, 467-32-3; III, 3893-35-4; IV, 38436-21-4; VIII, 3282-32-4.

Acknowledgment.—The authors wish to thank Dr. H. Sugiyama (Research Institute for nonaqueous solution, Tohoku University) for his ^{13}C nmr measurement.

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(14) J. J. Ritter and G. M. Wiedemen, *J. Amer. Chem. Soc.*, **51**, 3583 (1929).

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Stereochemistry in Trivalent Nitrogen Compounds. XVIII. Slow Rotation about the Nitrogen-to-Carbonyl Bonds in *N,N'*-Biscarboethoxy-3,3,4,4-tetramethoxy-1,2-diazetidene[1a]

E. H. CARLSON, A. P. SCHAAP, AND M. RABAN* [1b]

Department of Chemistry, Wayne State University, Detroit, Michigan 48202

Received May 16, 1972

The conformational processes associated with nmr line shape changes in *N,N'*-biscarboalkoxy cyclic hydrazines have been the subject of considerable experimental work and speculation.[2] Three different types of conformational changes have been discussed as possible sources for the coalescence phenomena observed in such systems: (a) nitrogen inversion,[3] (b) rotation about amide bonds,[4] and (c) ring flexion in six-membered rings or even in bicyclic ring systems. We have examined the nmr spectral behavior of *N,N'*-biscarboethoxy-3,3,4,4-tetramethoxy-1,2-diazetidene (1) in order to examine a system in which two of these factors could be controlled.

(1) (a) Part XVII: D. Kost and M. Raban, *J. Amer. Chem. Soc.*, **94**, 2533 (1972). (b) Alfred P. Sloan Foundation Fellow, 1972–1974.

(2) (a) J. E. Anderson and J. M. Lehn, *Tetrahedron*, **24**, 123 (1968); **24**, 137 (1968); and papers cited therein; (b) W. D. Phillips, unpublished results cited in W. D. Phillips, in "Determination of Organic Structures by Physical Methods," Vol. 2, Academic Press, New York, N.Y., 1962, Chapter 6; (c) B. Price, I. O. Sutherland and F. G. Williamson, *Tetrahedron*, **22**, 3477 (1966).

(3) Reviews: (a) J. M. Lehn, *Fortschr. Chem. Forsch.*, **15**, 311 (1970); (b) A. Rauk, L. C. Allen, and K. Mislow, *Angew. Chem., Int. Ed. Engl.*, **9**, 400 (1970); (c) J. Lambert in "Topics in Stereochemistry," Vol. VI, E. L. Eliel and N. L. Allinger, Ed., Wiley, New York, N. Y., 1971, p 19.

(4) Reviews: (a) W. E. Stewart and T. H. Siddall, III, *Chem. Rev.*, **70**, 517 (1970); (b) H. Kessler, *Angew. Chem., Int. Ed. Engl.*, **9**, 219 (1970).

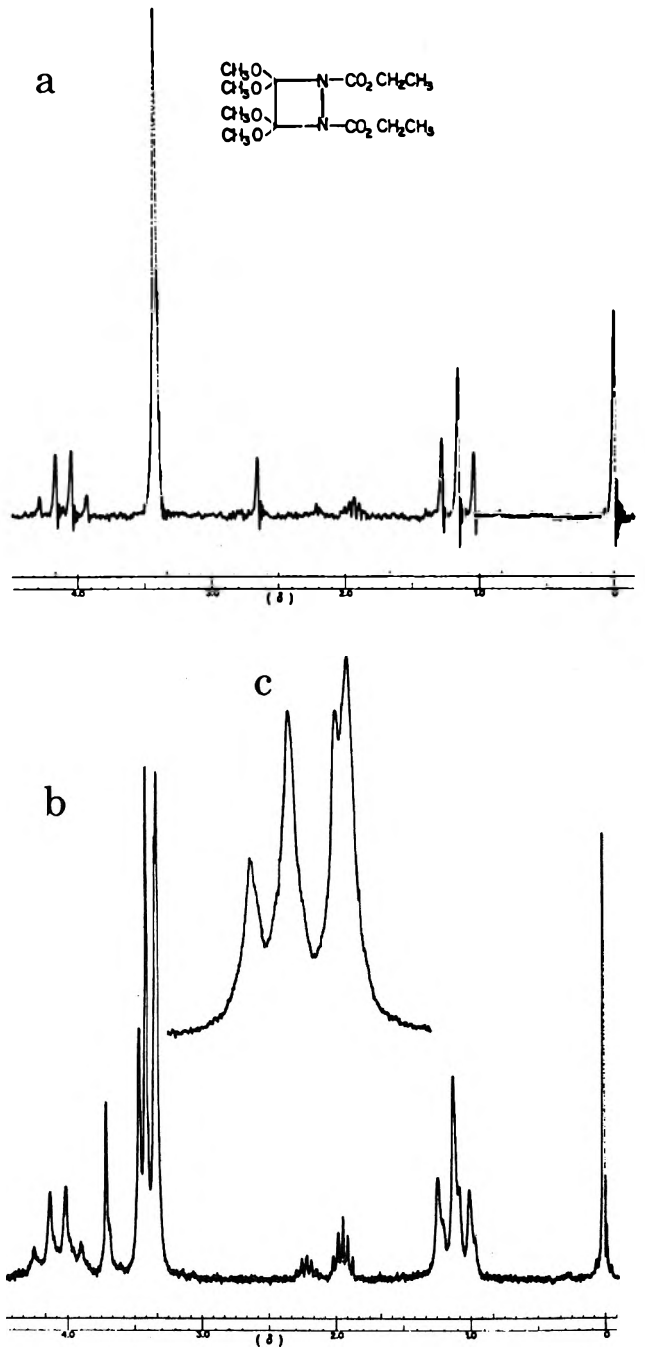
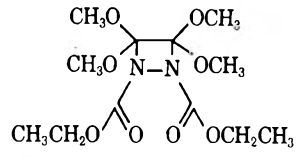


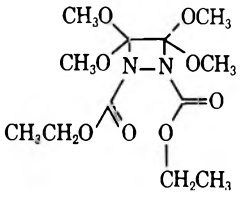
Figure 1.—Nmr spectra of 1 in acetone-d_6–toluene-d_8. (a) Spectrum recorded at room temperature; the peaks at δ 1.9, 2.2, and 2.7 are due to impurities toluene-d_7, acetone-d_5, and water, respectively. (b) Spectrum recorded at −65°. The peaks for acetone-d_5 and toluene-d_7 are unchanged, but the peak for the water impurity is shifted to δ 3.7. (c) Expanded scale spectrum of the methoxy region recorded at −65°.

The presence of the small ring system in **1** might be expected to affect both barriers to a and c. The ring strain present in four-membered rings is known to lower barriers to ring reversal and to increase barriers to nitrogen inversion. As a result, while the barrier to rotation about the nitrogen–carbonyl bond should be approximately the same in **1** as in six-membered ring analogs, the nitrogen inversion barrier should be higher, and the barrier to ring reversal should be much lower or absent. The only previous study on a similar compound is an investigation of *N,N'*-biscarboethoxy-3,3,4,4-tetrafluorodiazetidene.[2b] The chemical shift nonequivalence of geminal fluorine atoms observed in that study is consistent with barrier to nitrogen inversion[2b] or ring flexion.[2c] No evidence for slow rotation about amide bonds could be detected.

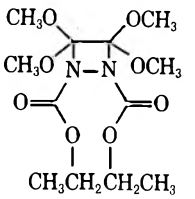
The variable-temperature nmr spectra of **1** exhibit only a single coalescence phenomenon in the neighborhood of −40 to −20°. Below this temperature range the methoxy groups appear as four singlets in acetone-d_6–toluene-d_8 (Figure 1), or as two singlets in acetone-d_6. The coalescence of the four methoxy singlets is consistent with the interconversion of the three isomers **1a**, **1b**, and **1c**.



1a



1b



1c

The most deshielded of the low-field singlets most likely arises from the methoxyl groups in the *out–out* isomer **1c**, which appear from models to be in the deshielding region of the carbamate carbonyl groups. The other low-field singlet would then arise from the methoxyls cis to the carbonyl in the *in–out* isomer, **1b**. The upfield methoxy singlets are associated with **1a** and the methoxy groups cis to the ethoxy group in **1b**. Based on the integrated intensities of the four peaks obtained by computer simulation, A:B:C:D = 18:29:24:29, we estimate the relative concentrations of **1a**:**1b**:**1c** to be 24:58:18. The differences in free energies of formation were thus obtained by complete line shape analysis: $\Delta G_{-65°}$ (**1b** → **1a**) = 0.3 kcal/mol, $\Delta G_{-65°}$(**1b**→**1c**) = 0.5 kcal/mol; as was the free energy of activation: $\Delta G_{-27°}^{\ddagger}$ (**1b** → **1a**) = 13.6 kcal/mol.

In acetone-d_6 the low-field pair of singlets ("out" methoxyls) apparently coincide, as do the two high-field singlets ("in" methoxyls), and only two singlets are observed. The torsional barrier was obtained at the coalescence point in acetone-d_6 using the approximate formula,[5] $k_c = (\pi/\sqrt{2})\Delta\nu$: $T_c = -25°$, $\Delta\nu$ = 3 Hz, $\Delta G_c^{\ddagger}$ = 13.8 kcal/mol. The values obtained in both solvent systems are fairly similar to those obtained by Anderson and Lehn for restricted rotation in bicyclic analogs of **1**.[2a]

No evidence for slow nitrogen inversion could be detected down to −125°. Apparently, even with the ring strain present in the four-membered diazetidine ring and the presence of a nitrogen–heteroatom bond, nitrogen inversion remains rapid. Our results are in accord with the conclusions[2a] that slow nitrogen inversion is not responsible for nmr line shape changes in biscarboalkoxy cyclic hydrazines and that barriers in

(5) For evidence of the reliability of this approach, see D. Kost, E. Carlson, and M. Raban, *Chem. Commun.*, 656 (1971).

the neighborhood of 13–14 kcal/mol can be ascribed to amide torsional barriers. Our results, however, are in striking contrast with those reported for the analagous compound in which the methoxy groups are replaced by fluorine atoms.[2b] Unless accidental equivalence is responsible for the differences in the two systems, it would appear that replacement of fluorine by methoxy both raises the amide barrier and lowers the barrier to nitrogen inversion[2b] (or ring reversal[2c]).

Experimental Section

N,N'-Biscarboethoxy-3,3,4,4-tetramethoxy-1,2-diazetidene was prepared as previously reported.[6]

The nmr spectra were measured on a Varian A-60A spectrometer equipped with a Varian variable-temperature probe using *ca.* 10% solutions. Temperatures were determined using methanol spectra as described in the Varian Manual. Rate constants and equilibrium constants were determined by matching experimental spectra with theoretical spectra. The theoretical spectra were generated using Saunder's Many Site NMR Lineshape Program.[7] This program allows the calculation of nmr spectra involving exchange between n sites ($2 \leq n \leq 25$) which must be uncoupled, but need not have the same population. The two "out" methoxy groups of **1b** which are diastereotopic with respect to the "in" methoxy groups were treated as two separate isomers. Exchange was assumed to be possible between **1a** and both sites in **1b** and between **1c** and both sites in **1b**, but not directly between **1a** and **1c**, nor between the "in" and "out" sites of **1b**. The chemical shift differences and the relative populations were temperature dependent and were determined by iterating to obtain the best fit.

Registry No.—**1**, 10200-65-4.

Acknowledgments.—We thank Daniel Combs and Bashir Kaskar for synthetic assistance, Dr. Eric Noe for assistance with nmr spectra, and Professor Martin Saunders for providing a copy of his multisite complete line shape analysis computer program. Support for this work was provided by the National Science Foundation (M. R.) and by the doners of the Petroleum Research Fund, administered by the American Chemical Society (A. P. S.).

(6) R. W. Hoffmann and H. Hauser, *Angew. Chem.*, **76**, 346 (1964).
(7) M. Saunders, *Tetrahedron Lett.*, 1699 (1963). See also C. S. Johnson, Jr., in "Advances in Magnetic Resonance," Vol. 1, J. S. Waugh, Ed., Academic Press, New York, N. Y., 1965, Chapter 2.

The Stereochemistry of the Hydroboration Reaction

GEORGE W. KABALKA* AND NEWELL S. BOWMAN

Chemistry Department, University of Tennessee, Knoxville, Tennessee 37916

Received September 26, 1972

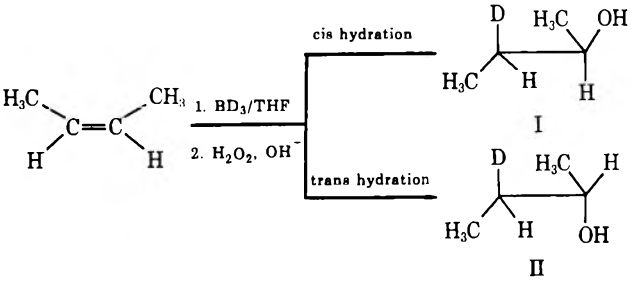
In the course of our efforts to elucidate the stereochemistry of various organoborane reactions, we had reason to deuterioborate *cis*- and *trans*-2-butene, respectively, and oxidize the resultant organoboranes. Nmr analysis of the resultant 2-butanol-*3-d* from the respective reaction mixtures demonstrates conclusively that the hydroboration–oxidation sequence is a stereospecific cis-hydration reaction.

The hydroboration–oxidation sequence is generally accepted as a method to achieve cis-hydration of alkenes. Evidence to that effect has been accumulating for a number of years.[1–5] However, essentially all of the studies have been carried out on cyclic systems. In general the products observed were the thermodynamically most stable ones. In one instance, it was demonstrated that isomeric acyclic alkenes could be hydroborated and then oxidized to produce different diastereomeric alcohols.[5] However, the configurations of the starting alkenes[6] and the product alcohols[7] were assigned by analogy to a related system.

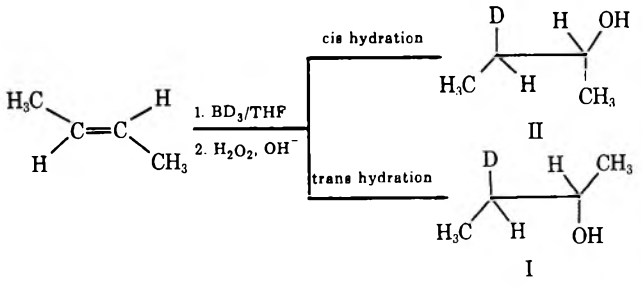
Results and Discussion

The 2-butene system would seem to be an ideal choice for the study of the stereochemistry of the hydroboration–oxidation sequence. The molecule contains a plane of symmetry with two stereoequivalent trigonal carbon atoms. Unlike cyclic or conjugated systems, free rotation of the tetrahedral addition or oxidation intermediates is possible, and if such rotation were to occur, there should be limited steric bias to affect the product distribution.

One could then visualize two possible products from the deuterioboration–oxidation sequence for *cis*-2-butene. The *erythro*-2-butanol-*3-d* (I) would arise from overall cis-hydration, whereas a trans-hydration would produce the *threo*-2-butanol-*3-d* (II).



The stereochemistry of the resultant products would, of course, be reversed in the case of *trans*-2-butene. The *threo*-2-butanol-*3-d* (II) would arise from overall cis-hydration, whereas a trans-hydration would produce the *erythro*-2-butanol-*3-d* (I).



(1) H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **81**, 247 (1959).
(2) W. Wechter, *Chem. Ind. (London)*, 294 (1959).
(3) H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **83**, 2544 (1961).
(4) H. C. Brown and J. H. Kawakami, *ibid.*, **92**, 1990 (1970).
(5) E. L. Allred, J. Sonnenberg, and S. Winstein, *J. Org. Chem.*, **25**, 26 (1960).
(6) D. J. Cram, *J. Amer. Chem. Soc.*, **71**, 3883 (1949).
(7) S. Winstein and G. C. Robinson, *ibid.*, **80**, 170 (1958).
(8) L. M. Jackman and N. S. Bowman, *ibid.*, **88**, 5565 (1966).

It has been demonstrated that the two possible products (*erythro*- and *threo*-2-butanol-*3-d*) can be readily differentiated *via* nmr spectroscopy.[8] The differentiation is based on the fact that the methylene protons in 2-butanol are magnetically nonequivalent.

We have deuterioborated *cis*-2-butene and find that the oxidized product exhibits an nmr spectrum identical with the published spectrum of *erythro*-2-butanol-*3-d*.[8] There is no evidence for the presence of the threo isomer within the accuracy of our nmr analysis (approximately 1%). In addition we have deuterioborated *trans*-2-butene and find that the oxidized product exhibits an nmr spectrum identical with the published spectrum of *threo*-2-butanol-*3-d*[8] with no evidence for the presence of the erythro isomer.

Consequently, we conclude that the hydroboration–oxidation sequence achieves, exclusively, the stereospecific cis-hydration of simple, acyclic alkenes.

Experimental Section

Spectra.—The spectra were run on a Varian HA-100 spectrometer.

Materials.—Lithium deuteride (Merck Sharpe and Dohme), *cis*-2-butene (Matheson), and *trans*-2-butene (Matheson) were used as received. Diglyme (Ansul) and tetrahydrofuran (Fisher) were distilled from lithium aluminum hydride prior to use. Boron trifluoride etherate (Fisher) was distilled from calcium hydride prior to use.

Borane-d_3 in tetrahydrofuran was prepared according to standard procedures.[9,10]

Preparation of *erythro*-2-Butanol-*3-d*.—*cis*-2-Butene (4.1 ml, 50 mmol) was condensed at −78° and then introduced (as a gas) to a stirred solution of borane-d_3 (8.3 mmol) in THF which was maintained at 0°. The introduction of the *cis*-2-butene is readily accomplished by attaching the flask containing the condensed alkene to the reaction flask *via* a section of Tygon tubing and then allowing the alkene to warm to room temperature. This affords a slow addition of the 2-butene to the borane-d_3 solution.

The reaction mixture was stirred at 0° for 30 min and then allowed to warm to room temperature. The resultant tri-*sec*-butylborane was oxidized at 50° (water bath) by the addition of 3 ml of 3 *N* sodium hydroxide followed by 3 ml of 30% hydrogen peroxide. The reaction mixture was stirred at 50° for 1 hr and then was saturated with potassium carbonate. The THF layer was separated and the water layer was extracted with 2 × 30 ml of ethyl ether. The ether layers were combined and dried ($MgSO_4$), and the solvent was removed under reduced pressure. Gc analysis of the product at this point (utilizing decane as an internal standard) indicated a 96% yield of pure 2-butanol-*3-d*. The product was isolated by preparative gc (10% Carbowax on Chromosorb W, 20 ft).

Preparation of *threo*-2-Butanol-*3-d*.—The synthesis was carried out exactly as described above for the *erythro*-*3-d* except that *trans*-2-butene (4.1 ml, 50 mmol) was utilized rather than *cis*-2-butene.

Gc analysis of the resultant 2-butanol-*3-d* (decane as internal standard) indicated a 92% yield of pure alcohol. The product was isolated by preparative gc (10% Carbowax on Chromosorb W, 20 ft).

Registry No.—I, 10277-59-5; II, 10277-60-8; *cis*-2-butene, 590-18-1; *trans*-2-butene, 624-64-6.

Acknowledgment.—The authors would like to thank Research Corporation for support of this work.

(9) H. C. Brown and G. Zweifel, *Org. React.*, **13**, 32 (1961).

(10) H. C. Brown, K. J. Murray, L. J. Murray, J. A. Snover, and G. Zweifel, *J. Amer. Chem. Soc.*, **82**, 4233 (1960).

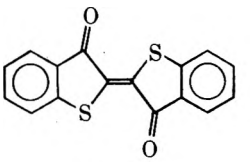
The Configuration of the Thioindigo Anion Radical

RAYMOND CHANG,* DAVID G. KEHRES,[1] AND J. HODGE MARKGRAF

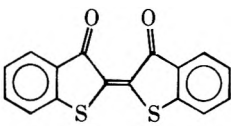
Department of Chemistry, Williams College, Williamstown, Massachusetts 01267

Received October 31, 1972

Although thioindigo was first reported in 1906,[2] the question of cis–trans isomerism does not appear to have been treated explicitly until 45 years later. Wyman and Brode established that the relative amounts of cis and trans isomers in solution were a function of temperature and irradiation.[3] Subsequently, Wyman studied the photochemical aspects of this system in greater detail.[4,5] We have recently elucidated the structure of the stilbene anion radical by ultraviolet and electron spin resonance spectroscopic techniques.[6] As part of a study to define the utility of this combined uv–esr procedure, we directed our attention to the thioindigo system (**1**).



trans-**1**



cis-**1**

From the visible spectrum of **1** in 1,2-dimethoxyethane (DME) it was determined that the cis:trans ratio was 15:85. These relative concentrations were estimated by computer simulation, based on the line shapes reported by Blanc and Ross.[7] When a small amount of thioindigo anion radical ($\mathbf{1}^-$) was generated by reduction with potassium, the visible spectrum of the solution was altered. The result was a complete shift to the trans isomer. The fact that no change in the spectrum was observed when the solution was quenched by exposure to air demonstrated that the anion radical concentration was very low. From these data it can be concluded that the anion radical does not affect the absorption curves but only serves to shift the relative concentrations toward the trans isomer; this behavior is the same as that observed in the stilbene system.[6] The isomerization can be considered to proceed *via* those species shown in Scheme I.[8] Simple molecular orbital calculations suggest that the conversion of **1** to $\mathbf{1}^-$ is accompanied by a decrease in the bond order of the central ethylenic linkage. Since the cis isomer is presumably less stable owing to repulsion between the carbonyl groups, the

(1) Based in part on the Honors Thesis of D. G. K., Williams College, 1972.

(2) P. Friedländer, *Ber.*, **39**, 1060 (1906).

(3) G. M. Wyman and W. R. Brode, *J. Amer. Chem. Soc.*, **73**, 1487 (1951).

(4) D. A. Rogers, J. D. Margerum, and G. M. Wyman, *ibid.*, **79**, 2464 (1957).

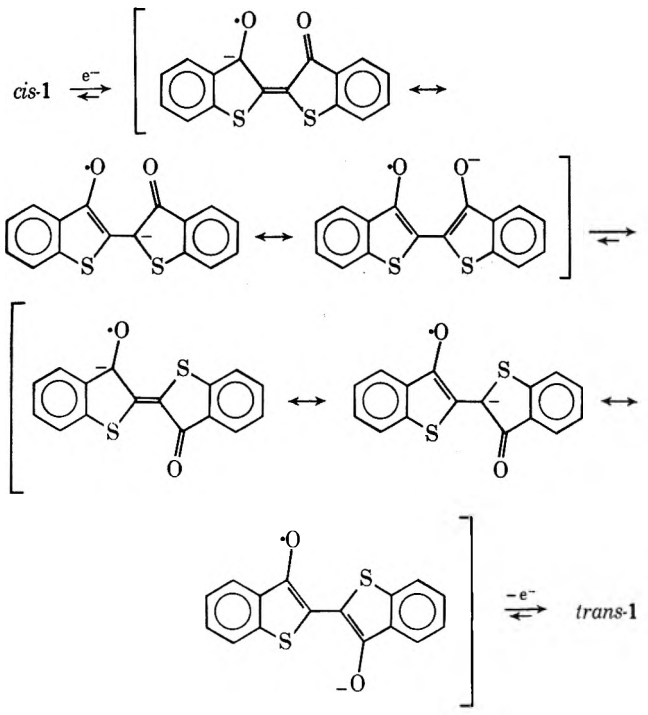
(5) G. M. Wyman, *Chem. Commun.*, 1332 (1971).

(6) R. Chang and J. H. Markgraf, *Chem. Phys. Lett.*, **13**, 575 (1972).

(7) J. Blanc and D. L. Ross, *J. Phys. Chem.*, **72**, 2817 (1968).

(8) Only those contributing structures of the anion radical which seem pertinent to the isomerization are represented, although it is known from the esr spectrum that the unpaired electron is delocalized throughout both benzene rings.

SCHEME I



observed isomerization of *cis*-**1** to *trans*-**1** is in accord with these considerations.

The complementary portion of the investigation involved esr spectra. Although such a spectrum has been reported for $\mathbf{1}^-$, no configurational assignments were discussed.[9] Ideally it is desirable to observe $\mathbf{1}^-$ in the presence of **1**, while irradiating at the appropriate wavelengths. Wyman and Brode[3] showed that when a neutral solution of **1** was irradiated with blue light the conversion to the trans isomer was almost quantitative, whereas the cis isomer was the major product when yellow light was employed. Thus irradiation with blue light of a solution of **1** in the presence of $\mathbf{1}^-$ should increase the esr line width as a result of faster electron transfer between the neutral molecule and the anion, if the latter also has the trans configuration. Conversely, a decrease in line width should be observed upon irradiation with yellow light.[10]

Since a saturated solution of **1** in DME was not greater than 10^{-3} M,[12] only an upper limit of the transfer rate could be estimated. No line width alterations were observed over a temperature range of -60 to 35°. Based on the analogy to the stilbene system, it was inferred that the species present was the trans isomer. Irradiation with blue light, therefore, would not bring a change in the line width; this was indeed observed. Although it was anticipated that irradiation with yellow light would sharpen the esr lines, such a procedure caused no detectable change.[13] Two factors may contribute to this absence of line sharpening. One is the low initial concentration of **1**; the other comprises the following relative rate considerations. The equilibria in the present example involve the neutral cis and trans molecules (c and t) and the corresponding anion radicals (c^- and t^-). Unlike the stilbene case,

$$t \underset{}{\overset{k_1}{\rightleftharpoons}} c \qquad (1)$$

$$t^- + t \overset{k_2}{\rightleftharpoons} t + t^- \qquad (2)$$

$$t^- + c \overset{k_3}{\rightleftharpoons} t + c^- \qquad (3)$$

$$c^- \overset{k_4}{\rightleftharpoons} t^- \qquad (4)$$

the rate constant for eq 3 was comparable in magnitude to that of eq 2. In fact, k_3 was so fast that immediately after irradiation with yellow light there was no detectable change in the visible spectrum. The fact that k_3 was comparable to k_2 ($>10^7$ M^{-1} sec^{-1}) was not totally unexpected in view of the overall similarity in shape of the two geometric isomers. Therefore, the absence of line sharpening is a consequence of the inability to increase the steady-state concentration of the neutral cis species.

From the results with stilbene and thioindigo we conclude that configurations of radicals can be deduced most effectively by the combined uv–esr method only when the geometries differ significantly. Although it is difficult to specify the precise spatial requirements necessary for electron transfer reactions, our studies of these two systems constitute a preliminary understanding of the dependence of such rates on structure.

Experimental Section

Thioindigo (**1**) was kindly supplied by Dr. George M. Wyman (Durham, N. C.); high-resolution mass spectral analysis established the absence of impurities.[14] Tetrahydrofuran and 1,2-dimethoxyethane were refluxed over calcium hydride for 24 hr, distilled, and stored over sodium–potassium alloy prior to use.

The usual high-vacuum methods for the preparation of the anion radicals were employed.[15] A deoxygenated solution of **1** in a completely sealed system was brought into brief contact with a potassium mirror, which was isolated from the rest of the system by a breakseal. The resulting solution was then poured into the appropriate sidearm to obtain either esr or visible spectra. The former were recorded on a Varian E-3 spectrometer with a variable temperature controller; the latter were recorded on a Cary Model 14 spectrophotometer. For combined esr–optical studies the sample was irradiated in the cavity with a PEK 100-W high-pressure mercury lamp. A 5-cm quartz cell containing water was used to filter infrared radiation; blue or yellow filters were used for isomerization studies.

Registry No.—*cis*-**1**, 3583-39-9; *trans*-**1**, 3844-31-3; *cis*-$\mathbf{1}^-$, 38425-40-0; trans-$\mathbf{1}^-$, 38425-41-1.

(9) M. Bruin, F. Bruin, and F. W. Heineken, *J. Chem. Phys.*, **37**, 135 (1962). The coupling constants obtained in our study are essentially the same as those reported by these authors.

(10) The dependence of electron transfer rate on structure is based on the Franck–Condon principle, which was first employed in this manner by Libby[11] to explain certain inorganic electron transfer reactions. In essence, this application states that electron transfer from one species to another in a collision complex may be treated as if it were an electronic transition and that to lower the free energy of activation both species must have similar configurations.

(11) W. F. Libby, *J. Phys. Chem.*, **56**, 863 (1952).

(12) Other solvents proved no more suitable. The solubility of **1** in tetrahydrofuran was comparable to that in DME. In benzene and toluene, in which **1** was more soluble, $\mathbf{1}^-$ was very unstable.

(13) At low temperature a reversible dimerization of the thioindigo anion radical was observed with concomitant formation of a diamagnetic species. Under more drastic conditions of irradiation at least two different types of neutral radicals were produced from either **1** or $\mathbf{1}^-$.

(14) C. W. Koch and J. H. Markgraf, *J. Heterocycl. Chem.*, **8**, 225 (1971).

(15) D. E. Paul, D. Lipkin, and S. I. Weissman, *J. Amer. Chem. Soc.*, **78**, 116 (1956).

A Novel McLafferty Rearrangement of Alkyl Sulfinyl Amines

JOHN R. GRUNWELL* AND ANDREW KOCHAN

Department of Chemistry, Miami University, Oxford, Ohio 45056

Received August 31, 1972

The problem of geometrical isomerism associated with N-substituted sulfinyl amines has received little attention except that we predicted that *N*-methylsulfinyl amine is more stable trans than cis by 13 kcal/mol.[1] We now report the mass spectral data, which give evidence for the validity of this prediction.

Recently, the mass spectra of several aryl sulfinyl amines showed significant migration of the aryl group from nitrogen to oxygen.[2] We do not find this rearrangement in the spectra of alkyl sulfinyl amines.

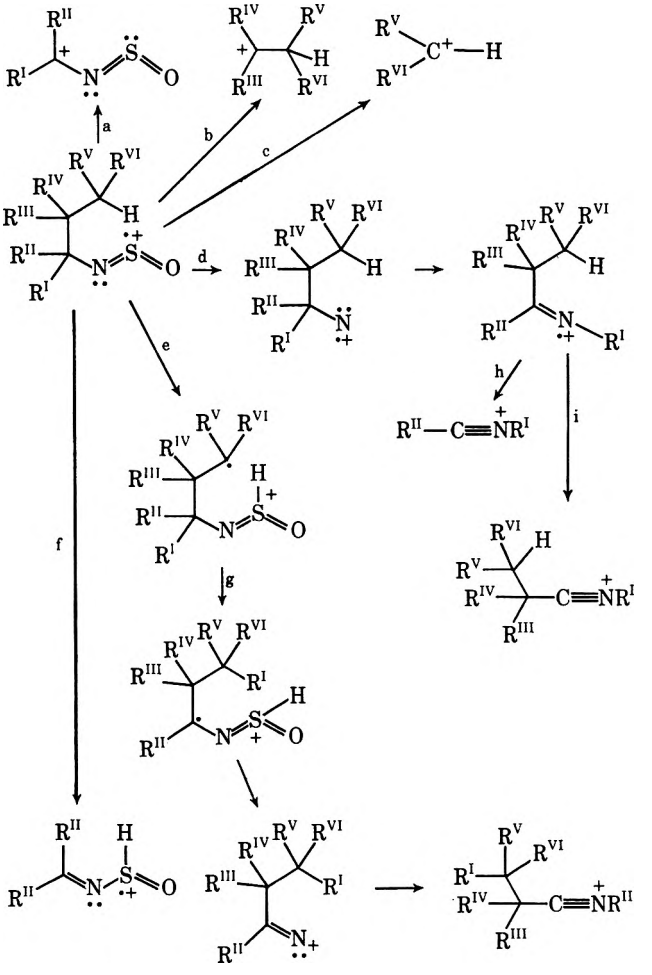
The mass spectra of di-*tert*-butylsulfur diimide and di-*n*-butylsulfur diimide reveal a double McLafferty rearrangement giving an ion at *m/e* 62 ($HN^+{=}S{=}NH$),[3] but *N*-alkyl sulfinyl amines do not fragment to give an ion at *m/e* 63 ($HOS^+{\equiv}N$). This latter result suggests that the alkyl group is trans to oxygen in the sulfinyl amines. A general scheme for the fragmentation pattern of sulfinyl amines is presented in Scheme I. The molecular ions are in low abundance compared to the aryl derivatives.

N-1-Butylsulfinylamine radical cation ($R^I = R^{II} = R^{III} = R^{IV} = R^V = H$; $R^{VI} = CH_3$) suffers the loss of propene to form the ion *m/e* 77 (pathway f) while the *N*-2-butylsulfinylamine cation ($R^I = CH_3$; $R^{II} = R^{III} = R^{IV} = R^V = R^{VI} = H$) loses ethylene to form the ion *m/e* 91. Fragmentation of the cation of *N*-3-methyl-1-butylsulfinylamine ($R^V = R^{VI} = CH_3$; $R^I = R^{II} = R^{III} = R^{IV} = H$) gives an ion *m/e* 77 and the cation of *N*-2-pentylsulfinylamine ($R^I = R^{VI} = CH_3$; $R^{II} = R^{III} = R^{IV} = R^V = H$) fragments to an ion at *m/e* 91.

These ions arise *via* a McLafferty rearrangement in which hydrogen is abstracted from the γ-carbon atom by sulfur as shown in Scheme I by step f. However, when the α-carbon atom is highly substituted, then simple cleavage of the α,β carbon–carbon bond is more prominent than the McLafferty rearrangement just mentioned. This cleavage (pathway a) is exemplified by *N*-1,1-dimethyl-1-propylsulfinylamine ($R^I = R^{II} = CH_3$; $R^{III} = R^{IV} = R^V = R^{VI} = H$), which loses an ethyl group to form an ion at *m/e* 104, the most abundant ion in the spectrum. The same ion is the result of the most important fragmentation of *N*-2-methyl-2-propylsulfinylamine.

However, when the β carbon is highly substituted, then the positive charge becomes associated with the alkyl fragment (pathway b), a pattern which is shown by *N*-2,2-dimethyl-1-propylsulfinylamine ($R^I = R^{II} = R^V = R^{VI} = H$; $R^{III} = R^{IV} = CH_3$) giving the *tert*-butyl cation as the base peak. Pathway c is only important for *N*-3-methyl-1-butylsulfinylamine.

SCHEME I



Another important fragmentation pathway involves the initial loss of sulfur monoxide. For example, *N*-2-butylsulfinylamine forms an ion at *m/e* 71 which subsequently fragments to ions at *m/e* 56 and 42 by cleavage of methyl and ethyl radicals, respectively. This pathway is represented by steps d to i and h. The same process occurs in *N*-2-pentylsulfinylamine, except that the ion at *m/e* 85 fragments to *m/e* 70 and 42 by loss of methyl and propyl radicals.

Some of the sulfinylamines, particularly those which undergo an efficient McLafferty rearrangement, suffer loss of the elements of HS=O as represented by step g following e. *N*-1-Butylsulfinylamine shows a prominent peak at *m/e* 70, while *N*-3-methyl-1-butylsulfinylamine gives an ion at *m/e* 84.

When the alkyl group of a sulfinyl amine is trans to the oxygen atom, then the rearrangement shown in step f of Scheme I may occur. In analogy with the mass spectrum of bis-*tert*-butylsulfur diimide (**1**) (the nmr spectrum[4] of **1** at $-40°$ is two peaks of equal intensity showing that one *tert*-butyl group is cis), an ion at *m/e* 63 ($HOSN^+$) may be expected if the alkyl group is cis to the oxygen of a sulfinyl amine. None of the sulfinyl amines exhibit a peak at *m/e* 63, while several of them fragment according to mechanism f. These observations suggest that the alkyl group of sulfinyl amines is trans. Further, *N*-1-butylsulfinylamine does not pyrolyze to 1-butene, which is the product of the pyrolysis of the corresponding sulfur diimide.[4]

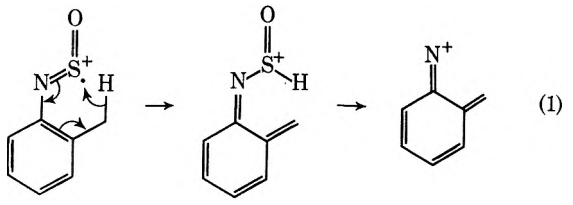
(1) J. R. Grunwell and W. C. Danison, *Tetrahedron*, **27**, 5315 (1971).

(2) J. H. Bowie, F. C. V. Larsson, G. Schroll, S.-O. Lawesson, and R. G. Cooks, *Tetrahedron*, **23**, 3743 (1967).

(3) J. L. Downie, R. Maruca, and J. R. Grunwell, *Chem. Commun.*, 298 (1970).

(4) J. R. Grunwell, J. A. Rieck, and C. Hoyng, unpublished results.

In view of the observed McLafferty rearrangement, the loss of the elements HS=O from 2-methylsulfinylaniline may be reinterpreted in terms of trans isomer (eq 1).



(1)

Although the molecular ions were in extremely small abundance, the nmr spectra and elemental analyses provide convincing evidence that the sulfinylamines are pure. The nmr spectrum of *N*-2,2-dimethyl-1-propylsulfinylamine showed a singlet resonance at δ 3.8 ppm for the methylene protons on carbon adjacent to nitrogen. This signal did not split or broaden at $-100°$, so that if rapid interconversion between trans and cis isomers is occurring at room temperature it should be slowed sufficiently at $-100°$ to observe two signals unless the cis isomer is a maximum on the rotational potential surface or is much less stable than the trans isomer. Also, *N*-2-methyl-2-propylsulfinylamine has a singlet proton resonance at δ 1.50 ppm which does not change at $-100°$.

Experimental Section

All mass spectra were measured with a Hitachi Perkin-Elmer RMU-6 mass spectrometer operating at 70 eV and with the inlet system at 200°. All nmr spectra were measured with a Jeolco C-60H spectrometer with TMS as the internal reference (δ = 0.00 ppm). Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

General Procedure. Synthesis of Sulfinyl Amines.— Sulfinyl amines were prepared by the method described by Michaelis and Stornbeck[5] by adding thionyl chloride (0.095 mol in 75 ml of ether) to the appropriate alkyl amine (0.29 mol in 100 ml of ether) maintained at 0° for 1 hr. The ether was filtered and then removed by distillation at atmospheric pressure. The remaining residue is placed on a high vacuum line (10^{-5} mm) and fractionated through three traps maintained at $-45°$ (chlorobenzene slush), $-77°$ (Dry Ice–acetone), and $-196°$ (liquid N_2). Pure sulfinyl amine was obtained from the $-45°$ trap by distilling into bulbs fitted with a stopcock for all mass spectral samples, into nmr tubes which were sealed off under vacuum, and into 3-mm tubing sealed under vacuum for all analytically pure samples. A satisfactory analysis could not be obtained for *N*-3-methyl-1-butylsulfinylamine because this compound suffers a mysterious decomposition at room temperature within 0.5 hr, turning yellow and finally solid after a couple of days.

N-1-**Butylsulfinylamine**[6] had mass spectrum (70 eV) *m/e* (rel intensity) 77 (89), 76 (14), 75 (11), 71 (14), 70 (54), 55 (11), 50 (13), 43 (100), 42 (16), 41 (86), 39 (23), 30 (13), 29 (35), 27 (65).

N-2-**Butylsulfinylamine** had mass spectrum (70 eV) *m/e* (rel intensity) 104 (5), 91 (58), 90 (100), 89 (17), 71 (28), 70 (11), 63 (14), 60 (20), 57 (15), 56 (35), 55 (11), 44 (53), 43 (49), 42 (71), 41 (44), 39 (17), 29 (61), 27 (54); nmr δ (multiplicity) 0.90 (3 H, t, J = 7.0 Hz), 1.33 (3 H, d, J = 7.0 Hz), 1.50 (2 H, q, J = 7.0 Hz), and 4.73 (1 H, sextet, J = 7.0 Hz).

Anal. Calcd for C_4H_9NSO: C, 40.31; H, 7.61; N, 11.76; S, 26.90. Found: C, 40.43; H, 7.68; N, 11.47; S, 26.77.

N-2-**Methyl-2-propylsulfinylamine**[7] had mass spectrum (70 eV) *m/e* (rel intensity) 104 (100), 74 (12), 57 (49), 56 (19), 42 (17), 41 (60), 39 (15), 29 (22), 27 (13); nmr δ (multiplicity) 1.50 (9 H, s).

N-2-**Pentylsulfinylamine** had mass spectrum (70 eV) *m/e* (rel intensity) 91 (78), 90 (34), 89 (14), 70 (34), 56 (11), 55 (19), 43 (100), 42 (53), 41 (55), 39 (24), 29 (20), 27 (47); nmr δ (multiplicity) 0.90 (3 H, t, J = 7.0 Hz), 1.00 (2 H, q, J = 7.0 Hz), 1.22 (3 H, d, J = 7.0 Hz), 1.47 (2 H, q, J = 7.0 Hz), 4.83 (1 H, sextet, J = 7.0 Hz).

Anal. Calcd for $C_5H_{11}NSO$: C, 45.08; H, 8.33; N, 10.51; S, 24.07. Found: C, 45.30; H, 8.43; N, 10.33; S, 23.90.

N-**3-Methyl-1-butylsulfinylamine** had mass spectrum (70 eV) *m/e* (rel intensity) 85 (17), 84 (24), 77 (74), 76 (19), 69 (16), 57 (63), 55 (36), 43 (80), 42 (26), 41 (100), 39 (33), 30 (16), 39 (70), 27 (40); nmr δ (multiplicity) 0.93 (6 H, d, J = 6.0 Hz), 1.57 (3 H, m), and 3.97 (2 H, t, J = 7.0 Hz). A satisfactory analysis was not obtained.

N-**1,1-Dimethyl-1-propylsulfinylamine** had mass spectrum (70 eV) *m/e* (rel intensity) 104 (100), 74 (17), 71 (13), 56 (12), 55 (20), 43 (29), 42 (34), 41 (34), 40 (17), 39 (15), 31 (10), 29 (14), 27 (46); nmr δ (multiplicity) 0.93 (3 H, t, J = 7.0 Hz), 1.47 (3 H, s), and 1.73 (2 H, q, J = 7.0 Hz).

Anal. Calcd for $C_5H_{11}NSO$: C, 45.08; H, 8.33; N, 10.15; S, 24.07. Found: C, 44.95; H, 8.40; N, 10.37; S, 23.85.

N-**2,2-Dimethyl-1-propylsulfinylamine** had mass spectrum (70 eV) *m/e* (rel intensity) 118 (3), 77 (4), 76 (3), 57 (100), 55 (13), 41 (47), 39 (14), 29 (35), 27 (12); nmr δ (multiplicity) 1.00 (9 H, s), 3,80 (2 H, s).

Anal. Calcd for $C_5H_{11}NSO$: C, 45.08; H, 8.33; N, 10.51; S, 24.07. Found: C, 45.25; H, 8.42; N, 10.39; S, 24.01.

Registry No.—*N*-1-Butylsulfinylamine, 13165-70-3; *N*-2-butylsulfinylamine, 13165-71-4; *N*-2-methyl-2-propylsulfinylamine, 38662-39-4; *N*-2-pentylsulfinylamine, 38662-35-0; *N*-3-methyl-1-butylsulfinylamine, 38662-36-1; *N*-1,1-dimethyl-1-propylsulfinylamine, 38662-37-2; *N*-2,2-dimethyl-1-propylsulfinylamine, 38662-38-3.

Acknowledgments.—We wish to thank the Miami University Faculty Research Committe for support and for a Summer Faculty Research Fellowship to J. R. G.

(5) A. Michaelis and O. Stornbeck, *Justus Liebigs Ann. Chem.*, **274**, 190 (1893).

(6) D. Klamann, C. Sass, and M. Zelenka, *Ber.*, **92**, 1910 (1959).

(7) W. T. Smith, P. A. Thio, and M. Grasley, *J. Org. Chem.*, **27**, 692 (1962).

Studies in the 1,4-Diphosphoniacyclohexadiene System. New Organophosphorus Heterocycles[1]

MOHINDER S. CHATTHA AND ADAM M. AGUIAR*

Rutgers University, Newark, New Jersey 07102

Received September 8, 1972

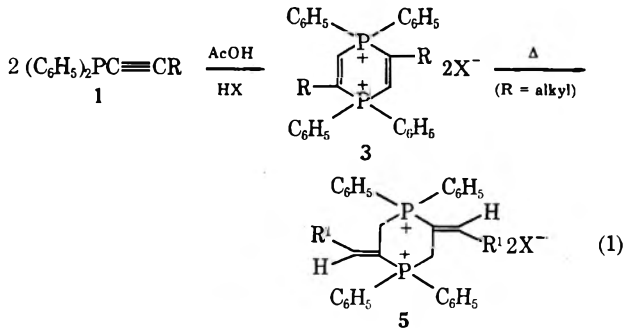
Some years ago it was found that alkynyl-1-phosphines **1** and **2** on treatment with HBr (or HCl) in glacial acetic acid produce the endocyclic dienes **3** and **4**, respectively (eq 1 and 2).[2-4] The endocyclic dienes **3** (R = primary or secondary alkyl) were found to readily isomerize on heating to the exocyclic dienes **5**;[3] however, unlike the P-phenylated dienes **3**, the P-alkylated dienes **4** failed to thermally isomerize to the corresponding P-alkylated exocyclic dienes **6** (eq 1 and 2).[4]

(1) Abstracted in part from the Ph.D. Dissertation of M. S. Chattha, Tulane University, New Orleans, La., 1971.

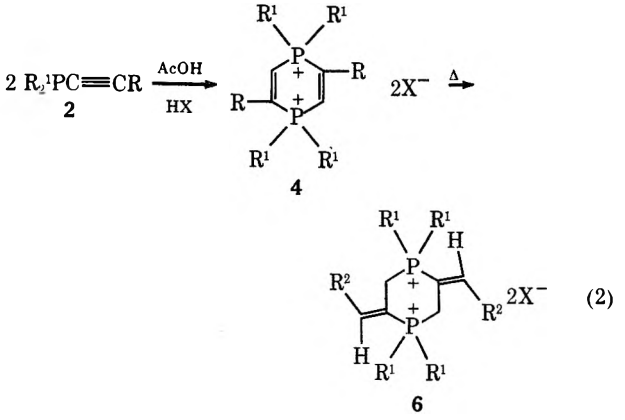
(2) A. M. Aguiar, K. C. Hansen, and G. S. Reddy, *J. Amer. Chem. Soc.*, **89**, 3067 (1967).

(3) A. M. Aguiar, G. W. Prejean, J. R. S. Irelan, and C. J. Morrow, *J. Org. Chem.*, **34**, 4024 (1969).

(4) A. M. Aguiar, J. R. S. Irelan, G. W. Prejean, J. P. John, and C. J. Morrow, *ibid.*, **34**, 2681 (1969).



R = alkyl, phenyl; X = Cl, Br; R^1 = alkyl, H

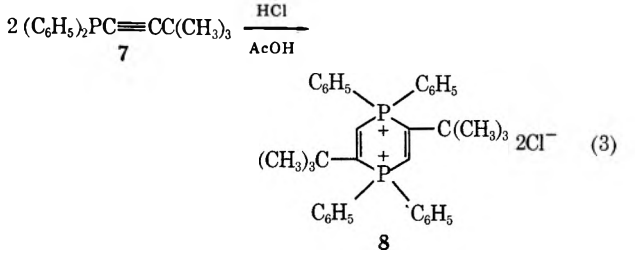


R = alkyl, phenyl; R^1 = alkyl; X = Br, Cl

However, the ^{31}P nmr spectra of the endocyclic dienes **4** displayed negative chemical shifts (relative to 85% phosphoric acid) similar to those of the exocyclic dienes **5**.

In order to study the effects exerted by various groups on phosphorus on the chemical shifts in the ^{31}P nmr spectra, and also on the amount of bond isomerization in the ring system, it was decided to synthesize a 1,4-diphosphoniacyclohexadiene system having an alkyl and a phenyl group on each phosphorus atom. Secondly, it was thought desirable to synthesize an endocyclic diene **3** with *tert*-butyl groups in the 2 and 5 positions; this compound would not isomerize to the exocyclic form and hence should permit us to investigate the effects exerted on the ^{31}P chemical shifts of the dienes **3** by the alkyl groups in the 2 and 5 positions.

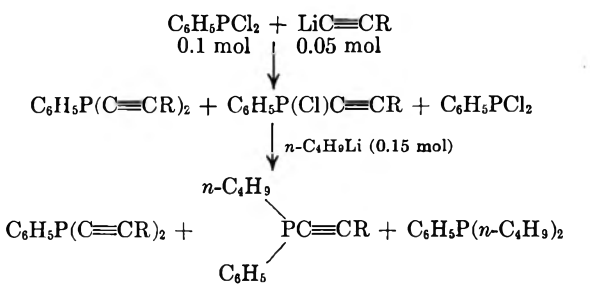
In order to synthesize a diene having *tert*-butyl groups at the 2 and 5 positions, the precursor, diphenyl-3,3-dimethylbutynylphosphine (**7**), was prepared by the reaction of diphenylphosphinous chloride with 3,3-dimethylbutynyllithium. Compound **7**, on treatment with HCl in glacial acetic acid, produced 1,1,4,4-tetraphenyl-1,4-diphosphonia-2,5-di-*tert*-butylcyclohexadiene 2,5-dichloride (**8**) in 70% yield (eq 3).



The ir spectrum (KBr) of **8** showed significant absorption bands at 6.12 (C=C) and 6.95 μ (PC_6H_5) and the nmr spectrum in trifluoroacetic acid (TFA) exhibited, in addition to the peaks corresponding to the phenyl and alkyl protons, a "pseudotriplet" (J = 28 Hz) at δ 8.46. This feature of the nmr spectrum seems to be very characteristic for these endocyclic dienes.[2-4] The structure of **8** was confirmed by the elemental analysis of its dipicrate.

To extend the investigation to the 1,4-diphosphoniacyclohexadiene system having an alkyl and a phenyl group on each phosphorus atom, alkyl phenyl alkynyl-1-phosphines **9** were needed as precursors. The alkynyl-1-phosphines **9** constitute a new class of unsaturated phosphorus compounds which have not yet been described. The phosphines **9** were prepared starting from phenylphosphonous dichloride and lithium alkynylides as shown in Scheme I.

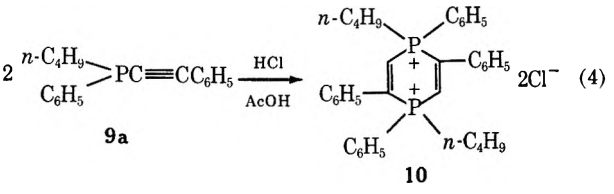
SCHEME I



a, R = C_6H_5; b, R = n-C_3H_7; c, R = n-C_4H_9

The usual work-up[3] and fractional distillation under reduced pressure afforded **9a-c** in 52-61% yield.

Treatment of **9a** with HCl in hot glacial acetic acid produced 1,4-di-*n*-butyl-1,2,4,5-tetraphenyl-1,4-diphosphoniacyclohexadiene 2,5-dichloride (**10**) in 41% yield (eq 4).

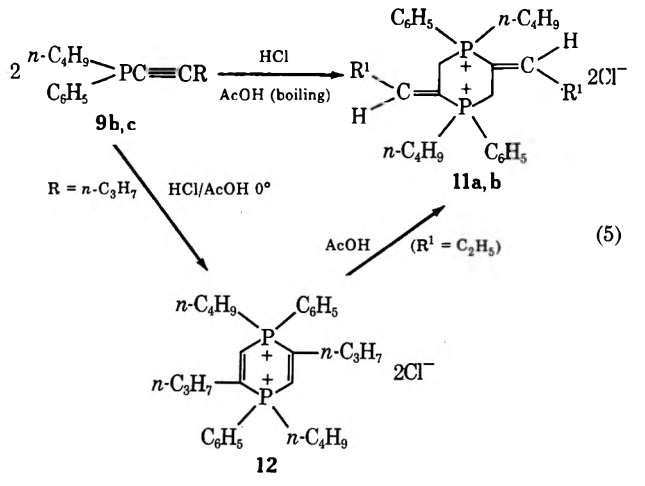


The ir and nmr spectra and the elemental analysis of the dipicrate of **10** supported its structure.

The phosphines **9b** and **9c**, when treated with HCl in hot glacial acetic acid, produced 1,4-di-*n*-butyl-1,4-diphenyl-1,4-diphosphonia-2,5-dialkylidenecyclohexane dichlorides (**11a** and **11b**, respectively, Scheme II). However, when **9b** was treated with HCl in glacial acetic acid at 0°, the endocyclic diene **12** was produced (Scheme II).

The ir spectra (KBr) of the dienes **11a,b** displayed strong absorption bands at 6.19 (C=C) and 6.95 μ (PC_6H_5) and the nmr spectra (TFA) of **11a,b** exhibited, in addition to other proton signals, a triplet (J = 13 Hz) at δ 4.25 and a doublet of two triplets (J_{PH} = 20, J_{HH} = 7 Hz) at 7.08. The triplet was assigned to the ring methylene protons, which are coupled to both the phosphorus atoms.[3] The signal centered at δ 7.08 is attributed to the olefinic protons, coupled to the vicinal chain methylene protons (J = 7 Hz).[3] The

SCHEME II



R = n-C_4H_9, n-C_4H_9; R^1 = C_2H_5, n-C_3H_7

stereochemistry of the butyl and phenyl groups on phosphorus in **10**, **11a**, and **11b** is not yet clear.

In order to demonstrate the thermal isomerization of the 1,4-diphosphoniacyclohexadienes, **12** was refluxed in acetic acid for 1 hr. The nmr spectra showed that **12** had completely isomerized to the corresponding exocyclic diene **11a** (R^1 = C_2H_5). At elevated temperatures the endocyclic dienes, having primary groups at the 2 and 5 positions, isomerize to the corresponding exocyclic dienes. It is also possible that at elevated temperatures, the P-phenylated alkynyl-1-phosphines rearrange to allene intermediates, which then cyclize to give the exocyclic isomers directly.

The only significant structural difference between the diphenylated exocyclic dienes **11a,b** and the tetraphenylated exocyclic dienes **5** is that the former compounds (**11a,b**) have one n-butyl and one phenyl group instead of two phenyl groups on each phosphorus atom. With this subtle difference, it seems reasonable to assume that the conformations of all these exocyclic dienes, in solution, are essentially the same. Based upon this assumption a comparison of ^{31}P chemical shifts of the diphenylated exocyclic dienes **11a,b** with those of tetraphenylated exocyclic dienes **5** (Table I) shows that

TABLE I

^{31}P CHEMICAL SHIFTS

Compd	Shift, ppm[a]
3 (R = C_6H_5)	+3.5[2]
10	−3.4
8	+3.7
5 (R^1 = n-C_5H_{11})	−17.0
11a	−23.2
11b	−23.3

[a] All the spectra were taken in methanol solution and the chemical shifts are relative to 85% phosphoric acid.

the phenyl groups on the phosphorus atoms exert a shielding effect on these atoms. Similarly, it may be assumed that the endocyclic diene **10** has the "boat" conformation like that of the endocyclic diene **3** (R = C_6H_5).[5] Again, the ^{31}P chemical shifts of these two endocyclic dienes, **3** (R = C_6H_5) and **10**, suggest that the phenyl groups on phosphorus atoms significantly shield these atoms. Further support for this is obtained from the fact that replacing a phenyl group by a n-butyl group on each phosphorus atom, in both the endocyclic and the exocyclic dienes, causes an essentially constant difference in the ^{31}P chemical shifts (Table I). The nature of this shielding is not yet well understood, but a possible explanation is a 2p–3d orbital overlap giving $p\pi$–$d\pi$ interaction; our current investigations are directed toward the understanding of these interactions.

(5) Dr. Louis Trefonas, Louisiana State University at New Orleans, private communication.

Experimental Section

General.—Reactions involving phosphines and organometallics were carried out under dry nitrogen. Diethyl ether was dried over sodium. Phenylphosphonous dichloride and diphenylphosphinous chloride were redistilled before use. Acetic acid was dried by addition of 50 ml of acetic anhydride to 1 gallon of reagent grade glacial acetic acid. Infrared spectra were taken with a Beckman IR-5A infrared spectrophotometer. Proton nuclear magnetic resonance spectra were taken with a Varian A-60 spectrometer. Melting points were determined in a Mel-Temp melting point apparatus and are uncorrected. All proton chemical shifts reported are in parts per million (δ) relative to an internal standard of tetramethylsilane.

Diphenyl 3,3-Dimethylbutynyl-1-phosphine (**7**).—This phosphine was prepared by the reaction of 3,3-dimethylbutynyllithium (0.05 mol) with diphenylphosphinous chloride (0.05 mol) in 250 ml of ether.[3] The usual work-up afforded the phosphine in 81% yield: bp 151–152° (0.2 mm); ir 4.6 μ (C≡C); nmr ($CDCl_3$) δ 7.85–7.18 (m, 10 H, phenyls), 1.32 (s, 9 H, *tert*-butyl group).

Anal. Calcd for $C_{18}H_{19}P$: C, 81.18; H, 7.19; P, 11.63. Found: C, 81.25; H, 7.07; P, 11.55.

Preparation of Phosphines 9a-c. General Procedure.—The alkyne (0.05 mol) was dissolved in 100 ml of ether under nitrogen and cooled with Dry Ice. A hexane solution of n-butyllithium (0.05 mol) was added slowly with continuous stirring. After 0.5 hr of stirring, this suspension of alkynyllithium was transferred to a dropping funnel with the help of a delivery tube under nitrogen pressure and then added dropwise to a Dry Ice cooled solution of 0.1 mol of phenylphosphonous dichloride in 100 ml of ether in a 500-ml three-necked flask. The reaction mixture was stirred for 45 min and then 0.15 mol of n-butyllithium solution in hexane was added slowly with Dry Ice cooling and continuous stirring. The reaction mixture was stirred for an additional 15 min and then 100 ml of saturated ammonium chloride solution was slowly added and the reaction mixture was stirred well. With the help of a bent tube under nitrogen pressure, the contents of the reaction vessel were transferred to a separatory funnel and the layers were separated. The organic layer was dried (Na_2SO_4), filtered, and fractionally distilled under reduced pressure. The second fraction was the desired product in each case.

n-Butylphenylphenylethynylphosphine (**9a**) had bp 170° (0.07 mm); yield 53%; ir ($CHCl_3$) 4.61 μ (C≡C); nmr ($CDCl_3$) δ 7.90–7.15 (m, 10 H, phenyl), 2.1–1.15 (m, 6 H, methylenes), 0.85 (t, J = 6.5 Hz, 3 H, methyl).

Anal. Calcd for $C_{18}H_{19}P$: C, 81.18; H, 7.19; P, 11.63. Found: C, 80.99; H, 7.11; P. 11.71.

n-Butylphenylpentynyl-1-phosphine (**9b**) had bp 143° (0.1 mm); yield 61%; ir ($CHCl_3$) 4.56 μ (C≡C); nmr ($CDCl_3$) δ 7.9–7.2 (m, 5 H, phenyl), 2.38 (close pair of t, J = 6.5 Hz, 2 H, C≡CCH_2), 1.85–1.25 (m, 8 H, methylenes), 1.02 (close pair of t, J = 6.9 Hz, 6 H, methyl).

n-Butylphenylhexynyl-1-phosphine (**9c**) had bp 159–160° (0.1 mm); yield 60%; ir ($CHCl_3$) 4.59 μ (C≡C); nmr ($CDCl_3$) 7.82–7.18 (m, 5 H) phenyl), 2.35 (close pair of t, 2 H, C≡CCH_2), 1.82–1.2 (m, 10 H, methylenes), 0.95 (crude pair of t, 6 H, methyl).

Anal. Calcd for $C_{16}H_{23}P$: C, 78.02; H, 9.41; P, 12.57. Found: C, 77.56; H, 9.38; P, 12.61.

Preparation of 8, 10, and 11a,b. General Procedure.—The alkynyl-1-phosphine (0.01 mol) was dissolved in 75 ml of acetic acid and a slow stream of HCl was passed through the solution for 1 hr. Owing to heat of solution of HCl, the reaction mixture started boiling. The reaction flask was cooled to room tempera-

ture, stoppered, and kept overnight. The acetic acid was distilled off under reduced pressure. The pale-white solid residue was washed twice with 25-ml portions of acetone and crystallized from mixed acetone–methanol solvent.

1,1,4,4-Tetraphenyl-2,5-di-*tert*-butyl-1,4-diphosphoniacyclohexadiene 2,5-dichloride (8) had mp 285–287°; yield 73%; ir (KBr) 6.12 (C=C), 6.95 μ (PC_6H_5); nmr (TFA) δ 8.45 (t, J = 28 Hz, 2 H, vinyl), 7.94 (m, 20 H, phenyl), 1.33 (s, 18 H, *tert*-butyl groups).

A methanol solution of **8** on treatment with a methanol solution of sodium picrate produced an orange, crystalline precipitate of dipicrate. The precipitate was recrystallized from methanol, mp 278–279°.

Anal. Calcd for $C_{48}H_{44}N_6O_{14}P_2$ (picrate): C, 57.60; H, 4.43; N, 8.40; P, 6.19. Found: C, 58.00; H, 4.54; N, 8.35; P, 5.96.

1,4-Di-*n*-butyl-1,2,4,5-tetraphenyl-1,4-diphosphoniacyclohexadiene 2,5-dichloride (10) had mp 257–259°; ir (KBr) 6.48 (C=C), 6.96 μ (PC_6H_5); nmr (TFA) 8.17 (t, J = 29 Hz, 2 H, vinyl), 7.21–8.65 (m, 20 H, phenyl), 3.11 (m, 4 H, PCH_2), 1.69 (m, 8 H, methylenes), 1.01 (t, J = 7 Hz, 6 H, methyl). The dipricrate of **10** was prepared as described under **8**, mp 265–267°.

Anal. Calcd for $C_{48}H_{44}N_6O_{14}P_2$: C, 57.60; H, 4.43; N, 8.40; P, 6.19. Found: C, 57.76; H, 54.2; N, 8.46; P, 6.33.

1,4-Di-*n*-butyl-1,4-diphenyl-1,4-diphosphonia-2,5-dipropylidenecyclohexane dichloride (11a) had mp 240–241°; yield 32%; ir 6.19 (C=C), 6.96 μ (PC_6H_5); nmr δ 7.10 (2 H, vinyl), 4.27 (t, J = 13 Hz, 4 H, ring methylenes), 3.02 (m, 4 H, PCH_2), 2.49 (d, J = 7 Hz, 4 H, allylic), 1.58 (m, 8 H methylenes), 1.22 (two t, J = 7.5 Hz, 12 H, methyl).

1,4-Di-*n*-butyl-1,4-diphenyl-1,4-diphosphonia-2,5-dibutylidenecyclohexane dichloride (11b) had mp 249–251°; yield 27%; ir 6.20 (C=C), 7.01 μ (PC_6H_5); nmr (TFA) δ 7.95 (m, 10 H, phenyl), 7.08 (crude d of t, J_{PH} = 20, J_{HH} = 7 Hz, 2 H, vinyl), 4.25 (t, J = 13 Hz), 4 H, ring methylenes), 2.98 (m, 4 H, PCH_2), 2.48 (d, J = 7 Hz, 4 H, allylic), 1.56 (m, 12 H, methylenes), 1.02 (12 H, methyls).

1,4-Di-*n*-butyl-1,4-diphenyl-2,5-di-*n*-propyl-1,4-diphosphoniacyclohexadiene 2,5-Dichloride (12).—*n*-Butylphenylpentynyl-1-phosphine (1.16 g, 0.005 mol) was dissolved in 25 ml of glacial acetic acid and cooled to 0°. A slow stream of HCl was passed through the solution for 1 hr with continuous stirring while the temperature was kept at 0°. The acetic acid was stripped off under reduced pressure at room temperature. The residue on trituration with acetone gave the desired product in 20% yield, melting at 229–235°. The ir spectrum (KBr) showed characteristic absorption bands of 6.21 (C=C) and 6.98 μ (PC_6H_5) and the nmr spectrum (AcOH) exhibited the characteristic pseudotriplet (J = 27 Hz) at δ 8.24 and all the other proton resonance signals also checked with the assigned structure. Similarly, the nmr spectrum in methanol was found to be in agreement with the structure. However, nmr spectrum in TFA showed that **12** had isomerized to **11a**. Also when **12** was refluxed with acetic acid for 1 hr, the nmr spectra in all the three solvents, AcOH, TFA, and methanol, showed that **12** had isomerized to the exocyclic form **11a**. Compounds described here are available from Strem Chemical Co., Danvers, Mass.

Registry No.—**7**, 33730-51-7; **8**, 38565-20-7; **8** dipicrate, 38565-21-8; **9a**, 38592-33-5; **9b**, 38565-22-9; **9c**, 38565-23-0; **10**, 38565-24-1; **10** dipicrate, 38565-25-2; **11a**, 38565-26-3; **11b**, 38565-27-4; **12**, 38565-28-5; 3,3-dimethylbutyryllithium, 37892-71-0; diphenylphosphinous chloride, 1079-66-9; phenylethyne, 536-74-3; 1-pentyne, 627-19-0; 1-hexyne, 693-02-7.

Acknowledgment.—We wish to acknowledge the National Institutes of Health for support of this work under Grant GM-16828 and the National Science Foundation under Grant GP-10739. We also wish to thank Hoffmann-La Roche, Inc., Nutley, N. J., for their unrestricted grant which helped to complete the work.

The Reaction of Phenylphosphonic Dichloride with Dimethyl Sulfoxide[1]

RICHARD J. BROOKS AND CLIFFORD A. BUNTON*

Department of Chemistry, University of California, Santa Barbara, California 93106

Received November 28, 1972

Dimethyl sulfoxide (DMSO) will convert chlorides of pentavalent phosphorus into their acids.[2] To date this reaction has been used only with monochlorides, but we find it to be a convenient method for the single-step conversion of phenylphosphonic dichloride (I) into methyl phenylphosphonate (II).

$$\underset{\text{I}}{\text{PhPOCl}_2} \xrightarrow[\text{2. MeOH}]{\text{1. DMSO}} \underset{\text{II}}{\text{PhPO(OH)OMe}}$$

Experimental Section

DMSO (2 g, 0.0256 mol) in CH_2Cl_2 (15 ml, dried over CaH_2) was added to stirred phenylphosphonic dichloride (5 g, 0.0256 mol) in dry CH_2Cl_2 (100 ml) during a period of 5 min. The reaction was followed by ir spectroscopy using matched NaCl cells and CH_2Cl_2 as a reference. After *ca.* 30 min, the absorptions at 1258 (P=O) and 1110 cm^{-1} (PPh) due to the phosphonic dichloride had reached a minimum and a new absorption at 1230 cm^{-1} (P=O) had reached a maximum. A fivefold excess of MeOH was then added and after several hours the solvent was removed on a rotary evaporator. The residue, dissolved in dry Me_2CO, was neutralized with cyclohexylamine (Congo Red). The cyclohexylammonium salts of II and phenylphosphonic acid precipitated. (A small amount of dimethyl phenylphosphonate remained in solution, and was identified by nmr.)

Cyclohexylammonium methyl phenylphosphonate (III) was extracted with hot Me_2CO, in which the salt of the diacid is insoluble. The cyclohexylammonium methyl phenylphosphonate (III) had mp 156–158° after recrystallization from Me_2CO, and the overall yield was 52%. *Anal.* Calcd: C, 57.5; H, 8.2; N, 5.2. Found: C, 57.4; H, 8.4; N, 5.0. It had a strong P=O stretch at 1188 cm^{-1}, and the barium salt had a P=O stretch at 1220 cm^{-1}. [That of barium phenylphosphonate is at 1258 cm^{-1}, and that of the free acid is at 1145 cm^{-1}, and the dichloride shows strong absorptions at 1258, 1110, and 580 cm^{-1} (PCl)]. The 60-MHz nmr spectrum of III (in D_2O, Varian T-60) had a multiplet (cyclohexyl) at δ 0.86–1.96 (10.9), a doublet (OMe) at 3.22 and 3.40 (J = 11 Hz, 3.0),[5] and a multiplet (phenyl) at 7.31–7.76 (5.2). The values in parentheses are peak areas. Dimethyl phenylphosphonate in $CDCl_3$ had a doublet (methoxy) at δ 3.69 and 3.87 (J = 11 Hz) and a multiplet (phenyl) at 7.41–8.08.

In an initial experiment the reaction mixture was left for 1 hr after addition of DMSO under N_2 and the yield of III was 40% after recrystallization, but only the salt of the diacid was isolated from an experiment using an twofold excess of DMSO.

Results

This reaction appears to provide a simple alternative to the usual method of dealkylation with halide ion for the preparation of monomethyl phosphates or

(1) Support of this work by the Arthritis and Metabolic Diseases Institute of the USPHS is gratefully acknowledged.

(2) E. H. Amonoo-Neizer, S. K. Ray, R. A. Shaw, and B. C. Smith, *J. Chem. Soc.*, 4296 (1965); 6250 (1965). For general discussion see ref 3, 4.

(3) N. Kharasch and B. S. Thyagarajan, *Quart. Rep. Sulfur Chem.*, **1**, 16 (1966).

(4) W. W. Epstein and F. W. Sweat, *Chem. Rev.* **67**, 247 (1967).

(5) This $^{31}P-^{1}H$ coupling is typical of compounds of this general structure.[6]

(6) J. F. Nixon and R. Schmutzler, *Spectrochim. Acta*, **22**, 565 (1966).

related compounds.[7] We have not tested its general applicability, but it gives better results than the direct reaction of the dichloride with MeOH. The general course of the reactions of DMSO with acid chlorides has been discussed extensively.[2-4]

The reaction generates chloromethyl methyl sulfide, which can react further with DMSO, but this reaction is slower than that of DMSO with a phosphonic dichloride, *cf.* ref 8, and causes no problems.

Registry No.—I, 824-72-6; III, 38555-73-6; DMSO, 67-68-5.

(7) J. R. Cox and O. B. Ramsay, *Chem. Rev.*, **64**, 317 (1964).
(8) R. Ratz and O. L. Sweeting, *J. Org. Chem.*, **28**, 1612 (1963).

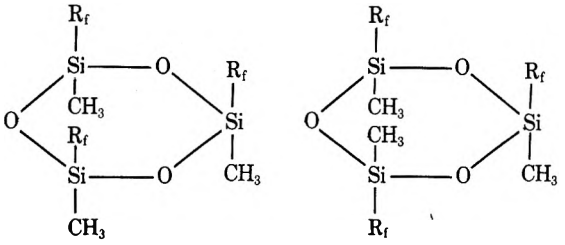
Isomeric 2,4,6-Tris(3,3,4,4,5,5,6,6,6-nonafluorohexyl)-2,4,6-trimethylcyclotrisiloxanes

YUNG K. KIM,* ARTHUR G. SMITH, AND OGDEN R. PIERCE

Advanced Research Laboratories, Dow Corning Corporation, Midland, Michigan 48640

Received October 17, 1972

Diorganocyclosiloxanes are an important segment of silicone chemistry and have been studied extensively;[1] however, fluorine-containing diorganocyclosiloxanes are a relatively new class of compounds.[2] Although numerous studies involving diorganocyclosiloxanes have been described in the literature,[1] the isolation and characterization of the stereoisomeric diorganocyclosiloxanes are limited to methylphenylsiloxane[3] and methyl-(3,3,3-trifluoropropyl)siloxane[4] systems. We now wish to report the synthesis and characterization of the *cis*- and *trans*-2,4,6-tris(3,3,4,4,5,5,6,6,6-nonafluorohexyl)-2,4,6-trimethylcyclotrisiloxanes (1 and 2).



1, cis 2, trans

$R_f = CF_3CF_2CF_2CF_2CH_2CH_2$

The synthetic route for the preparation of the cyclotrisiloxanes 1 and 2 is shown in Scheme I. The free

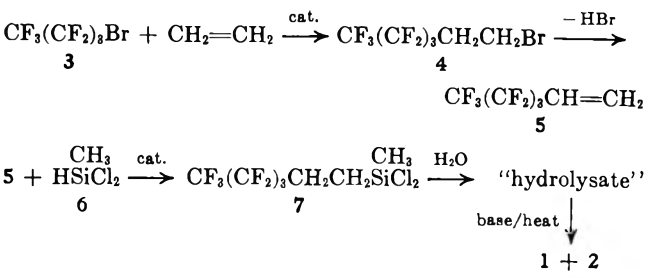
(1) (a) J. B. Carmichael, D. J. Gordon, and F. J. Isackson, *J. Phys. Chem.*, **71**, 2011 (1967); (b) F. P. Adams, J. B. Carmichael, and R. J. Zeman, *J. Polym. Sci., Part A-1*, **5**, 741 (1967); (c) C. L. Lee and O. K. Johannson, *ibid.*, **4**, 3013 (1966); (d) C. L. Lee, *J. Organometal. Chem.*, **6**, 620 (1966); (e) W. Noll, "Chemistry and Technology of Silicones," Academic Press, New York, N. Y., 1968, Chapters 5 and 6.

(2) (a) P. Tarrant, G. W. Dyckers, R. Dunmire, and G. B. Butler, *J. Amer. Chem. Soc.*, **79**, 6536 (1957); (b) O. R. Pierce, G. W. Holbrock, O. K. Johannson, J. C. Saylor, and E. D. Brown, *Ind. Eng. Chem.*, **52**, 783 (1960).

(3) (a) K. A. Andrianov, S. E. Yakushina, V. S. Svistunov, and B. A. Lavrukkin, *Dokl. Akad. Nauk SSSR*, **188**, 345 (1969); (b) V. E. Ditsent, I. I. Skorokhodov, N. A. Terrent'eva, and M. N. Zolotareva, *Zh. Fiz. Khim.*, **46**, 544 (1972).

(4) (a) L. L. Burshtein, Yu. A. Yuzhelevskii, E. V. Kogan, and A. L. Klebanskii, *Zh. Obshch. Khim.*, **33**, 2789 (1963); (b) Yu. A. Yuzhelevskii, E. V. Kogan, A. L. Klebanskii, and O. N. Larionova, *ibid.*, **34**, 1780 (1964).

SCHEME I



radical catalyzed addition of ethylene to the bromide **3**[5] followed by dehydrobromination of the resulting adduct **4** gave the olefin **5** in high yield. In the ethylene addition, some of the higher telomers and a small amount of 1,1,1,2,2,3,3,4,4-nonafluorohexane (**8**) were formed in addition to the adduct **4**. The silane **7** was prepared in 86% yield by the addition of silane **6** to olefin **5** using chloroplatinic acid as a catalyst at reflux temperature. The base-induced "cracking" of the hydrolysate of silane **7** at 225–250° yielded a mixture of two stereoisomeric cyclotrisiloxanes (**1** and **2**), a high-melting crystalline solid (mp 36–37°), and a low-melting liquid [mp 22–23°, bp 96° (0.17 mm)], in a ratio (glc) of approximately 1:2, respectively. The stereoisomers were both isolated in gas chromatographically pure form by crystallization from pentane and by fractional distillation, respectively. Both isomers gave a satisfactory elemental analysis and molecular weight for 2,4,6-tris(3,3,4,4,5,5,6,6,6-nonafluorohexyl)-2,4,6-trimethylcyclotrisiloxane. The characteristic cyclotrisiloxane band (Si–O, 9.8 μ)[6] was observed in the infrared absorption spectra of the isomers.

On the basis of thermodynamic considerations[7] and the measurement of the dipole moments (high-melting form, 5.67 D, and low-melting form, 2.75 D),[8] the high-melting form was assigned the cis configuration (**1**) while the low-melting isomer was assigned the trans configuration (**2**). In the infrared absorption spectra, bands at 12.7 and 12.4 μ have been observed for the cis and trans isomers **1** and **2**, respectively. Bands at 12.7 and 12.4 μ were also observed for the *cis*- and *trans*-2,4,6-tris(3,3,3-trifluoropropyl)-2,4,6-trimethylcyclotrisiloxanes, respectively, and appear to be characteristic bands for the respective stereoisomers.[9] It may be of interest to note that the trans isomer was found to be the high-melting solid in the case of 2,4,6-tris(3,3,3-trifluoropropyl)-2,4,6-trimethylcyclotrisiloxanes.[4a]

Experimental Section

All melting points and boiling points are uncorrected. All melting points were measured by placing a sample in a cooling device and the observations were made using a Lietz hot stage microscope. Infrared absorption spectra were determined on a Perkin-Elmer Model 521 grating infrared spectrophotometer. The ^{19}F resonance spectra were measured on a Varian high-

(5) R. N. Haszeldine, *J. Chem. Soc.*, 4259 (1952).

(6) (a) N. Wright and M. J. Hunter, *J. Amer. Chem. Soc.*, **69**, 803 (1947); (b) C. W. Young, P. C. Servais, C. C. Currie, and M. J. Hunter, *ibid.*, **70**, 3758 (1948).

(7) The stronger reciprocal repulsions of the bulky and electronegative nonafluorohexyl groups would tend to make the formation of the cis isomer less favorable than that of the trans isomer. The trans/cis ratio observed is approximately two.

(8) Since all electronegative nonafluorohexyl groups in the cis isomer are on the one side of the plane of the siloxane ring, a greater dipole moment should be expected for the cis isomer than for the trans isomer.

(9) H. M. Klimisch and R. R. Buch, unpublished results.

resolution nmr spectrometer operating at 56.4 MHz. Chemical shifts are determined in parts per million using CCl_3F as an internal standard (δ 0 ppm). The proton resonance spectra were obtained on a Varian A-60 nmr spectrometer using tetramethylsilane as an internal standard (δ 0 ppm). Gas chromatography was carried out on a Hewlett-Packard Model 5750 using a 10 ft × 0.25 in. column containing 20% Dow Corning FS 1265 Fluid (10,000 cSt) on Anakron 90–100 mesh ABS. The dipole moments were determined by the infinite dilution method at 25° (benzene as solvent).

Addition of Ethylene to 1-Bromononafluorobutane (3).—Into a 2-l. stainless steel stirred pressure reactor were placed 990 g (3.31 mol) of **3** and 33.8 g (0.232 mol) of di-*tert*-butyl peroxide, and the system was flushed with ethylene. The reaction mixture was heated to about 100°, after which ethylene was introduced to a total pressure of about 190 psi. The reaction was then continuously heated to 130–135° and maintained at that temperature throughout the reaction. As the reaction proceeded, the ethylene pressure decreased to about 150 psi; then, additional ethylene was again added to a total pressure of 190 psi. This process was repeated for 2 hr, after which a constant ethylene pressure of about 110 psi was maintained for 16 hr. Distillation of the crude product (1030 g) gave, in addition to intercuts, 350 g (35% recovery) of starting material **3**, bp 44–46°, 363 g (51% yield) of 1-bromo-3,3,4,4,5,5,6,6,6-nonafluorohexane (**4**), bp 42° (35 mm), $n^{25}D$ 1.3330, 55 g (7% yield) of 1-bromo-5,5,6,6,7,7,-8,8,8-nonafluorooctane (**9**), bp 86° (28 mm), $n^{25}D$ 1.3580, and 46 g of still residue.

Anal. Calcd for $C_6H_4F_9Br$: C, 22.04; H, 1.23. Found: C, 22.2; H, 1.37.

Anal. Calcd for $C_8H_8F_9Br$: C, 27.06; H, 2.27. Found: C, 27.2; H, 2.39.

The ^{19}F and ^1H nmr spectra of **4** and **9** are consistent with the assigned structures, respectively. In making several runs of this reaction, a third component was isolated and identified as 1,1,1,2,2,3,3,4,4-nonafluorohexane (**8**), bp 67°, $n^{25}D$ *ca.* 1.28.

Anal. Calcd for $C_6H_5F_9$: C, 29.04; H, 2.03; F, 68.93. Found: C, 28.8; H, 2.20; F, 68.6.

The ^{19}F nmr spectrum of **8** shows signals centered at δ 81.6 (3 F), 117.1 (2 F), 124.3 (2 F), and 126.2 (2 F). The ^1H nmr spectrum is comprised of signals centered at δ 1.6–2.6 ($-CF_2CH_2-$, 2 H) and 1.12 (CCH_3, 3 H).

Dehydrobromination of 1-Bromo-3,3,4,4,5,5,6,6,6-nonafluorohexane (4).—Into a stirred solution of 220 g of potassium hydroxide in 800 ml of ethanol was added slowly 668 g (2.04 mol) of **4** at room temperature (<45°). After completion of the addition, the mixture was stirred at room temperature overnight. Then, about 700 ml of water was added to the mixture, and the organic layer was separated, washed with water, and dried over Drierite to yield 470 g (93% yield) of crude product. Distillation gave 425 g (85% yield) of analytically pure 3,3,4,4,5,5,-6,6,6-nonafluorohexene-1 (**5**), bp 59–59.5°, $n^{26}D$ *ca.* 1.28.

Anal. Calcd for $C_6H_3F_9$: C, 29.28; H, 1.23; F, 69.49 Found: C, 29.2; H, 1.40; F, 70.2.

The spectral properties are in agreement with the olefin **5**.

Addition of Methyldichlorosilane (6) to 3,3,4,4,5,5,6,6,6-Nonafluorohexene-1 (5).—Into a stirred and refluxing mixture of 383 g (1.56 mol) of olefin **5** and 1.5 ml of a 0.1 *M* solution of chloroplatinic acid hexahydrate in isopropyl alcohol was added slowly 280 g (2.44 mol) of methyldichlorosilane. After the addition was complete, the mixture was continuously heated under reflux (about 43°) while stirring slowly. At the end of 20 hr, an additional 1 ml of the catalyst was introduced into the mixture, and heating was continued for an additional 48 hr. The resulting mixture, deep yellow in color, was distilled to give 475 g (84% yield) of (3,3,4,4,5,5,6,6,6-nonafluorohexyl)methyldichlorosilane (**7**), bp 78.5° (31 mm), $n^{26}D$ 1.3540.

Anal. Calcd for $C_7H_7F_9SiCl_2$: C, 23.28; H, 1.95; F, 47.35; Si, 7.78; Cl, 19.64. Found: C, 23.5; H, 1.96; F, 48.2; Si, 7.90; Cl, 19.0.

The ^{19}F nmr spectrum shows signals centered at δ 82.3 (3 F), 116.3 (2 F), 124.3 (2 F), and 126.4 (2 F), indicating the presence of nonafluorobutyl group.

Preparation of a Mixture of the *cis*- and *trans*-2,4,6-Tris(3,3,4,4,5,5,6,6,6-nonafluorohexyl)-2,4,6-trimethylcyclotrisiloxanes (1 and 2).—Into a flask containing stirred water (1 l.) was added a solution of 927 g (2.6 mol) of the silane **7** in about 700 ml of ether at room temperature. After the addition was complete, the mixture was stirred at room temperature for several hours, and then the organic layer was separated, washed with aqueous sodium bicarbonate (5%), and dried over Drierite. After removal of ether *in vacuo*, the resulting liquid hydrolysate (790 g) was mixed with 30 g of powdered potassium hydroxide. The mixture was distilled *in vacuo* using a 1 ft vacuum-jacketed bubble-cap column at a pot temperature of 225–250°. Under a heavy reflux, the distillate boiling between 138 and 149° (3 mm) was collected to yield 559 g of a mixture of the cis and trans isomers **1** and **2**. Gas chromatographic analysis indicates that the isomeric mixture (cis:trans = ~1:2) is fairly pure.

Redistillation of the isomer mixture through a bubble-cap column (1 ft × 0.75 in.) with a reflux ratio of 1:50 gave the following fractions (Table I).

TABLE I

Fraction	Bp, °C (1–2 mm)	wt, g	Approx cis:trans (glc)
1	93–136	40	Forecut
2	139–140	23	3:1
3	139–144	25	2:1
4	141	80	1:1
5	141	46	1:1
6	143–144	24	1:2
7	142	38	1:2
8	142–144	40	1:3
9	142	44	1:4
10	142–143	22	1:10
11	Still residue	51	Mostly trans

Isolation of *cis*-2,4,6-Tris(3,3,4,4,5,5,6,6,6-nonafluorohexyl)-2,4,6-trimethylcyclotrisiloxane (1).—A mixture of cis and trans isomers **1** and **2** (175 g, cis:trans *ca.* 1) was cooled briefly (−20°), and the solid was quickly collected by filtration to yield 68 g of an isomeric mixture of **1** and **2** (cis:trans *ca.* 2). This isomeric mixture was dissolved in warm pentane (50 ml), filtered while warm, and then cooled. A white solid was collected by filtration and dried *in vacuo* to yield gas chromatographically pure cis isomer **1**, mp 36–37°, $n^{42}D$ 1.3348.

Anal. Calcd for $C_{21}H_{21}F_{27}O_3Si_3$: C, 27.45; H, 2.30; Si, 9.17; mol wt, 919. Found: C, 27.80; H, 2.42; Si, 9.17; mol wt, 880 (vpo).

The ^{19}F nmr spectrum shows signals centered at δ 82.1 (CF_3), 117.1 (CF_2CH_2), 125.1 (CF_2), and 126.8 (CF_2). The ^1H nmr spectrum is comprised of signals centered at δ 0.24 ($SiCH_3$), 0.65–1.1 ($SiCH_2$), and 1.6–2.6 (CH_2CF_2). The infrared spectrum shows bands at 8.1 and 8.2 (CF), 9.8 (SiOSi), and ~12.7 μ.

Isolation of *trans*-2,4,6-Tris(3,3,4,4,5,5,6,6,6-nonafluorohexyl)-2,4,6-trimethylcyclotrisiloxane (2).—A mixture of cis and trans isomers **1** and **2** (mostly trans isomer) was distilled *in vacuo* using a spinning band column (36 × 0.75 in.; *ca.* 35 theoretical plates) to yield a greater than 98% stereochemically pure trans isomer **2**: bp 96° (0.17 mm); mp 22–23°; $n^{25}D$ 1.3403; d^{25}_4 1.495.

Anal. Calcd for $C_{21}H_{21}F_{27}O_3Si_3$: C, 27.45; H, 2.30; F, 55.84; Si, 9.17; mol wt, 919. Found: C, 27.30; H, 2.52; F, 55.9; Si, 9.15; mol wt, 907 (vpo).

The ^{19}F nmr spectrum is comprised of signals centered at δ 81.0 (CF_3), 116.5 (CF_2CH_2), 124.5 (CF_2), and 126.0 (CF_2). The ^1H nmr spectrum is identical with that of the cis isomer. The infrared spectrum shows bands at 8.1 and 8.2 (CF), 9.8 (SiOSi), and ~12.4 μ.

Registry No.—**1**, 38521-58-3; **2**, 38521-59-4; **3**, 375-48-4; **4**, 38436-14-5; **5**, 19430-93-4; **6**, 75-54-7; **7**, 38436-16-7; **8**, 38436-17-8; **9**, 38436-18-9; ethylene, 74-85-1.

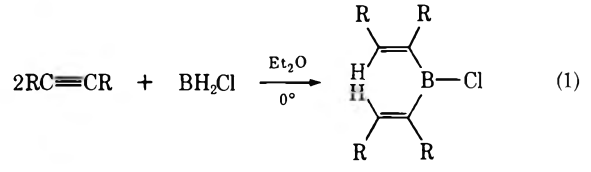
See Editorial, *J. Org. Chem.*, **38**, No. 19, 4A (1972)

Reaction of Representative Alkynes with Monochloroborane Diethyl Etherate. A Simple Convenient Synthesis of Dialkenylchloroboranes *via* Hydroboration

Summary: Monochloroborane diethyl etherate ($BH_2Cl \cdot OEt_2$) reacts with alkynes to give dialkenylchloroboranes which are easily isolated and, if desired, readily converted into the corresponding dienes, alkenes and carbonyl compounds.

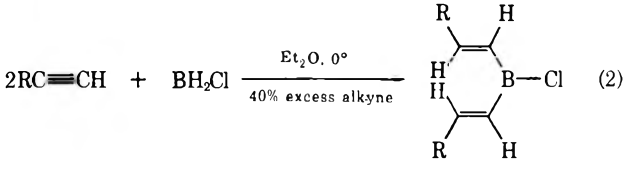
Sir: The reaction of monochloroborane diethyl etherate ($BH_2Cl \cdot OEt_2$) with alkynes can be controlled to provide the hitherto difficultly accessible dialkenylchloroboranes. These dialkenylchloroboranes are easily isolated by simple distillation under reduced pressure. They can be protonolyzed to the alkenes, oxidized to aldehydes or ketones, or converted into cis,trans dienes on treatment with sodium hydroxide and iodine. Consequently, this development provides a remarkably simple route to such cis,trans dienes.

$BH_2Cl \cdot OEt_2$ in ethyl ether solution readily hydroborates a variety of olefins providing a simple synthesis of dialkylchloroboranes.[1] Investigation of the reaction of this reagent with representative alkynes revealed that internal alkynes, such as 3-hexyne and 1-phenylpropyne, undergo monohydroboration rapidly at 0° by the reagent used in stoichiometric amounts to form the dialkenylchloroboranes cleanly, as shown in eq 1. In the case of terminal alkynes, the reaction



(1)

involving stoichiometric amounts of the reagent produces only 60–70% of the monohydroboration product.[2] However, essentially quantitative formation of the desired dialkenylchloroborane can be achieved in these cases by using excess alkyne (~40%) (eq 2). All of



(2)

the terminal alkynes tested behaved in the same manner. The dialkenylchloroboranes are easily isolated by distillation under low pressure. A few representative dialkenylchloroboranes were synthesized, isolated, and characterized by pmr and elemental analysis (Table I).

(1) H. C. Brown and N. Ravindran, *J. Amer. Chem. Soc.*, **94**, 2112 (1972).

(2) In this case, the alkyne underwent considerable dihydroboration. The nature of the dihydroboration product is currently under investigation.

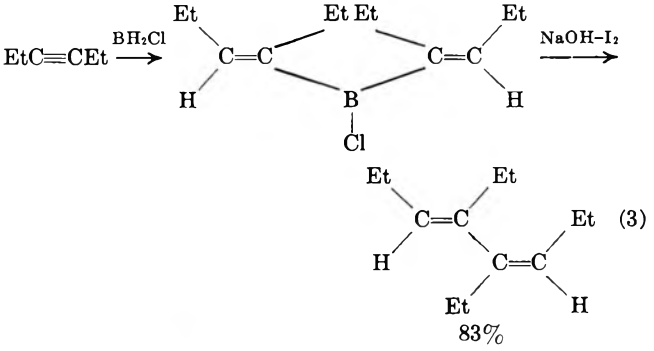
Table I

Synthesis of Dialkenylchloroboranes by the Monohydroboration of Alkynes with Monochloroborane Diethyl Etherate

Alkyne	Dialkenylchloroborane[a]	Isolated yield, %	Bp, °C (mm)
1-Hexyne	Bis(*trans*-1-hexenyl)-chloroborane	81	79–81 (0.05)
3,3-Dimethyl-1-butyne	Bis(*trans*-3,3-dimethyl-1-butenyl)chloroborane	80	52–53 (0.09)
Cyclohexyl-ethyne	Bis(*trans*-2-cyclohexyl-1-ethenyl)chloroborane	76	122–124 (0.025)
3-Hexyne	Bis(*cis*-3-hexenyl)-chloroborane	88	66–68 (0.10)

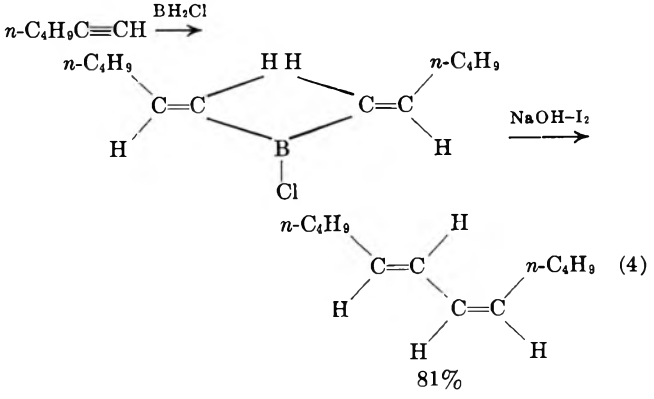
[a] The stereochemistry of the products were determined by pmr. The isolated dialkenylchloroboranes all gave correct elemental analyses.

Zweifel and coworkers have reported that thexyl dialkenylborinates, obtained by the oxidation of thexyldialkenylboranes with trimethylamine oxide, are converted into cis,trans dienes on treatment with NaOH–I_2.[3] The dialkenylchloroboranes can be directly transformed into cis,trans dienes by Zweifel's procedure (eq 3 and 4). Consequently, this development now provides a remarkably simple route to such dienes.



(3)

83%



(4)

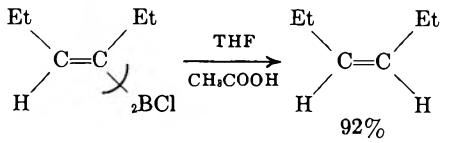
81%

Like the other alkenylboranes,[4] the dialkenylchloroboranes undergo protonolysis with acetic acid in tetra-

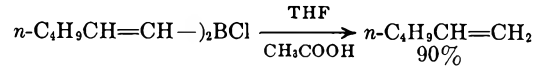
(3) G. Zweifel, N. L. Polston, and C. C. Whitney, *J. Amer. Chem. Soc.*, **90**, 6243 (1968).

(4) H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **83**, 3834 (1961).

hydrofuran to give stereochemically pure olefins (eq 5 and 6). Oxidation of dialkenylchloroboranes with

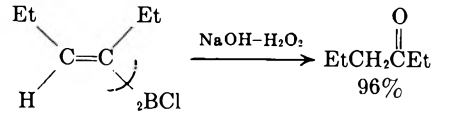


(5)

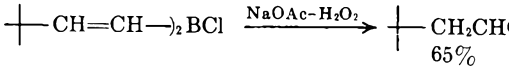


(6)

alkaline hydrogen peroxide gives the corresponding carbonyl compounds (eq 7 and 8).



(7)

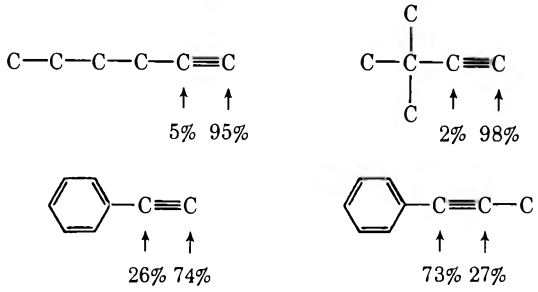


(8)

The directive effect in the monohydroboration of representative alkynes with $BH_2Cl \cdot OEt_2$ was examined. Analysis of the hydroboration mixture for residual alkyne and hydride established that quantitative conversion to the dialkenylchloroborane was achieved. The reaction mixture was then oxidized and the resulting carbonyl products were reduced to the alcohols with alkaline sodium borohydride. The alcohols were analyzed by gc. In the case of terminal alkynes, the amount of the internal alcohols found corresponds to the fraction of boron in the internal position. Since the formation of dialkenylchloroborane was quantitative, the remainder of the boron must have gone to the terminal position. (Oxidation of terminal vinylboranes to aldehydes in quantitative yield is more difficult.) The results are presented in Chart I. The

CHART I

DISTRIBUTION OF BORON IN THE MONOHYDROBORATION OF ALKYNES WITH $BH_2Cl \cdot OEt_2$



results reveal that the directive effect in the hydroboration of terminal acetylenes with $BH_2Cl \cdot OEt_2$ is less than that observed in the hydroboration of olefins with this reagent.[5] However, it is not possible to compare the directive effects achieved with $BH_2Cl \cdot OEt_2$ with those of borane itself, because the latter reagent converts terminal acetylene predominantly to the dihydroboration product.[4,6] The greater control of monohydroboration of acetylenes provided by chloroborane represents a major advantage of this reagent.

The following experimental procedures for the synthesis and reactions of bis(*cis*-3-hexenyl)chloroborane are representative. To a solution of 100 mmol of 3-hexyne in 15 ml of ethyl ether was added dropwise 50 mmol of BH_2Cl in ethyl ether[1] (37 ml) at 0° and this mixture was stirred under nitrogen for 2 hr. The ether was removed using a water aspirator and the bis(*cis*-3-hexenyl)chloroborane was distilled at 66–68° (0.1 mm). The product, obtained in 88% yield, was characterized by pmr and elemental analysis. In the experiment involving terminal alkynes, the procedure was identical except that 140 mmol of alkyne (40% excess) was used instead of the stoichiometric amount.

For the synthesis of diene, 50 mmol of bis(*cis*-3-hexenyl)chloroborane (ether removed, but not distilled) was dissolved in 40 ml of tetrahydrofuran. Aqueous sodium hydroxide (3 *M*, 200 mmol) was then added at 0°, followed by dropwise addition of tetrahydrofuran solution of iodine until a slight color of iodine persisted. The excess iodine was destroyed by stirring with excess sodium thiosulfate solution at 25°. The diene was extracted into pentane, washed with dilute thiosulfate solution, dried, and distilled at 62–64° (8 mm). The *cis,trans*-4,5-diethyl-3,5-octadiene, obtained in 83% yield, was characterized by pmr.[3]

To achieve the protonolysis, 4 mmol of bis(*cis*-3-hexenyl)chloroborane was dissolved in 2 ml of tetrahydrofuran and stirred with 2 ml of glacial acetic acid at 25° for 3 hr. The yield of *cis*-3-hexene formed was 92% (gc analysis).

Oxidation of 10 mmol of bis(*cis*-3-hexenyl)chloroborane in 10 ml of ether was carried out by adding, at 0°, 20 mmol of aqueous sodium hydroxide (3 *M*), followed by 2 ml of 30% hydrogen peroxide (dropwise) and 10 ml of ethanol, and stirring at 25° for 30 min. The yield of 3-hexanone was 96% (gc analysis).

The present development provides, for the first time, a general convenient procedure for the synthesis of dialkenylchloroboranes.[7] The ready availability of these compounds by the present simple procedure should facilitate the exploration of the chemistry of this interesting class of compounds. Diene formation, protonolysis, and oxidation are synthetically useful reactions of these compounds, and other interesting applications may be anticipated.

(7) The only compound of this class reported to date is the diethenylchloroborane obtained in 35% yield by the fractionation of a mixture of products from the reaction of tetraethenyltin with boron trichloride at 60°: F. E. Brinckman and F. G. A. Stone, *J. Amer. Chem. Soc.*, **82**, 6218 (1960).

(8) Postdoctoral research associate on National Science Foundation Grant No. 27742X.

RICHARD B. WETHERILL LABORATORY
PURDUE UNIVERSITY
LAFAYETTE, INDIANA 47907

HERBERT C. BROWN*
N. RAVINDRAN[8]

RECEIVED JANUARY 12, 1973

Conformational Effect on Observable Magnetic Nonequivalence of Diastereotopic Protons. III. 3-Axial Alkyl Effect[1]

Summary: The diastereotopic, benzylic protons of a substituted 1-benzylpiperidine appear as an AB quartet in the nmr spectrum if a 3-alkyl substituent is either axially oriented or is a branched chain and equatorial.

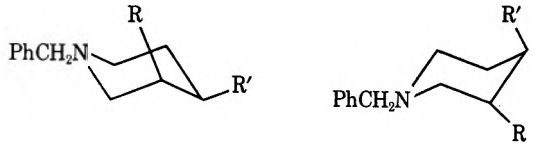
Sir: The diastereotopic relationship of two hydrogens is a necessary but not a sufficient requirement for

(5) H. C. Brown and N. Ravindran, *J. Org. Chem.*, **38**, 182 (1973).
(6) G. Zweifel and H. Arzoumanian, *J. Amer. Chem. Soc.*, **89**, 291 (1967).

them to have pmr signals showing different chemical shifts. It has been shown that the diastereotopic protons of the methylene group of an *N*-benzylpiperazine or -piperidine appear to have identical chemical shifts if the lack of symmetry results from a 2-axial group or from a 3 substituent.[1,2] These relationships have permitted a qualitative conformational analysis of substituted *N*-benzyl six-membered heterocycles.[3]

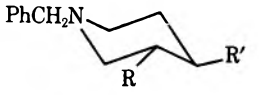
An extension of this investigation has provided another generalization which will be of value in the stereochemical studies of nitrogen heterocycles. A 3-axial but not a 3-equatorial alkyl substituent on a 1-benzylpiperidine causes observable nonequivalence of the benzylic, methylene protons.

A series of 1-benzyl 3,4-disubstituted piperidines (**1**) were prepared by hydrogenation of the corresponding pyridines. The reactions gave primarily one isomeric form of the product shown to be the cis isomer **1**. On the basis of the previous results[2,3] it was anticipated that the products **1** and **2** would show singlets for the methylene protons of the *N*-benzyl group due to undetectable chemical shift differences, and indeed this was the nmr observation made with **2**. The signals for these protons in the cis isomers **1a–c**, however, all appeared as AB quartets of ~10–12-Hz difference in chemical shifts of the diastereotopic hydrogens when measured with a 100-MHz spectrometer.



axial (ax) equatorial (eq)

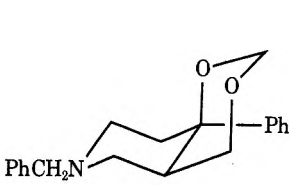
	Δδ
1a, R = CH_3; R′ = CH_2CH_3	12.2
b, R = CH_2CH_3; R′ = CH_3	10.4
c, R = CH_3; R′ = CH_3	10.0



2, R = CH_3; R′ = CH_2CH_3 (s)

A consideration of the relative stability of the two chair conformers of **1** (ax-**1** and eq-**1**) leads to the prediction that the 4-axial substituent of eq-**1** should introduce an unfavorable steric strain, described in terms of $-\Delta G_{CH_3}°$, of ~1.8 kcal/mol. The 3-axial substituent of ax-**1** should cause a smaller unfavorable steric interaction by ~0.6–0.8 kcal/mol, since one syn axial hydrogen has been replaced by the nitrogen free pair.[4] Thus ax-**1** should be present in excess to the extent of ~70% in the conformational equilibrium of **1**. Since the 4 substituent in any conformation is symmetrically disposed toward the N substituent, it is apparent that it is the 3-axial substituent that is causing the observed nonequivalence of the diastereotopic protons of the methylene of the *N*-benzyl group. The 3-equatorial alkyl groups of 3-methyl- (**7a**),[5] 3-ethyl- (**7b**), and *trans*-3-methyl-4-ethyl-1-benzylpiperidine (**2a**) led to singlets for the benzylic methylene protons. That the 3-axial alkyl group produces a *detectable* magnetic anisotropic effect on the diastereotropic protons of the N substituent should have been expected in view of the recent observations of the anomalous 3-axial substituent effect on the optical rotatory dispersion of cyclic six-membered-ring ketone.[6] Both of these experimental observations result from the close steric proximity of a 3-axial substituent to the tercovalent ring atom at position 1.

The application of this observation can be illustrated by providing confirmation for the assignment based on long range coupling made by Casy and coworkers[7] of the "O inside" conformation (**4**) rather than the "O outside" form (**5**) for the product of the Prins reaction with 1-benzyl-4-phenyl-1,2,3,6-tetrahydropyridine. The product gave a singlet for the methylene protons of the 1-benzyl group requiring that there be no axial 3 substituent such as that present in **5**.



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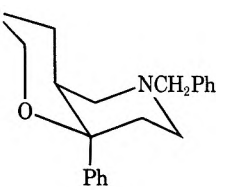
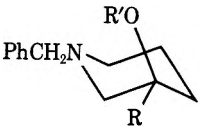


5

A 3-axial hydroxyl or acetoxyl group did not lead to an observable AB quartet for the diastereotopic benzylmethylene in three 1-benzyl 3,3-disubstituted piperidines (**6a–c**). The AB quartet observed for 1-benzyl-3-acetoxy-3-ethylpiperidine (**6d**) may result from an



	Δδ
6a, R = C_2H_5; R′ = H	s
b, R = Ph; R′ = H	s
c, R = Ph; R′ = Ac	s
d, R = C_2H_5; R′ = H	7.2

effect of the ethyl group, for it was found that, unlike an equatorial 3-methyl group (**7a**), a larger substituent such as a 3-benzyl (**7c**), isopropyl (**7d**), or *tert*-butyl (**7e**) group in the equatorial conformation of 1-benzylpiperidine gave AB quartets for the benzylic methylene protons in the pmr spectra. A consideration of the relative stabilities of the rotomers about the bond attaching these groups to the 3 position shows that the

(1) For previous papers in this series, see (a) R. E. Lyle and J. J. Thomas, *Tetrahedron Lett.*, 897 (1969); (b) R. E. Lyle, J. J. Thomas, and D. A. Walsh, in "Conformational Analysis," G. Chiurdoglu, Ed., Academic Press, New York, N.Y., 1971, pp 157–164.

(2) (a) R. K. Hill and T. H. Chan, *Tetrahedron*, **21**, 2013 (1965); (b) Y. L. Chow and C. J. Colon, *Can. J. Chem.*, **5**, 2559 (1967).

(3) L. N. Pridgen, Ph.D. Thesis, University of New Hampshire, 1972.

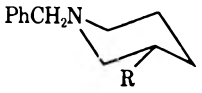
(4) P. J. Brignell, K. Brown, and A. R. Katritzky, *J. Chem. Soc. B*, 1462 (1968); F. G. Ridell, *Quart. Rev.*, **21**, 364 (1967).

(5) Y. L. Chow, S. Black, J. E. Blier, and M. M. Tracy, *Can. J. Chem.*, **48**, 2134 (1970).

(6) (a) Y. H. Pao and D. P. Santry, *J. Amer. Chem. Soc.*, **88**, 4157 (1966); (b) G. Snatzke, B. Ehrig, and H. Klein, *Tetrahedron*, **25**, 5601 (1969); (c) M. E. Herr, *et al.*, *J. Org. Chem.*, **35**, 3607 (1970); (d) C. Coulombeau and A. Rassat, *Bull. Soc. Chim. Fr.*, 516 (1971); (3) G. Snatzke and H. Klein, *Chem. Ber.*, **105**, 244 (1972); (f) D. N. Kirk, W. Klyne, and W. P. Mose, *Tetrahedron Lett.*, 1315 (1972); (g) H. J. C. Jacobs and E. Havinga, *Tetrahedron* **28**, 135 (1972); (h) G. Snatzke and K. Kinsky, *Tetrahedron*, **28**, 295 295 (1972); (i) J. F. Tocanne, *Tetrahedron*, **28**, 389 (1972), and references therein.

(7) A. F. Casy, A. B. Simmonds, and D. Staniforth, *J. Org. Chem.*, **37**, 3189 (1972).

more stable rotomer or rotomers have a methyl or phenyl group in a pseudoaxial arrangement for **7c**, **7d**, and **7e**.



	Δδ
7a, R = CH_3	s
b, R = CH_3CH_2	s
c, R = $PhCH_2$	12.9
d, R = $(CH_3)_2CH$	6.7
e, R = $(CH_3)_3C$	13.0

The appearance of the diastereotopic protons of the methylene group of an *N*-benzyl substituent as an AB quartet in the nmr spectrum of an alkylated piperidine or piperazine has been shown to be positive evidence for a 2-equatorial alkyl, a 3-axial alkyl or a large 3-equatorial alkyl substituent. The appearance of the methylene signal as a singlet is evidence for the absence of these conformational features.

Acknowledgment.—The nmr spectra were determined with a Joel MH-100 obtained from Grants NSF GP 29176 and NIH 5S05-FR-07108. The authors also wish to express appreciation to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of the research. Appreciation is also expressed to Dr. H. C. Brown for a generous sample of 3-*tert*-butylpyridine and to Dr. O. Frank Beumel and Foote Mineral for *n*-butyllithium used in this research.

(8) This research was abstracted from the thesis of L. N. P submitted to the Graduate School of the University of New Hampshire in partial fulfillment of the Ph.D. degree. Martin Luther King and Petroleum Research Fund Fellow, 1969–1972.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF NEW HAMPSHIRE
DURHAM, NEW HAMPSHIRE 03824

ROBERT E. LYLE*
LENDON N. PRIDGEN[8]

RECEIVED FEBRUARY 5, 1973

Fundamental Studies of Substituted Ferrocenes. VII.[1] Proton Magnetic Effects in Trimethylsilylferrocene

Summary: Specific deuterium labeling of trimethylsilylferrocene shows that the upfield two-proton apparent triplet at δ 4.07 ppm can be assigned to the 2,5-position protons and thus the downfield two-proton apparent triplets at δ 4.30 ppm can be assigned to the 3,4-position protons.

Sir: In a previous publication[2] we had advanced the hypothesis based on chemical shift data that the response of a ferrocene ring to an electron-donating substituent (typified by an amino group) was "principally manifested at the 3,4 positions," care being taken at that time to avoid use of the term resonance. Since then other monosubstituted ferrocenes containing electron-donating substituents have been shown to exhibit similar pmr behavior.[1,3] We now propose that this phenomenon be interpreted as a resonance effect[4] and offer as proof the herein documented observation of electron withdrawal from the 3,4 positions of trimethylsilylferrocene as determined by pmr. Since the trimethylsilyl group in several instances has been found to participate in (p–d) π-electron withdrawal[5] (although in most instances the result is not marked), our proposal amounts to suggesting that correct assignment of chemical shifts according to two distinct π-resonance effects in an unknown system constitutes satisfactory identification of such effects in said system.

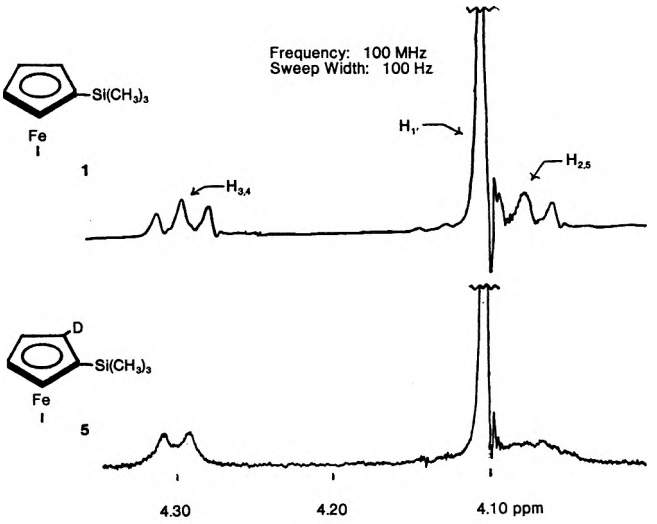


Figure 1.

Trimethylsilylferrocene (**1**) possesses chemical shift shielding values for the $H_{2,5}$ and $H_{3,4}$ proton resonances in accordance with resonant electron withdrawal by the trimethylsilyl group from the 3,4 positions. The pmr spectrum of **1** exhibits two unsymmetrical triplets[6,7] for the homoannular proton resonances. Assignments for these resonances have been made on the basis of comparative spectra of trimethylsilylferrocene and 2-deuteriotrimethylsilylferrocene ($CDCl_3$) as shown in Figure 1. Attenuation of the resonance at δ 4.07 ppm and the change in splitting of the resonance of δ 4.30 ppm from a triplet to a doublet with introduction of a deuterium at the 2 position permits equivocal assignment of the resonance at high field to the $H_{2,5}$ protons and that at low field to the $H_{3,4}$ protons.

The deuterated trimethylsilylferrocene was prepared by the series of reactions shown in Scheme I. Treatment of chloroferrocene (**2**) with *n*-butyllithium under conditions reported[8,9] to give metalation of chloroferrocene and now documented to provide 2 metalation,[1] followed by addition of trimethylchlorosilane, afforded 2-chlorotrimethylsilylferrocene (**3**) as an oil. Sodiation of **3** with dispersed sodium and deuterolysis of the sodiated intermediate (**4**) with excess deuterium oxide produced trimethylsilylferro-

(1) Part VI: D. W. Slocum, W. E. Jones, and C. R. Ernst, *J. Org. Chem.*, **37**, 4278 (1972).

(2) D. W. Slocum, P. S. Shenkin, T. R. Engelmann, and C. R. Ernst, *Tetrahedron Lett.*, 4429 (1971).

(3) D. W. Slocum, B. P. Koonsvitsky, and C. R. Ernst, *J. Organomet. Chem.*, **38**, 125 (1972).

(4) Other effects such as field, inductive, and (for pmr) anisotropy would be expected to be strongest at the 2,5 positions.

(5) M. E. Freeburger and L. Spialter, *J. Amer. Chem. Soc.*, **93**, 1894 (1971).

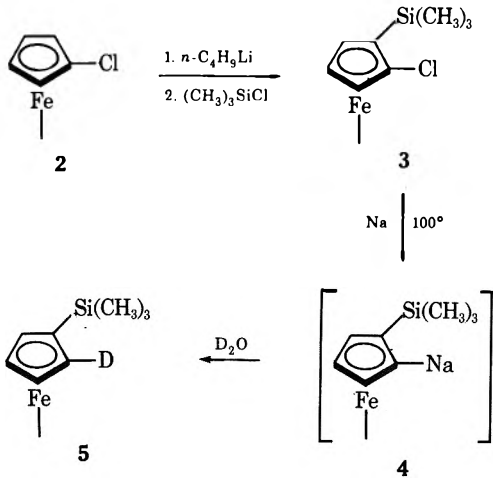
(6) M. D. Rausch and M. Mark, *J. Org. Chem.*, **28**, 3225 (1963).

(7) M. I. Levenberg and J. H. Richards, *J. Amer. Chem. Soc.*, **86**, 2634 (1964).

(8) J. Huffman, L. Keith, and R. Ausbury, *J. Org. Chem.*, **30**, 1600 (1958).

(9) A. N. Nesmeyanov, *Dokl. Akad. Nauk SSSR*, **176**, 598 (1968).

SCHEME I



2 3 4 5

cene[10] containing a total of 0.88 deuterium atom as analyzed by the falling drop method.

Trimethylsilylferrocene has been the only monosubstituted ferrocene studied to date which exhibits enhanced deshielding of the 3,4-position protons with respect to the 2,5-position protons. Since earlier studies[2] have demonstrated that resonance effects in the ferrocene system detected by pmr spectroscopy are manifested chiefly at the 3,4 positions, the observation of significant deshielding of the $H_{3,4}$ protons in **1** can be attributed to a resonance withdrawal by the d orbitals on silicon from the 3,4 positions.[11]

Acknowledgment.—Thanks are due for a graduate followship from Southern Illinois University for C. R. E and support by the donors of the Petroleum Research Fund, administered by the American Chemical Society. Appreciation is expressed to Mr. Joseph Nemeth, University of Illinois, for the falling drop analysis.

(10) M. Rausch, M. Vogel, and H. Rosenberg, *J. Org. Chem.*, **23**, 900 (1958).

(11) A referee has pointed out that the sequence of chemical shifts in trimethylsilylferrocene is the same as that in the α-ferrocenyl carbonium ion as initially assigned by Cais, *et al.*[12] However, the carbonium ion is a charged intermediate or transition state where charge delocalization would be expected to override secondary ground-state effects as described herein. Interestingly, this ground-state effect in **1** can now be explained as a simple resonance interaction without recourse to arguments involving ring/metal atom movement.[13]

(12) M. Cais, J. J. Dannenberg, A. Eisenstadt, M. I. Levenberg, and J. H. Richards, *Tetrahedron Lett.*, 1695 (1966).

(13) For a recent summary and criticism of this concept, *cf.* J. Feinberg and M. Rosenblum, *J. Amer. Chem. Soc.*, **91**, 4324 (1969).

NECKERS LABORATORY
SOUTHERN ILLINOIS UNIVERSITY
CARBONDALE, ILLINOIS 62901

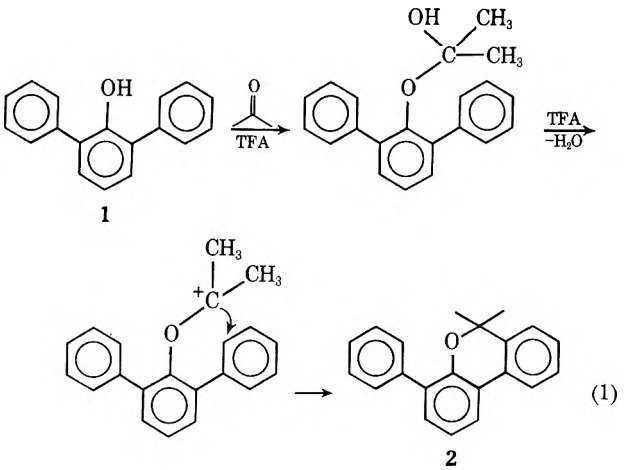
D. W. SLOCUM*
C. R. ERNST

NOVEMBER 11, 1972

A New Reaction of 2-Phenylphenols with Carbonyl Compounds Yielding Dibenzopyrans

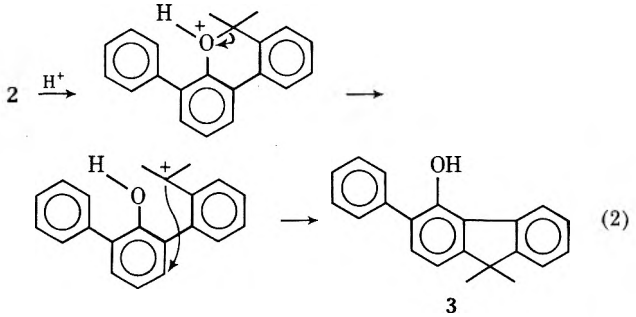
Summary: A new synthesis of dibenzopyrans, fluorenols, and indenofluorenols is described.

Sir: The acid-catalyzed condensation of carbonyl compounds with phenols to yield bisphenols is a well-known reaction of broad scope.[1] However, it was reported by Kahovec and Pospisil[2] that 2,6-diphenylphenol (**1**) did not react with acetone in the presence of conventional acid catalysts such as hydrogen chloride. This observation was confirmed in our laboratory, but, when **1** was combined with acetone under more strongly acidic conditions, for example, in refluxing trifluoroacetic acid (TFA) (H_0 −3.0),[3] a new condensation reaction occurred yielding 4-phenyl-6,6-dimethyl-6*H*-dibenzo[*b*,*d*]pyran (**2**): mp 79–80°; 64%; *m/e* 286 (M^+), 271 ($M^+ - 15$); nmr ($CDCl_3$) δ 1.55 (s, 6, CH_3), 6.90–7.80 ppm (m, 12, ArH); ir (KBr) 1360 and 1380 (*gem*-dimethyl), 700 cm^{-1} (monosubstituted aryl); satisfactory analysis for $C_{21}H_{18}O$. It is assumed that the reaction proceeds *via* the reversible formation of the phenol hemiacetal of acetone. Protonation and loss of water from the hemiacetal generates a carbonium ion which attacks either of the flanking phenyl groups to form the pyran **2** as shown in eq 1.



The threshold of acidity (H_0) required for pyran formation was approximately −3.0. No reaction occurred with hydrogen chloride, formic acid (H_0 −2.2),[4] formic-hydrochloric acid, or 50:50 (v/v) formic-trifluoroacetic acid mixtures.

Prolonged refluxing of **2** in TFA rearranged this tertiary benzylic ether to 9,9-dimethyl-3-phenyl-4-fluorenol (**3**) (eq 2): mp 106–107°; ir (KBr) 3540,



703 cm^{-1}; nmr ($CDCl_3$) δ 1.50 (s, CH_3), 5.68 (s, 1, ArOH), 7.00–8.15 ppm (m, 11, Ar H); *m/e* 286 (M^+), 271 ($M^+ - 15$); analyzed for $C_{21}H_{18}O$.

The rearrangement regenerated an *o*-phenylphenol which in the presence of acetone reacted further to form the indenodibenzopyran (**4**): mp 112–113°; nmr ($CDCl_3$) δ 1.47 (s, 6, CH_3), 1.73 (s, 6, CH_3), 6.93–8.25 (m, 10, Ar H); *m/e* 326 (M^+), 311 ($M^+ - 15$);

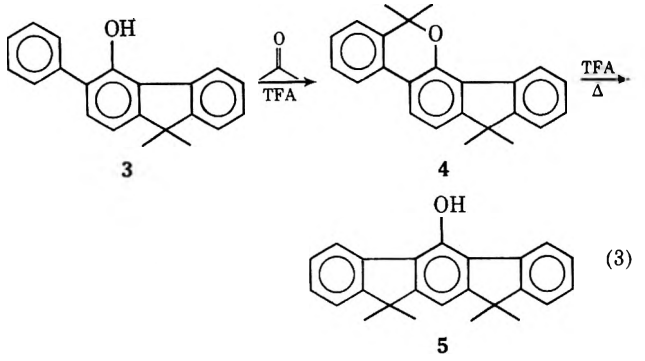
(1) H. Schnell and H. Krimm, *Angew. Chem., Int. Ed. Engl.*, **2**, 373 (1963).

(2) J. Kahovec and J. Pospisil, Collect. *Czech. Chem. Commun.*, **34**, 2843 (1969).

(3) H. H. Hyman and R. A. Garber, *J. Amer. Chem. Soc.*, **81**, 1847 (1959).

(4) R. Stewart and T. Mathews, *Can. J. Chem.*, **38**, 602 (1960).

analyzed for $C_{24}H_{22}O$. **4** in turn rearranged to the indenofluorenol (**5**): mp 210–211°; ir (KBr) 3600 cm^{-1}; nmr ($CDCl_3$) δ 1.41 (s, 12, CH_3), 7.00–8.12 (m, 9, Ar H); *m/e* 326 (M^+), 311 ($M^+ - 15$), 296 ($M^+ - 30$); analyzed for $C_{24}H_{22}O$ (eq 3).



(3)

Each compound (**2**–**5**) has been isolated in pure form by the proper choice of reaction time, acid strength, and stoichiometry.[5] In anhydrous hydrofluoric acid (H_0 −10.2)[6] at 19° with excess acetone all intermediates are cleanly driven to **5** in high yield.

Details and scope of this dibenzopyran synthesis will be reported later.

(5) Complete experimental details on all compounds described in this communication will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth Street, N.W., Washington, D.C. 20036, by referring to code number JOC-73-1621. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

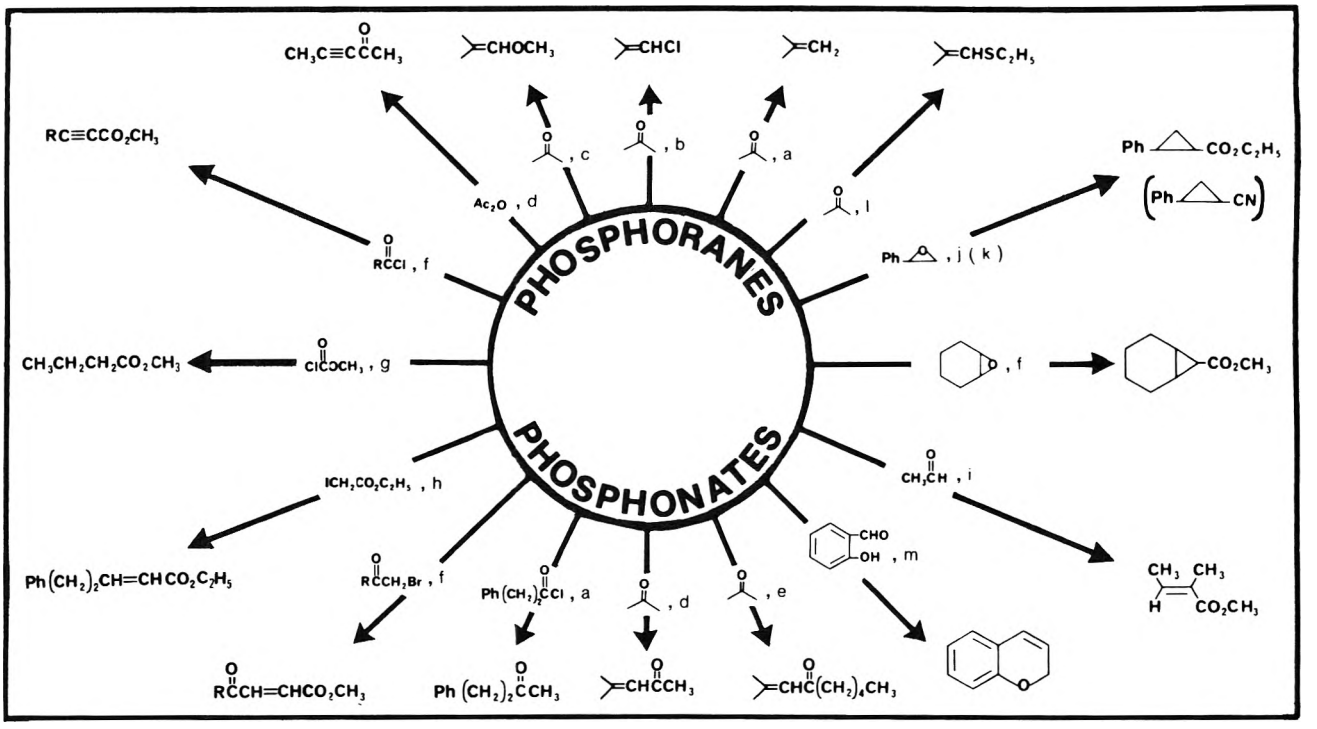
(6) H. H. Hyman, M. Kilpatriek, and J. J. Katz, *J. Amer. Chem. Soc.*, **79**, 3668 (1957).

GENERAL ELECTRIC RESEARCH AND DEVELOPMENT CENTER
CHEMICAL LABORATORY
SCHENECTADY, NEW YORK 12301

JIMMY L. WEBB*
W. L. HALL

RECEIVED SEPTEMBER 15, 1972

WITTIG REACTIONS AT A GLANCE



Reagents: *a*, $Ph_3P{=}CH_2$; *b*, $Ph_3P{=}CHCl$; *c*, $Ph_3P{=}CHOCH_3$; *d*, $Ph_3P{=}CHC(O)CH_3$; *e*, $(CH_3O)_2P(O)CH_2C(O)(CH_2)_4CH_3$, NaH; *f*, $Ph_3P{=}CHCO_2CH_3$; *g*, $Ph_3P{=}CHC_2H_5$; *h*, $Ph_3P{=}CH(CH_2)_2Ph$; *i*, $Ph_3P{=}C(CH_3)CO_2CH_3$; *j*, $(EtO)_2P(O)CH_2CO_2Et$, NaH; *k*, $(EtO)_2P(O)CH_2CN$, NaH; *l*, $(EtO)_2P(O)CH_2SEt$,[6,7] BuLi; *m*, $Ph_3P^+CH{=}CH_2\,Br^-$, NaH

Wittig reagents [1-7] through carbonyl olefination lead to olefins, vinyl halides, vinyl ethers (hence, aldehydes), ketones, α,β-unsaturated ketones and esters, acetylenic ketones and esters, etc. A host of heterocyclic compounds such as chromenes, dihydroquinolines, dihydrofurans, etc., are possible using Schweizer's reagent (15,019-3). Since the reaction of phosphoranes and phosphonates is not limited to the carbonyl, the chemist has a variety of choices for his particular needs in synthesis. A partial list of our phosphonium salts, phosphoranes and phosphonates is shown below.

References:

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(3) A. W. Johnson, 'Ylid Chemistry', Academic Press, New York, 1966.
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15,807-0	Acetonyltriphenylphosphonium chloride	25g-$7.00; 100g-$22.00
C510-6	(Carbethoxymethylene)triphenylphosphorane	25g-$13.50; 34.8g†-18.00; 100g-$36.00
C5762-6	(Chloromethyl)triphenylphosphonium chloride	25g-$15.10
D9170-5	Diethyl cyanomethylphosphonate	17.7g†-$4.25; 100g-$18.20
15,653-1	Diethyl (ethylthiomethyl)phosphonate	5g-$6.80; 25g-$21.20
11,613-0	Diethyl vinylphosphonate	10g-$15.15; 16.4g†-$19.50; 25g-$25.20
15,793-7	Dimethyl (2-oxoheptyl)phosphonate	10g-$12.00; 22.2g†-$24.50; 50g-$48.00
10,000-5	(Methoxymethyl)triphenylphosphonium chloride	34.3g†-$11.00; 100g-$19.50
13,007-9	Methyltriphenylphosphonium bromide	25g-$4.55; 35.7g†-$7.25; 100g-$11.95
15,792-9	Methyl (triphenylphosphoranylidene)acetate	25g-$13.50; 100g-$36.00
13,156-3	*n*-Propyltriphenylphosphonium bromide	100g-$10.50
T6130-1	Triethyl phosphonoacetate	22.4g†-$4.20; 100g-$13.30
T7975-8	Trimethyl phosphonoacetate	18.2g†-$4.50; 100g-$14.35
T8440-9	Triphenylphosphine	100g-$6.30; 262.3g†-$14.25; 1Kg-$41.80
15,019-3	Vinyltriphenylphosphonium bromide	25g-$12.00; 36.9g†-$18.00; 100g-$40.00

†Designates molar units