VOLUME 37 MARCH 10, 1972 NUMBER 5 JOCEAH

THE JOURNAL OF Organic Chemistry

PUBLISHED BIWEEKLY BY THE AMERICAN CHEMICAL SOCIETY

THE JOURNAL OF Organic Chemistry

Published biweekly by the American Chemical Society at 20th and Northampton Streets, Easton, Pennsylvania

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.

Production Staff: Manager, Editorial Production, CHARLES R. BERTSCH; Production Editor, EILEEN SEGAL; Assistant Editor, FERN S. JACKSON; Editorial Assistants, ANDREW J. D'AMELIO and DEBORAH K. MILLER.

Advertising Office: Century Communication Corporation, 142 East Ave., Norwalk, Conn. 06851.

Business and Subscription Information

Correspondence concerning business matters should be sent to the Subscription Service Department, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036.

Claims for missing numbers will not be allowed (1) if received more than 60 days from date of issue plus time normally required for postal delivery of journal and claim; (2) if loss was due to failure to notify the Subscription Service Department of a change of address; or (3) if the reason for the claim is that a copy is "missing from files."

Change of address: Notify Subscription Service Department, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036. Such notification should include both old and new addresses and postal ZIP number. Please send an old address label, if possible. Allow 4 weeks for change.

Subscriptions should be renewed promptly, to avoid a break in your series. Orders should be sent to the Subscription Service Department, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036.

Subscription rates for 1972: $20.00 per volume to members of the ACS and $60.00 per volume to all others. Those interested in becoming members should write to the Admissions Department, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036. Add $5.00 per subscription for Canada and countries belonging to the Postal Union, and $6.00 for all other countries.

Single copies for current year: $3.00. Postage, single copies: to Canada and countries in the Pan-American Union, $0.15; all other countries, $0.20. Rates for back issues from Volume 20 to date are available from the Special Issues Sales Department, 1155 Sixteenth St., N.W., Washington, D. C. 20036.

This publication and the other ACS periodical publications are now available on microfilm. For information write to MICROFILM, Special Issues Sales Department, 1155 Sixteenth St., N.W., Washington, D. C. 20036.

Notice to Authors last printed in the issue of January 14, 1972

JOCEAH 37(5) 683-804 (1972)

THE JOURNAL OF Organic Chemistry®

VOLUME 37, NUMBER 5 MARCH 10, 1972

NOTES

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 37, NUMBER 5

MARCH 10, 1972

Hexachlorofulvene. I. Synthesis and Reactions under Diels–Alder Conditions[1]

E. T. McBEE,* E. P. WESSELER, D. L. CRAIN, R. HURNAUS, AND T. HODGINS

Department of Chemistry, Purdue University, West Lafayette, Indiana 47907

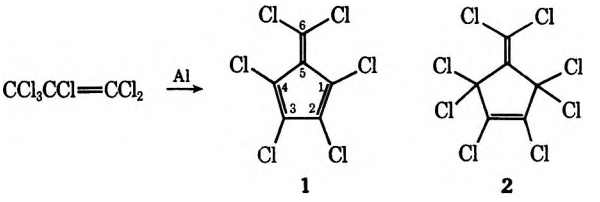
Received July 6, 1971

A new method for the preparation of hexachlorofulvene has been developed. The aluminum chloride catalyzed reaction of carbon tetrachloride and 1,2,3,4,5-pentachlorocyclopentadiene gave **4**, which underwent facile dechlorination to the desired **1**. The behavior of **1** under Diels–Alder conditions was investigated. Reaction with cyclopentadiene showed that **1** acts primarily as the dienophile to form **5**. Isomer **7** was also formed and indicated that **1** may also react as a diene. Hexachlorofulvene is an electron-deficient diene, but less reactive than hexachlorocyclopentadiene, possibly reflecting some stabilization from the dipolar resonance form. Treatment of **1** with $AlCl_3$ gave a dimer and a difulvene.

We have reported previously that the condensation between 1,2,3,4-tetrachlorocyclopentadiene and aromatic aldehydes[2] yields the corresponding 6-aryl-1,2,3,4-tetrachlorofulvenes. Another entry into this tetrachlorofulvene system, developed from tetrachlorodiazocyclopentadiene,[5,6] appears to have only limited applicability.

Substituent chlorine atoms modify the chemical behavior of these fulvenes, and enable reactions to be performed other than those to which hydrocarbon fulvenes[7] are normally susceptible. In order to clarify the extent of the similarities and differences between the two systems, we have subjected the parent chlorocarbon, hexachlorofulvene (**1**), to a representative set of reactions, described in this and subsequent papers. The results are also pertinent to work done in the area of alicyclic chlorocarbon chemistry.[8]

Roedig[9] reported the first preparation of hexachlorofulvene from the reaction of hexachloropropene and aluminum; a co-product of this reaction was octachloro-4-methylenecyclopentene (**2**). We have developed an alternate and more convenient synthesis of **1**, which together with a study of its behavior under Diels–Alder conditions constitutes the principal part of this report.



Results and Discussion

The aluminum chloride catalyzed reaction between carbon tetrachloride and 1,2,3,4,5-pentachlorocyclopentadiene (**3**)[10] gave octachloro-5-methylcyclopentadiene (**4**)[5,11] (Scheme I). The mechanism of this unusual reaction is not known, since both **3** and CCl_4 are capable of interacting with this Lewis acid.[13,14]

Dechlorination of **4** gave **1** in a yield of 94%. The reagent of choice was triethyl phosphite, although sodium iodide and stannous chloride were also effective. Using this procedure, 100-g quantities of **1** were made routinely. The fulvene formed deep red needles (hexane), mp 153–154°, appeared to be indefinitely stable in air, and was identical with a sample prepared

(1) Taken in part from the Ph.D. Thesis of D. L. Crain, Purdue University, 1958, and the Ph.D. Thesis of E. P. Wesseler, Purdue University, 1971. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

(2) E. T. McBee, R. K. Meyers, and C. F. Baranauckas, *J. Amer. Chem. Soc.*, **77**, 86 (1955). This procedure has been extended to give analogous fulvenes[3] and related derivatives.[4]

(3) J. S. Meek and P. Argabright, *J. Org. Chem.*, **22**, 1708 (1957).

(4) Y. Kitahara, I. Murata, M. Ueno, K. Sato, and H. Watanabe, *Chem. Commun.*, 180 (1966), and references cited therein.

(5) E. T. McBee, J. A. Bosoms, and C. J. Morton, *J. Org. Chem.*, **31**, 768 (1966).

(6) D. Bretches, Ph.D. Thesis, Purdue University, 1970.

(7) For a recent review on fulvenes, see P. Yates, *Advan. Alicycl. Chem.*, **2**, 59 (1968).

(8) R. West, *Accounts Chem. Res.*, **3**, 130 (1970).

(9) A. Roedig, *Justus Liebigs Ann. Chem.*, **569**, 161 (1950). Yields of **1**, mp 153°, were *ca.* 10%. The addition of chlorine to **1** gave **2**. This important result is mentioned here to exemplify the behavior of **1** under free radical conditions.

(10) E. T. McBee and D. K. Smith, *J. Amer. Chem. Soc.*, **77**, 389 (1955). An improved procedure gave **3** from the commercially available hexachlorocyclopentadiene in higher yields (Experimental Section).

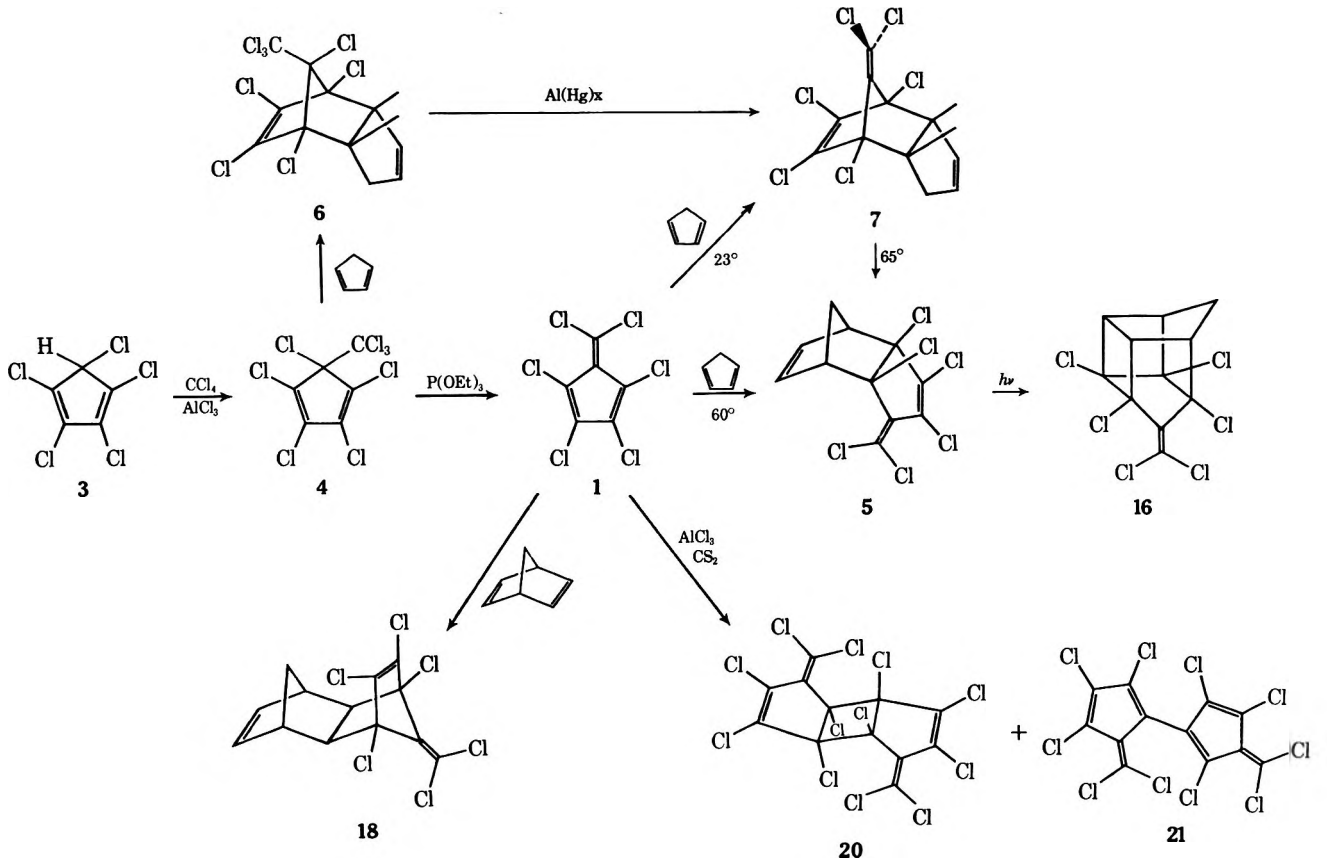
(11) This compound was prepared differently by H. J. Prins [*Recl. Trav. Chim. Pays-Bas*, **72**, 253 (1953)] and correctly identified later by spectral examination.[12]

(12) E. Ziegler, *Z. Anal. Chem.*, **213**, 9 (1965), and references cited therein.

(13) C. H. Wallace and J. E. Willard, *J. Amer. Chem. Soc.*, **72**, 5275 (1950).

(14) For example, see H. P. Fritz and L. Schäfer, *J. Organometal. Chem.* **1**, 318 (1964).

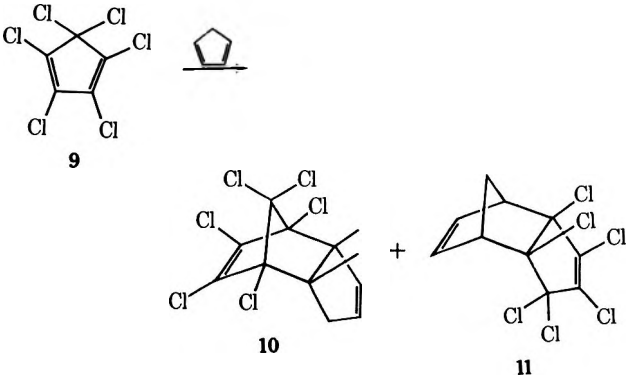
Scheme I



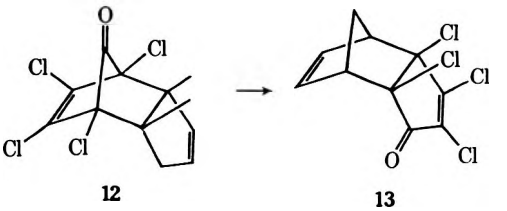
according to Roedig's procedure.[9,15,16] The ir double-bond stretching frequency of **1** was at 6.35 μ[17] and its uv absorption was at λ_{max} 296 and 307 nm (log ϵ 4.24 and 4.21, respectively).[18]

Diels–Alder Reaction.—Hydrocarbon fulvenes participate readily in this reaction,[7] although extensive studies have not been undertaken. In this work, we sought reactions which would demonstrate behavior of **1** both as a diene and as a dienophile.

In benzene at 60°, **1** and cyclopentadiene gave adduct **5** exclusively. The isomeric adduct **7** was synthesized by an alternative procedure, and was shown to isomerize quantitatively to **5** at this temperature. Repetition of this Diels–Alder reaction at 23° gave **5** and **7** in an approximate ratio of 4:1, together with some *endo*-dicyclopentadiene (**8**), as shown by nmr analysis. The adduct **7** was stable under these conditions. In addition, a sample of **1** in benzene at room temperature or at 60° was also recovered unchanged after 4 days (tlc); no evidence for Diels–Alder dimerization was found. In a related system, hexachlorocyclopentadiene (**9**) and cyclopentadiene are known[19,20] to yield the two adducts, **10** and **11**, in a 5:1 ratio; this reaction was repeated in order to determine the nmr parameters of these products. This data also verified the accuracy of the previous structural assignments.[19]



The rearrangement of **7** and **5** is of interest. Generally, analogous behavior has been observed in Diels–Alder adducts containing the *endo*-dicyclopentadiene skeletal structure. For example, the isomerization of **11** to **10** and of **12** to **13** have been reported.[19,21] Re-



(15) **1** has been obtained in small quantities both by A. E. Kulikova, N. M. Pinchuk, and E. N. Zil'berman [*Zh. Org. Khim.*, **3**, 1388 (1967)] and G. W. Calundann [Ph.D. Thesis, Purdue University, 1967].

(16) The attempted conversion of **2** to **1** with triethyl phosphite at room temperature failed.

(17) Compare the similar absorptions at 6.05 and 6.20 μ for **2**, and 6.22 μ for perchlorocyclopentene.

(18) (a) Fulvenes also possess a longer wavelength band of much lower intensity which extends into the visible region, accounting for the color of fulvenes.[7] This broad band reportedly[9] possesses a maximum at 450 nm for **1**. (b) The mass spectrum of **1** has been recorded by S. Meyerson and E. K. Fields [*J. Chem. Soc. B*, 1001 (1966)].

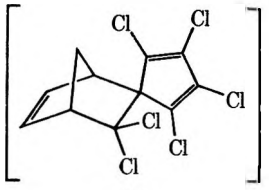
(19) M. Liva, P. Klucho, and M. Paldan, *Tetrahedron Lett.*, 141 (1963).

(20) (a) R. Riemschneider, *Monatsh. Chem.*, **83**, 802 (1952); (b) R. Riemschneider, *Botyu Kagaku*, **28**, 83 (1963).

(21) P. Yates and P. Eaton, *Tetrahedron*, **12**, 13 (1961).

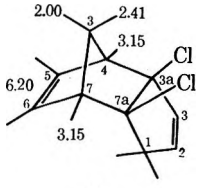
arrangements of this type are generally held to be intramolecular,[22] and the unusually low temperature (60°) required for the isomerization of **7** to **5** supports this contention. It may also be noted that the strain due to the exo chlorines in **11** is relieved somewhat in **10**, but apparently with **5** and **13** the increased conjugation and the release of strain in the sp^2 carbon is of more importance.

The structure of **5** was elucidated by comparison of its nmr spectrum with those of **11** and other norbornene derivatives.[23] In particular, the broadened methine proton signals and the 0.15 ppm coupling constant between the methylene protons, which appear as the upfield AB quartet, are features normally diagnostic of such systems. Apparently, dienophilic fulvenes undergo reaction at one of the endocyclic rather than the exocyclic double bond.[24] That the behavior of **1** was consistent with this precept, and did not yield **14**,



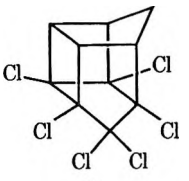
14

was supported by the following information. First, the uv spectrum of **5** contained absorptions at 267, 274, and 284 nm (log ϵ 4.26, 4.37, and 4.26, respectively); these extinction coefficients are about an order of magnitude larger than the values for chlorinated cyclopentadienes.[5,25] Second, a model was constructed[28] whereby the chemical shifts shown were estimated for compound **15**. Agreement with the corresponding



15

values for **5** (and also **11**) was reasonable except for the C-7 proton, which, as would be expected, is influenced strongly by the chlorine substituents. Lastly, the photocyclization of **5**, a reaction for which there is considerable precedent,[30] gave **16** together with some unidentified products. The mass spectrum of **16** contained the molecular ion with the correct isotopic pattern. In addition, the nmr spectrum of **16** was similar to that of **17**, and the ir spectra of these two compounds



17

were nearly identical between 6.9 and 8.4 μ. There was also a strong double-bond stretching absorption for **16** at 5.98 μ.[17] Compound **17**[31] was prepared by irradiation of **10**. This product, identified primarily from the method of preparation, gave an nmr spectrum which contained a single resonance (4 H) for the methine protons and an upfield AB quartet for the methylene bridge (2 H).

The isolation and subsequent dechlorination of **6**, obtained from **4** and cyclopentadiene (Scheme I), provided the first important chemical evidence supporting the structure assigned[12] to **4**, which was shown to be stable to the Diels–Alder conditions. Compound **6** was identified by the extremely close similarity of its nmr spectrum with that of **10**. Differences in the chemical shifts between corresponding protons were less than 0.17 ppm. For this reason, the C-8 chlorine substituent was assigned the position anti to the chlorinated double bond. None of the isomeric *syn*-chloro analog of **6** was isolated. The factors that control the stereochemistry in this type of reaction are not understood. In probably the only systematic study of consequence, Williamson and coworkers[32] examined the reaction of **3** with a series of dienophiles and established that the appropriate products contained isomers, which differed according to whether the chloro substituent on the bridging methylene group occupied a syn or anti position. These results were rationalized[32] in terms of the steric effects, electrostatic interactions, and substituent polarizabilities operating in the reactant complex.[33] The structure of **6** is consistent with these concepts,[32,33] particularly in that the bulky trichloromethyl substituent occupies the less sterically demanding syn position.

The structure of **7** followed from the methods of preparation and from spectral data. Thus, the nmr

(22) R. B. Woodward and T. J. Katz, *Tetrahedron*, **5**, 70 (1959).

(23) (a) K. Tori, K. Aono, Y. Hata, R. Muneyuki, T. Tsuju, and H. Tanida, *Tetrahedron Lett.*, 9 (1966); (b) P. Laszlo and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **86**, 1171 (1964); (c) P. M. Subramanian, M. T. Emerson, and N. A. LeBel, *J. Org. Chem.*, **30**, 2624 (1965).

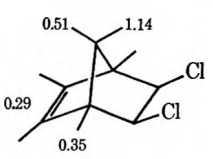
(24) See ref 7, p 142.

(25) The following are uv data: **9**, 322 nm (log ϵ 3.17);[26] **4**, 326 nm (log ϵ 3.23); and 5-methylpentachlorocyclopentadiene,[27] 308 nm (log ϵ 3.025).

(26) H. E. Ungnade and E. T. McBee, *Chem. Rev.*, **58**, 249 (1958).

(27) R. A. Halling, Ph.D. Thesis, Purdue University, 1965.

(28) Examination of the literature data[23] on the nmr chemical shifts of halo- and dihalonorbornenes gave the approximate *incremental* values (parts per million), relative to norbornene, for the protons in the unknown *exo-cis*-5,6-dichlorononorbornene (i). These values were added subsequently to the



i

corresponding ones in *endo*-dicyclopentadiene[29] to obtain the results for **15**. The incremental values shown in i resulted necessarily from personal judgments and should be treated accordingly.

(29) T. Hodgins, unpublished results.

(30) W. L. Dilling, H. P. Braendlin, and E. T. McBee, *Tetrahedron*, **23**, 1211 (1967), and references cited therein.

(31) (a) L. Vollner, W. Klein, and F. Korte, *Tetrahedron Lett.*, 2967 (1969); (b) F. Korte, W. Klein, and B. Drefahl, *Naturwiss. Rundsch.*, **23**, 445 (1970).

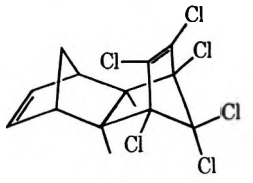
(32) (a) K. L. Williamson, Y-F. L. Hsu, R. Lacko, and C. H. Youn, *J. Amer. Chem. Soc.*, **91**, 6129 (1969); (b) K. L. Williamson and Y-F. L. Hsu, *ibid.*, **92**, 7385 (1970).

(33) Bulky 5 substituents in cyclopentadienes, lying between the parallel planes which define the reactant complex, tend to hinder product formation. In principle, the least hindrance occurs in the limiting case, when the 5-carbon atom in the cyclopentadiene has sp^2 hybridization; a situation that could result with a good leaving group at the 5 position. In such circumstances, a developing carbonium ion at this position would be better stabilized when the transition stage resembles the product with the leaving group in an anti position.[34]

(34) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1959, p 599.

spectrum of **7** was very similar to those of **10** and **6**. The compound exhibited ir double-bond stretching absorptions at 5.98 and 6.1 μ, comparable to the corresponding ones[17] found in **2**. Also, the uv data (λ_{max} 205 nm, log ϵ 4.26)[35] confirmed that **7** did not contain a conjugated double-bond system.

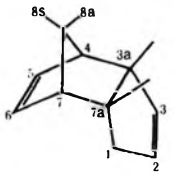
The formation of **7** from **1** and cyclopentadiene demonstrated the ability of **1** to act as the diene under Diels–Alder conditions. Another example was found in the reaction of **1** with norbornadiene. Product **18** (Scheme I) was identified readily by comparison[36] of its nmr spectrum (Table I) with that of aldrin (**19**).

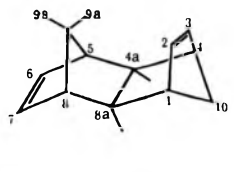


19

TABLE I

NUCLEAR MAGNETIC RESONANCE DATA[a]





	4[b]	5 and 6[c]	7[b]	8 syn[d]	8 anti
5	3.27	6.10	3.81	2.00	2.50
11	3.18	6.24	3.46	2.05	2.58
	1	2	3	3a	7a
6[e]	2.38	5.60	5.85	3.98	3.60
7[e]	2.43	5.61	5.83	3.70	3.21
10[e]	2.42	5.65	5.8	3.83	3.43
	4a and 8a[f]	5 and 8[b]	6 and 7[c]	9 syn[g]	9 anti
18	2.57	2.90	6.32	1.35	1.52
19	2.73	2.90	6.32	1.32	1.61

[a] Chemical shifts (δ) in parts per million downfield from TMS. [b] Singlet with fine structure. [c] Vinylic signal centered at this position. [d] J_{8s-8a} = 9.5 Hz. [e] All signals were complex multiplets and errors may be present in the estimated chemical shifts. [f] Singlet. [g] J_{9s-9a} = 11.0 Hz.

On the other hand, **1** and 6-phenyltetrachlorofulvene are reported[3,9] to be unreactive toward maleic anhydride, even under more extreme conditions.[37,38] Thus, the behavior of **1** as a diene parallels that of **9**, which also reacts faster with cyclopentadiene than with maleic anhydride.[40] This order of reactivity appears to be characteristic of electron-deficient dienes.

The early stages of a competition reaction between **1** and **9** with norbornadiene (an electron-rich dienophile) were monitored by nmr. The results showed that **9** was 1.7 times more reactive.[41] The lower reactivity of **1** compared to **9** with both norbornadiene and maleic anhydride depends in part on the intrinsic reactivity of the dienes, which is unrelated to the nature of the dienophile. For example, benzene is normally unreactive as a diene under Diels–Alder conditions. Hence, the reactivity of **1** may merely reflect its partial aromatic character.[43]

In concluding this section, the preferred dienophilic reaction of **1** with cyclopentadiene is emphasized.[44] This study demonstrated that **1** can participate in the Diels–Alder reaction both as a diene and a dienophile, and that the substituent chlorine atoms exert an important but not overriding influence.

Dimerization.—Although **1** was found to be stable at 105° as shown by tlc, decomposition[45] occurred at 196°. In the latter case, no evidence for thermal dimerization was obtained. Instead, the major product was found to be **2**. Some red, oily material was also isolated, but not identified. Dimerization was observed when **1** was treated with approximately a 0.5 mole ratio of aluminum chloride. The product mixture included some **2** and a difulvene. Both the dimer and the difulvene appeared to be homogeneous (tlc, melting point) and were tentatively assigned structures **20** and **21**, respectively (Scheme I). The molecular formulas of these compounds were established from elemental analyses and mass spectra, but their precise structure would not be proven rigorously because of numerous isomeric possibilities. Thus **20**, which reverted to **1** on heating, had a uv absorption at λ_{max} 272 nm (log ϵ 4.62); this wavelength is very similar to that of **5**, though the relative extinction coefficients are different by the significant factor of 1.78. This data eliminated the possibility of a norbornenyl system in **20** and suggested the presence of two identical but noninteracting chromophores as shown in the given structure. There are three other isomers of this type, with the cyclopentene systems on the same side of the cyclobutane ring or with the dichloromethylene substituents aligned. The choice of the centrosymmetric **20** was made by comparison of infrared data with that for a similar dimer derived in principle from tetrachlorocyclopentadienone.[46] The ir spectrum of **20** contained about the same number of absorption bands as in the model[46] and four of them occurred at similar wavelengths.

The isolation of **21** from the reaction mixture was unexpected since Lewis acid promoted dechlorinations are rare.[47] The red color of this product suggested a fulvene moiety and evidence for a difulvene structure was derived from spectral comparisons. Thus, the uv absorption of **21** was at 302 nm (log ϵ 5.53). The

(35) Octachlorocyclopentene[26] has λ_{max} 230 nm (log ϵ 4.00).

(36) (a) A. P. Marchand and J. E. Rose, *J. Amer. Chem. Soc.*, **90**, 3724 (1968); (b) Sadtler Standard Spectra, No. 6239.

(37) We have confirmed this result for **1**.

(38) Failure of **1** and maleic anhydride to react may be an equilibrium rather than a kinetic effect.[39]

(39) D. Craig, J. J. Shipman, J. Kiehl, F. Widmer, R. Fowler, and A. Hawthorne, *J. Amer. Chem. Soc.*, **76**, 4573 (1954). These authors observed facile dissociation of the Diels–Alder adduct from 6,6-dimethylfulvene and maleic anhydride. They noted the conversion of the adduct to a more stable isomer and suggested that this rearrangement proceeded *via* an intramolecular process.[21]

(40) (a) J. Sauer, D. Lang, and A. Mielert, *Angew. Chem., Int. Ed. Engl.*, **1**, 268 (1962); (b) J. Sauer and H. Wiest, *ibid.*, **1**, 269 (1962).

(41) The reaction conditions employed here are much less severe than those apparently needed for the reaction of cyclopentadiene and norbornadiene,[42] as would be predicted.[40]

(42) J. K. Stille and D. A. Frey, *J. Amer. Chem. Soc.*, **81**, 4273 (1959).

(43) A. discussion on this point is given by K. Hafner, *et al.*, *Angew. Chem., Int. Ed. Engl.*, **2**, 123 (1963).

(44) The ratio of **5** to **8** was >10:1 (nmr) in this reaction.

(45) Rearrangement of **1** to hexachlorobenzene was observed at 250–300° when bromine was present.[9]

(46) R. M. Scribner, *J. Org. Chem.*, **30**, 3657 (1965). This paper illustrates the difficulties encountered in differentiating complex chlorocarbon isomers. The tetrachlorocyclopentadienone dimer analog of **20** has ir absorptions at 5.71 (C=O), 6.33, 8.06–8.13, 8.34, 9.35, 9.75, 10.87, 12.84, and 13.89 μ.

(47) E. N. Zilberman, A. E. Kulikova, and E. G. Pomerantseva, *J. Org. Chem., USSR.*, **3**, 1158 (1967).

spectrum is similar to that of **1** except that the extinction coefficient is greater by a factor of 2.0. The ir spectrum of **21** is also very similar to that of **1**. Molecular models show that in the 2,2′-linked isomer there is a lack of steric distortion which would allow coplanarity of the fulvene rings and hence this isomer would be expected to have a bathochromic shift in the uv relative to **1**. The tentative choice of a 1,2′ linkage in **21** was made from the evidence (developed in a subsequent paper) that **1** is susceptible to attack by electrophiles at the 1 position, whereas the $AlCl_3$–**1** complex is electrophilic at the 2 position. The structure of **21** is consistent with this idea.

The formation of **2** and **21** is an interesting example of an aluminum chloride catalyzed redox process, although the exact mechanistic details are not known.

Experimental Section

Procedures and Equipment.—Melting points were determined with a Mel-Temp apparatus in sealed tubes and are uncorrected. Proton nmr spectra (Table I) were obtained on a Varian Associates A-60A spectrometer; carbon tetrachloride was used as a solvent with tetramethylsilane as an internal standard. Infrared spectra were determined on the compounds as KBr pellets using a Perkin-Elmer 221 or Beckman IR-8 infrared spectrophotometer. Ultraviolet spectra were determined in 95% ethanol on a Bausch and Lomb Spectronic 505 spectrophotometer. Thin layer chromatography (tlc) was carried out on glass plates coated with silica gel HF-254, E. Merck AG. Mass spectra were recorded on a Hitachi Perkin-Elmer HU-6D high-resolution mass spectrometer. Elemental analyses were performed by Dr. C. S. Yeh and her staff at Purdue University.

1,2,3,4,5-Pentachlorocyclopentadiene (3).—A solution containing 136.5 g (0.5 mol) of **9** in 50 ml of acetone was cooled with an external ice bath while 113 g (0.5 mol) of stannous chloride dihydrate in 200 ml of acetone was added at such a rate as to keep the temperature near 45°. The ice bath was then removed and the solution was stirred an additional 30 min. The solution was poured into 300 ml of water and the organic material was then extracted with CCl_4. After removing the solvent from the dried extract, the product was distilled (52–53° at 0.25 mm) rapidly to prevent dimerization, giving 95 g of monomeric **3** (80% yield).

Octachloro-5-methylcyclopentadiene (4).—A mixture of 95 g (0.4 mol) of **3**, 400 ml of CCl_4, and 10 g (0.075 mol) of $AlCl_3$ was stirred and heated on a water bath at 75° for 2 hr. After cooling, 300 ml of water was added and the organic material was extracted with CCl_4. This yielded 128 g of a brown solid, which was then dissolved in hot acetone to which decolorizing charcoal was added. After filtering, the acetone solution yielded 118 g (83%) of slightly yellow **4**. Further purification by recrystallization from CCl_4 gave colorless crystals: mp 93.5–94°; ir (KBr) 6.24 (s), 6.38 (w), 7.98 (s), 8.56 (m), 8.62 (m), 8.92 (w), 9.93 (m), 10.42 (m), 11.94 (s), 12.29 (s), and 14.16 μ (s).

Anal. Calcd for C_6Cl_8: C, 20.25; H, 0.00; Cl, 79.75. Found: C, 20.34; H, 0.00; Cl, 79.49.

A solution of **4** in benzene was refluxed for 65 hr. A 98% recovery of **4** was realized.

Hexachlorofulvene (1).—A solution of 118 g (0.33 mol) of **4** in 500 ml of hexane was cooled in an ice bath while 46 g (0.36 mol) of triethyl phosphite in 50 ml of hexane was added dropwise. After 15 min following the addition, the solvent was distilled off. The residue was recrystallized from CCl_4 and yielded 88 g (94%) of deep red needles: mp 153–154°; ir (KBr) 6.35 (s), 7.81 (s), 7.95 (s), 8.16 (m), 10.75 (m), 14.16 μ (m).

A solution of **4** in acetone, when treated with stannous chloride dihydrate or sodium iodide at room temperature, gave **1** in 63 and 98.2% yield, respectively. The latter conversion, however, was *ca.* 67%.

Synthesis of *endo*-2,3,3a,7a-Tetrachloro-1-dichloromethylene-3a,4,7,7a-tetrahydro-4,7-methanoindene (5). A. At 60°.—Hexachlorofulvene (10.0 g, 0.035 mol), cyclopentadiene (2.6 g, 0.04 mol), and benzene (30 ml) were sealed in a Carius tube and heated to 60° for 12 hr. The product was chromatographed on a 30 × 1.5 in. column packed with 200 mesh silica gel. Hexane was used as an eluent. The first fraction was 5.9 g of **1**. The second contained 4.7 g (41% conversion, 95% yield) of **5** as colorless crystals: mp 121–122°; ir (KBr) 6.24 (s), 6.34 (s), 6.86 (w), 7.53 (m), 8.00 (s), 8.07 (s), 8.17 (s), 10.26 (m), 10.61 (m), 10.79 (m), 10.90 (s), 11.53 (m), 12.77 (m), 13.07 (s), 13.82 (m), 14.14 (m), 14.64 μ (s).

Anal. Calcd for $C_{11}H_6Cl_6$: C, 37.65; H, 1.72; Cl, 60.63. Found: C, 37.30; H, 1.60; Cl, 61.00.

B. At 23°.—A solution containing 14.2 g (0.05 mol) of **1**, 10 g (0.15 mol) of cyclopentadiene, and 70 ml of benzene was stirred on a water bath (23°) for 71 hr. An aliquot removed at this time and one at 27 hr were analyzed by nmr, which indicated that the ratio of **5**:**7**:**8** was approximately 4:1:1 The product was chromatographed on a silica gel column which was eluted with hexane. Only 0.1 g of **1** was recovered as the first fraction. A later fraction yielded 13.1 g (77%) of adducts **5** and **7**.

Preparation of *endo*-4,5,6,7,8-*anti*-Pentachloro-8-*syn*-trichloromethyl-3a,4,7,7a-tetrahydro-4,7-methanoindene (6).—A solution of 13.2 g (0.037 mol) of **4**, 7 ml (0.086 mol) of cyclopentadiene, and 30 ml of benzene was heated to 83° for 2 days in a sealed ampule. The product was chromatographed on a silica gel column. Elution with hexane gave 7.8 g of **4** and later 4.0 g (62% yield) of **6** was isolated: mp 157–160° dec; uv max (95% EtOH) 214 nm (log ϵ 3.66); ir (KBr) 6.15 (s), 6.90 (m), 7.37 (m), 7.93 (s), 8.40 (s), 8.61 (m), 9.58 (s), 9.95 (s), 12.23 (s), 12.66 (s), 12.84 (s), 13.32 (s), 14.07 (m), 14.40 (s), 14.94 μ (s).

Anal. Calcd for $C_{11}H_6Cl_6$: C, 31.32; H, 1.53; Cl, 67.25. Found: C, 31.04; H, 1.33; Cl, 67.40.

***endo*-4,5,6,7-Tetrachloro-8-dichloromethylene-3a,4,7a-tetrahydro-4,7-methanoindene (7).**—Aluminum shot (1.0 g) was washed with 30 ml of 5% sodium hydroxide for 3 min, three times with water, and twice with ethanol and then amalgamated with a saturated solution of mercuric chloride (50 ml). The amalgam was washed with water, ethanol, and pentane. A solution of 1.38 g (0.0033 mol) of **6** in 20 ml of pentane and 20 ml of ethanol was added to the amalgam. After 3 hr with occasional agitation, the mixture was filtered. The product **7**, 1.12 g (98% crude yield), was isolated. After recrystallization from pentane a colorless solid was obtained: mp 108–109°; ir (KBr) 5.98 (s), 6.17 (s), 6.88 (s), 7.38 (m), 7.69 (w), 7.97 (s), 8.24 (w), 8.50 (m), 8.73 (m), 8.90 (s), 9.53 (s), 9.68 (m), 9.95 (s), 10.51 (m), 10.62 (m), 11.21 (s), 12.40 (s), 12.86 (s), 13.75 (s), 14.11 (s), 14.73 μ (s).

Anal. Calcd for $C_{11}H_6Cl_6$: C, 37.65; H, 1.72; Cl, 60.63; mol wt, 351. Found: C, 37.65; H, 1.88; Cl, 60.43; mol wt, 346.

A sample of **7** was heated in benzene at 60° for 18 hr. Nmr analysis showed that quantitative conversion to **5** occurred. A similar experiment at 23° left **7** unchanged.

1,7,8,9-Tetrachloro-10-dichloromethylenepentacyclo[5.3.0.-$0^{2,6}.0^{3,9}.0^{5,8}$]decane (16).—An irradiation flask, equipped with a Pyrex filter and 450 W Hanovia type L lamp, was filled with a solution of 2.8 g (0.008 mol) of **5** in 375 ml of spectral grade acetone. The progress of the reaction was followed by tlc, and after 6 days the reaction was terminated. A chromatographic column of *deactivated* silica gel was eluted with CCl_4 to separate the numerous products. Fraction three was a white solid: mp 128.5–129°; mass spectrum (75 eV) *m/e* 348 (M). The nmr spectrum of crude **16** contained a broad singlet at δ 3.23 (4 H) and 2.98 (impurity), and doublets at 1.73 (1 H) and 2.15 (1 H, J = 12.0 cps).

By comparison, the nmr of **17**, which was prepared similarly, exhibited a broad singlet at δ 3.30 (4 H) and doublets at 1.65 (1 H) and 2.40 (1 H, J = 12.5 cps).

1,2,3,4-Tetrachloro-10-dichloromethylene-1,4,4a,5,8,8a-hexahydro-1,4:5,8-*endo*-*exo*-dimethanonapththalene (18).—A solution of 2.0 g (0.007 mol) of **1** in 30 ml of norbornadiene was heated with an oil bath at 100° for 48 hr. The addition of acetone gave a solid material which, after recrystallization from ethanol, yielded 1.4 g (53%) of colorless crystals: mp 138–139°; uv max (95% EtOH) 215 nm (log ϵ 3.96); ir (KBr) 6.24 (s), 6.34 (s), 6.86 (w), 7.53 (m), 8.00 (s), 8.07 (s), 8.17 (s), 10.26 (m), 10.61 (m), 10.79 (s), 10.91 (s), 11.03 (m), 12.78 (m), 13.08 (s), 13.31 (m), 14.14 (m), 14.65 μ (s).

Anal. Calcd for $C_{13}H_8Cl_6$: C, 41.42; H, 2.14; Cl, 56.44. Found: C, 41.28; H, 2.24; Cl, 56.12.

Thermolysis of 1.—Hexachlorofulvene (1.0 g) was heated to 196° for 18 hr in a sealed tube under N_2. Column chromatography using silica gel separated the products on elution with hexane. Approximately 0.4 g of **2** was isolated and identified

by ir and melting point comparison with an authentic sample.[26] A red oil was also obtained, but not identified.

Dimerization of 1 with Aluminum Chloride.—To a solution of 2.84 g (0.01 mol) of 1 in 20 ml of carbon disulfide at 23° was added 0.67 g (0.005 mol)[48] of $AlCl_3$. After stirring for 24 hr, distilled water was added, and the product was extracted with CCl_4. The crude product was chromatographed on a 40-cm column of silica gel. Elution with hexane gave as the first fraction a small amount of 1 and approximately 0.4 g of **2**. A second larger red band consisted of a mixture of **20** and **21** (0.9 g, 46% yield). The latter two compounds were separated by recrystallization from ethyl acetate. Compound **20** was a colorless solid: mp 262° dec; ir (KBr) 6.29 (s), 8.07 (s), 8.34 (w), 9.66 (m), 10.70 (w), 10.97 (s), 12.02 (w), 12.81 (m), 13.52 μ (s).

(48) Larger ratios of 1 to $AlCl_3$ yield larger amounts of **21** and **2** at the expense of **20**.

Anal. Calcd for $C_{12}Cl_{12}$: C, 25.30; Cl, 74.70. Found: C, 25.14; Cl, 75.00.

Compound **21** is a stable red solid: mp 185–186°; ir (KBr) 6.36 (s), 6.44 (s), 7.85 (s), 7.93 (s), 8.22 (m), 10.33 (m), 10.82 (s), 11.53 (m), 13.92 μ (w); mass spectrum (75 eV) *m/e* 494 (M), 459 (M − Cl), 424 (M − Cl_2, base ion), 354 (M − Cl_4), 282 (M − Cl_6).

Anal. Calcd for $C_{12}Cl_{10}$: C, 28.90; Cl, 71.10. Found: C, 28.65; Cl, 71.40.

Registry No.—**1**, 6317-25-5; **3**, 25329-35-5; **4**, 6928-57-0; **5**, 33065-95-1; **6**, 33065-96-2; **7**, 33122-14-4; **10**, 33065-97-3; **11**, 33065-98-4; **16**, 33061-05-1; **18**, 33065-99-5; **19**, 309-00-2; **20**, 33066-00-1; **21**, 33061-04-0.

Protonation and Deuteration of the Isopropenylcyclopentadienyl Anion. Trapping of the Isomeric Product Mixture[1]

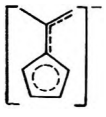
DAVID B. KNIGHT,* RAY L. HARTLESS,[2a] AND DAVID A. JARVIS[2b]

Department of Chemistry, The University of North Carolina at Greensboro, Greensboro, North Carolina 27412

Received July 7, 1971

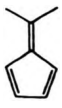
Protonation of the isopropenylcyclopentadienyl anion (**1**) gave a mixture of 15 ± 3% dimethylfulvene (**2**), 58 ± 3% 1-isopropenyl-1,3-cyclopentadiene (**3**), and 25 ± 2% 2-isopropenyl-1,3-cyclopentadiene (**4**). Deuteration of **1** afforded a mixture of 10 ± 4% **2**, 64 ± 3% **3**, and 26 ± 2% **4**. Mass spectral evidence indicates that a lower limit of 97% of the total product mixture was derived from reactions of **1**, while 3% of the product mixture was residual, un-ionized **2**. Chemical trapping of the isomeric product mixture as Diels–Alder adducts of tetracyanoethylene was accomplished. Isomers **2**, **3**, and **4** gave on treatment with tetracyanoethylene adducts 7-isopropylidene-5,5,6,6-tetracyanonorbornene (**6**), 3a,4,5,6,5-pentahydro-4,4,5,5-tetracyano-7-methylindene (**7**), and 2-isopropenyl-5,5,6,6-tetracyanonorbornene (**8**), respectively. The relative amounts of **6**, **7**, and **8** were within experimental error of the relative amounts of **2**, **3**, and **4**, in the mixtures from which the adducts were derived.

Hine and Knight[3] recently reported a study of the protonation of the isopropenylcyclopentadienyl anion (**1**) derived from the treatment of 6,6-dimethylfulvene

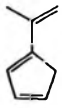


1

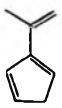
(**2**) with base. Kinetic control of the protonation was hoped for but was not conclusively demonstrated, largely because they did not show whether or not the dimethylfulvene present in the product mixture composed of **2**, 1-isopropenyl-1,3-cyclopentadine (**3**), and 2-isopropenyl-1,3-cyclopentadiene (**4**) was derived from **1** or was **2** that never was ionized.



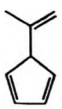
2



3



4



5

We have repeated part of this work and in addition report here a detailed study of the deuteration of **1**. Also we succeeded in chemically trapping the thermally unstable (due to Diels–Alder addition) mixture of **2**, **3**, and **4** as Diels–Alder adducts of tetracyanoethylene (TCNE).

(1) Delivered in part at the Combined Southeast–Southwest Regional Meeting of the American Chemical Society, New Orleans, La., Dec 1970.

(2) (a) Abstracted in part from the M.S. Thesis of R. L. H., University of North Carolina at Greensboro, 1971. (b) National Science Foundation Undergraduate Research Participant, summer, 1970.

(3) J. Hine and D. B. Knight, *J. Org. Chem.*, **35**, 3946 (1970).

Results and Discussion

Several repetitions of the isomerization of dimethylfulvene *via* protonation of anion **1** gave product mixtures in which the relative amounts of **2**, **3**, and **4** were in good agreement with previous work.[3] Table I summarizes the results of seven experiments in which anion **1** was deuterated.

TABLE I

DEUTERATION OF ISOPROPENYLCYCLOPENTADIENYL ANION 1[a]

Run	2, %	3, %	4, %
1	7	63	30
2	8	64	28
3	20	57	23
4	10	64	26
5	9	66	25
6	9	67	24
7	10	65	25
	10 ± 4	64 ± 3	26 ± 2

[a] Equivalent amounts of **2** and potassium *tert*-butoxide in bis(2-methoxyethyl) ether (diglyme) were mixed at room temperature. The homogeneous solution containing anion **1** was added to deuterium acetate in deuterium oxide. Products **2**, **3**, and **4** were quickly extracted into CCl_4 or light petroleum ether and stored at −78° until analyzed. No evidence for the formation of 5-isopropenyl-1,3-cyclopentadiene (**5**) was found.

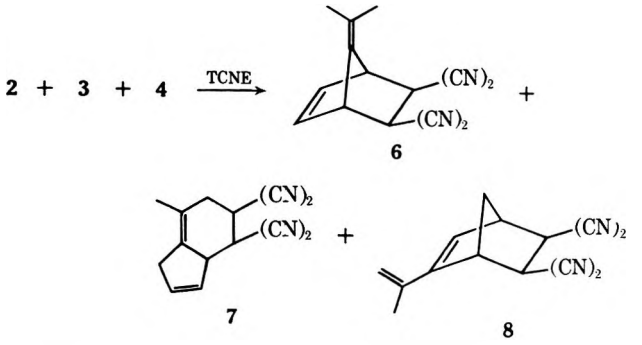
Relative amounts of **2**, **3**, and **4** in the deuteration–isomerization experiment were determined primarily by nuclear magnetic resonance (nmr) and by gas–liquid partition chromatography (glpc).[4] Deuterium uptake into **3** and **4** should occur at the ring methylene positions

(4) Details of the nmr spectra of **2**, **3**, and **4** are described in ref 3.

of these isomers. In the nmr spectrum of the deuterated isomer mixture in carbon tetrachloride, integration of absorption of the region τ 6.8–7.0, attributed to the ring methylene hydrogens of **3** and **4**, indicated the presence of 1.3–1.4 protons. This is consistent with the uptake of 60–70% of one deuterium into **3** and **4**. The mass spectrum of a sample of deuterated **2**, **3**, and **4** isolated by vacuum distillation indicated the presence of 65–70% of one deuterium in the mixture, within experimental error of the nmr analysis. It was impossible from the nmr spectrum of the deuterated isomer mixture to establish the extent of deuterium uptake into dimethylfulvene due to the overlap of absorptions of **2** with those of **3** and **4**. It was necessary to have an estimate of the extent of deuterium uptake into **2**, however, to confirm that the dimethylfulvene in the product mixture was in fact derived from anion **1** and was not residual, un-ionized **2**. In run 7 (Table I) the deuteration of **1** was carried out and the product mixture was analyzed by gas chromatography–mass spectrometry (gc–ms). Evidence from gc–ms indicated that in the fraction containing **3** and **4** (inseparable by glpc) there was 47% nondeuterated, 50% monodeuterated, and 3% dideuterated product.[5] The dimethylfulvene in the isomerization mixture was 60% nondeuterated, 38% monodeuterated, and 2% dideuterated.

Formation (and uptake of deuterium) of **3** and **4** is presumed to occur *via* reaction of **1**. Likewise, deuterium uptake into dimethylfulvene is presumed to involve reaction of **1**. In this experiment **1** reacted at the ring positions to form **3** and **4** about equally as readily with a proton donor as with a deuteron donor. It is expected that in the same medium the relative amounts of protium and deuterium uptake at the methyl position of **1** would likewise be similar. Hence in **2** derived from **1**, essentially equal amounts of protonation and deuteration are expected to have occurred. Thus 35–40% of the undeuterated **2** is presumed to come from **1**, leaving the possibility that 20–25% of the total dimethylfulvene recovered from the isomerization–deuteration experiment may be **2** that never was ionized by base. An upper limit, therefore, of approximately 3% of the isomerization product mixture is residual, un-ionized dimethylfulvene, while 97% of the mixture is derived from **1**.

Trapping of the Isomers 2, 3, and 4 as Adducts of Tetracyanoethylene.—As the composition of the isomerization product mixture changed on standing at temperatures much above −78°, due primarily to the formation of Diels–Alder adducts among **2**, **3**, and **4**, it was desirable to trap the isomers chemically to give a mixture whose composition was stable with time and which could be isolated. Accordingly, because of its high reactivity as a Diels–Alder dienophile, TCNE was added to the mixture of **2**, **3**, and **4** to trap the isomers as Diels–Alder adducts of TCNE. Of the several possible monoadducts that conceivably could be formed by reaction of TCNE with **2**, **3**, and **4**, only three were observed. 7-Isopropylidene-5,5,6,6-tetracyanonorbornene (**6**) was formed in the reaction of dimethylfulvene with TCNE, while 3a,4,5,-6,6-pentahydro-4,4,5,5-tetracyano-7-methylindene (**7**) formed by the action of TCNE on **3**. The remaining adduct, formed by treatment of **4** with TCNE, was 2-isopropenyl-5,5,6,6-tetracyanonorbornene (**8**).



Tetracyanoethylene acted as an efficient trap for the isomer mixture, as is indicated by the data in Table II.

TABLE II
RESULTS OF TRAPPING ISOMER MIXTURES 2, 3, AND 4 AS ADDUCTS OF TCNE

Run	2, %	3, %	4, %	6, %	7, %	8, %
1[a]	11	63	26	7	70	23
2[a]	13	60	27	11	65	24
3[b]	10	64	26	13	59	28
4[b]	9	66	25	8	68	24
	11 ± 2	63 ± 3	26 ± 1	10 ± 3	66 ± 5	25 ± 2

[a] Protonation experiment. [b] Deuteration experiment.

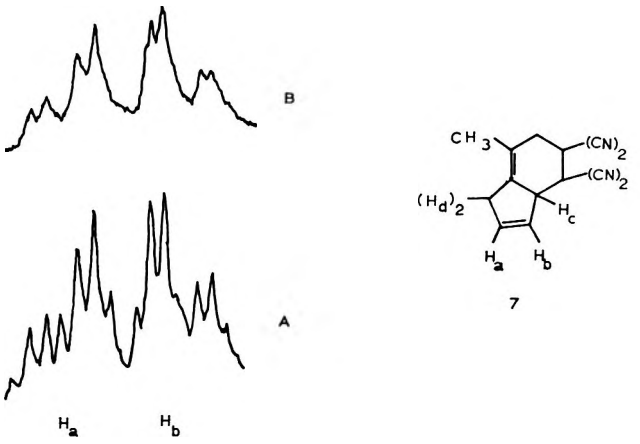
Material balance was not achieved on isolated adducts **6**, **7**, and **8**. Rather, the data in Table II were obtained from integration of nmr spectra of the isomer mixture and also the mixture of adducts. Each of the adducts **6**, **7**, and **8** was isolated and identified by its characteristic infrared and nmr spectra and in the cases of **7** and **8** by elemental analysis. The trapping experiment was also carried out in an nmr tube and the spectrum of the resulting mixture of adducts was exactly the sum of spectra of the individually isolated adducts, allowing estimation of the relative amounts of **6**, **7**, and **8** in the trapped mixture.

Adduct **6** is a known compound, having been reported by Kresze.[6] Adduct **7**, mp 92–93°, showed weak absorption in the infrared at 2245 cm^{-1} characteristic of nitriles having electron-withdrawing groups α to the cyano group.[7] The 100-MHz nmr spectrum of adduct **7** in acetone-d_6 showed absorption in four major bands, τ 8.18, 6.3–7.0, 5.85, and 3.55–3.95 with relative areas of 3.0:4.08:1.05:2.0. The broadened multiplet centered at τ 8.18 consisting of at least four lines was assigned to the methyl group. The basic feature of the absorption in the region τ 6.3–7.0 was a broadened AB quartet, J = 18.0 Hz, centered at τ 6.78. In benzene solution the AB feature was lost and this region showed only two broadened absorptions, each integrating for two protons. Adduct **7**, formed from deuterated **3**, showed a marked decrease in the intensity of the absorption centered at τ 6.78, allowing assignment of this

(5) The amount of nondeuterated product observed in this experiment is somewhat higher that that usually observed in the deuteration of **1**. A considerable amount of protonation is not surprising as an equivalent amount of *tert*-butyl alcohol is formed for each mole of **2** ionized (see footnote 13, ref 3), diluting the deuterium pool with protium. The unusually high proportion of nondeuterated product in this experiment is ascribed to the presence of adventitious moisture.

(6) G. Kresze, S. Rau, G. Sabelus, and H. Goetz, *Justus Liebigs Ann. Chem.*, **648**, 57 (1961).

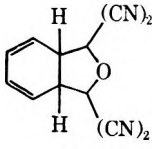
(7) L. J. Bellamy, "Advances in Infrared Group Frequencies," Richard Clay (The Chaucer Press), Bungay, Suffolk, 1968, pp 72–73.



7

Figure 1.—60-MHz spectra of the vinyl hydrogens H_a and H_b of 3a,4,5,6,6-pentahydro-4,4,5,5-tetracyano-7-methylindene (**7**): (A) normal spectrum, (B) decoupled spectrum (H_d irradiated).

absorption to H_d. The broadened AB pattern was then assigned to the six-membered ring methylene hydrogens H_e and H_f. Absorption at τ 5.85 was assigned to the methinyl proton, H_c. It is expected that an allylic hydrogen adjacent to geminal cyano groups should be quite deshielded. Support for this chemical shift assignment comes from the report of Linn and Benson[8] that a similar hydrogen in 1,1,3,3-tetracyano-1,3,3a,7a-tetrahydrobenzofuran (**9**) absorbs at τ 5.14.



9

On the basis of their low-field appearance the eight-line multiplet centered at τ 3.69 and the seven-line multiplet centered at τ 3.95 (each integrating for one proton) were assigned to vinyl hydrogens H_a and H_b, respectively. Examination of Barton models suggests that a favorable conformation of **7** exists in which the six-membered ring is a half-chair and the four cyano groups at C_4 and C_5 are almost perfectly staggered. This conformation places a cyano group of C_4 in a quasiequatorial position. The dihedral angle between this cyano group and H_b is approximately 27° in this conformation and places H_b within the expected diamagnetic shielding region of the cyano group.[9] Chemical shift assignments for H_a and H_b are made on the expectation that H_b, lying much closer in space to the C_4 quasiequatorial cyano group, should appear at higher field than H_a.

The combined effects of spin decoupling and deuteration in **7** give strong support to the above assignments. Irradiation of the five-membered ring methylene protons, H_d, results in an ABX pattern involving H_a, H_b, and H_c. The AB portion of this pattern is shown in Figure 1. Following the method outlined by Becker[10] which allows hand calculation of the computer-generated solution to the general ABX problem, coupling

(8) W. J. Linn and R. E. Benson, *J. Amer. Chem. Soc.*, **87**, 3657 (1965).
(9) G. S. Reddy, J. H. Goldstein, and L. Mandell, *J. Amer. Chem. Soc.*, **83**, 1300 (1961).
(10) E. D. Becker, "High Resolution NMR, Theory and Chemical Applications," Academic Press, New York, N. Y., 1969, pp 152–159.

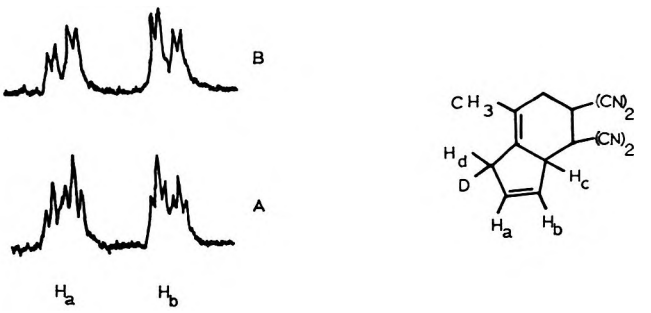


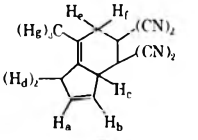
Figure 2.—100-MHz spectrum of the vinyl hydrogens H_a and H_b in 1-deuterio-3a,4,5,6,6-pentahydro-4,4,5,5-tetracyano-7-methylindene (deuterio **7**): (A) normal spectrum, (B) decoupled spectrum (H_c irradiated).

constants $J_{AC} = -2.03$, $J_{BC} = 2.43$, and $J_{AB} = 6.2$ Hz were derived.

Irradiation of methinyl H_c at τ 5.85 in deuterated **7** (deuterium at the five-membered ring methylene group) gives rise to an ABX pattern involving H_a, H_b, and H_d, the AB portion of which is shown in Figure 2. Coupling constants $J_{AD} = 2.80$ and $J_{BD} = -1.30$ Hz were assigned.

Four-bond allylic coupling constants are generally negative,[11,12] and the method outlined by Becker[10] indicates that these couplings in **7** are also negative. Irradiation of the methyl group at τ 8.18 causes a simplification of the absorptions due to H_d and also H_e and H_f, indicating coupling extending for four or five bonds. Irradiation of H_c caused an observable alteration of the methyl absorption that was unresolvable due to coupling with methyl by other protons in the molecule. Nmr assignments in **7** are listed in Table III.

TABLE III
CHEMICAL SHIFTS AND COUPLING CONSTANTS IN ADDUCT 7

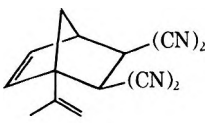


7

	τ, ppm		J, Hz
H_a	3.69[a]	4.33[b]	$J_{AB} = 6.2$
H_b	3.95	4.55	$J_{AC} = -2.03$
H_c	5.85	6.38	$J_{AD} = 2.80$
H_d	6.78	7.54	$J_{BD} = -1.30$
H_e	3.18 or 3.60	7.79	$J_{EF} = 18.0$
H_f	3.18 or 3.60	7.79	
H_g	8.18	8.93	

[a] 100 MHz in acetone-d_6. [b] 60 MHz in benzene-d_6.

That isomer **3** might have reacted with TCNE to form **10** is not supported by nmr. Also the infrared



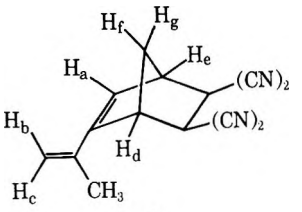
10

spectrum of the adduct **3** with TCNE lacks absorption in the region 890–910 cm^{-1}, characteristic of terminal

(11) M. Barfield and B. Chakrabarti, *Chem. Rev.*, **69**, 757 (1969).
(12) S. Sternhell, *Rev. Pure Appl. Chem.*, **14**, 15 (1964).

vinyl groups such as those present in the isopropenyl group of **10**.[13]

Adduct **8**, mp 156–157°, showed weak absorption in the infrared at 2245 cm^{-1} (C≡N) and strong absorption at 914 cm^{-1} (terminal olefin). The 100-MHz nmr spectrum of **8** in acetone-d_6 showed five separate bands centered at τ 3.50, 4.37, 4.67, 5.31, and 5.67, each integrating for one hydrogen. Present also were multiplets centered at τ 7.76 and 8.08 which integrated for two and three hydrogens, respectively. Chemical shift assignments in **8** were made primarily on compari-



8

son with the nmr spectrum of adduct **6**, and also in comparison with 5,5,6,6-tetracyanonorbornene, the adduct of cyclopentadiene and TCNE.

The broadened doublet (J = 3.2 Hz) centered at τ 3.50 was assigned to H_a, since the vinyl hydrogens of **6** appeared at τ 3.10. The broadened peaks at τ 4.37 and 4.67 were assigned to the isopropenyl vinyl hydrogens H_b and H_c. H_b is expected to appear downfield from H_c due to the anisotropy effects of the norbornenyl double bond.[3] Absorptions at τ 4.37 and 4.67 were assigned to bridgehead hydrogens H_d and H_e. Bridgehead absorption in **6** occurred at τ 4.04. Irradiation of the band at τ 4.67 caused a collapse of the H_a doublet to a broadened singlet. This peak was assigned to H_e since H_e is expected to couple more strongly than H_d with H_a[14,15] and also due to anisotropy effects of the isopropenyl double bond, H_d should be deshielded more than H_e. Absorption centered at τ 7.76 appeared as an AB pattern (J = 11.5 Hz) with each peak showing additional splitting. This pattern was assigned to the bridge methylene hydrogens of **8** (bridge hydrogens of **6** absorbed at τ 8.00). The bridge methylene hydrogens of 5,5 6,6-tetracyanonorbornene also showed an AB pattern, centered at τ 7.83. Numerous other reports of AB patterns arising from nonequivalent geminal bridge hydrogens in norbornene derivatives have been made,[16,17] supporting our assignments in this case. Absorptions at τ 8.08 was assigned to the isopropenyl methyl group.

Estimates of the extent of deuteration of **1** were also obtained from the nmr spectra of **7** and **8**. In isolated samples of **7** and **8** obtained by trapping the deuterated isomer mixture, integration of the region τ 6.3–7.0 in **7** showed the presence of 3.3–3.4 hydrogens while integration of the absorption centered at τ 7.76 in **8** indicated the presence of 1.35 hydrogens. These data indicate the uptake of 60–70% of one deuterium atom into **7** and **8** well within experimental error of other estimates of the extent of deuteration of **1**.

Conclusions

An accurate accounting of the origin of the dimethylfulvene formed in the quenching of the isopropenylcyclopentadienyl anion removes some uncertainties concerning the operation of kinetic control of this process left unresolved in the previous report.[3] However, as we have no direct evidence for the occurrence of **5** in the isomer mixture, it is still uncertain as to whether the mixture, of 10% **2**, 62% **3**, and 27% **4** corresponds to the first formed products. That some rearrangement of the first formed products occurs, probably by a carbanion mechanism, is indicated by the mass spectral observation of the uptake of more than one deuterium atom into the products. To the extent that this secondary ionization occurred, the system would tend toward equilibrium, resulting ultimately in an increase in the relative amount of **2** in the mixture. If changes in the first formed mixture occur only by a carbanion mechanism, the observed product mixture would differ most from that of kinetic control if no **2** were in the first formed mixture, but instead arose from subsequent ionization in the system. Such a rearrangement involving **5** cannot be ruled out by the available evidence. To the extent that **5** is removed from the mixture by a carbanion mechanism, the relative amounts of **2**, **3**, and **4** will increase in the product mixture in a ratio directly proportional to the ratio of the specific rate constants for their formation. If the amount of secondary ionization is minimal, such that the system does not move very far toward equilibrium, the ratio of **2**:**3**:**4** should be independent of the amount of **5** present.

That **5** may have formed on quenching of **1** and then subsequently rearranged by an uncatalyzed sigmatropic hydrogen migration to give **3** remains a possibility. The rearrangement of **5** → **3** must be considerably more rapid than the interconversion of **3** → **4** or **4** → **3**, since the latter processes were fairly slow at room temperature and not observed at all at low temperatures. McLean and Haynes[18] have shown that 5-methylcyclopentadiene is somewhat more reactive than 1-methylcyclopentadiene toward this type of rearrangement. They have also indicated that base-induced rearrangements in alkylcyclopentadienes are much more rapid than uncatalyzed rearrangements in these systems. Since some carbanion formation subsequent to quenching of **1** is indicated in our work, it is likely that the more rapid ionic mechanism would account for virtually all of the loss of any **5** that might have formed in this reaction.

The relative amounts of dimethylfulvene derived from the deuteration of **1** (~8%) indicates that any rearrangement (most reasonably by a carbanion mechanism) of the first formed products was not extensive. Hence, whether or not any **5** was formed in the quenching of **1**, the relative amounts of **2**, **3**, and **4** observed in this work are probably not far removed from the kinetically controlled product ratios.

(13) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1958, p 26.
(14) R. A. Finnegan and R. McNees, *J. Org. Chem.*, **29**, 3234 (1964).
(15) E. W. Garbisch, Jr., *Chem. Commun.*, 332 (1968).
(16) P. Subramanian, M. Emerson, and N. LeBel, *J. Org. Chem.*, **30**, 2624 (1965).
(17) J. D. Davis, Jr., and T. VanAuken, *J. Amer. Chem. Soc.*, **87**, 3900 (1965).
(18) S. McLean and P. Haynes, *Tetrahedron*, **21**, 2329 (1965).

Experimental Section[19]

Dimethylfulvene (2).—Dimethylfulvene (5-isopropylidene-1,3-cyclopentadiene) contaminated by 5–10% of dicyclopentadiene was prepared by the method of Freiesleben.[20] **2** was also prepared by the method of McCain[21] using the basic form (hydroxide) of a quaternary ammonium type (polystyrene) anion exchange resin, Amberlite CG-400, as base. This method gives **2** uncontaminated by dicyclopentadiene, but in lower yields.

Isomerization of Dimethylfulvene.—The procedure of Hine and Knight[3] was closely followed in the room temperature isomerization of **2** *via* protonation and deuteration of anion **1**. Several repetitions of the protonation experiment afforded product mixtures of 15 ± 3% **2**, 58 ± 3% **3**, and 27 ± 2% **4**. Pmr spectra (60 MHz) were obtained 15–20 min after quenching of the anion. The composition of the product mixture remained essentially unchanged on standing at −78°. Pmr spectra (100 Hz) were obtained after 0.5–2 days' storage at −78°. Dicyclopentadiene (~5–7%) was used as an internal standard for the glpc analysis.

In a separate experiment dimethylfulvene was also isomerized by the same method with the exception that hexamethylphosphoramide was used as solvent in the place of diglyme. A product mixture of 8% **2**, 65% **3**, and 27% **4** was obtained in this experiment, indicating little solvent effect on the course of the isomerization.

Deuteration of 1, Gas Chromatographic–Mass Spectral Analysis.—The isomerization was carried out as previously described on 4.02 g of **2** (92.8% **2**, 7.2% dicyclopentadiene). The anion was quenched with deuterium acetate in deuterium oxide, extracted into light petroleum ether, and washed with water to remove diglyme solvent. The product mixture was immediately stored at −78° until gc–ms analysis could be made. A ⅜ in. × 6 ft 3% SE-30 on Chromosorb W column at 80° was used for the glpc separation. Retention times of 0.70 (**3** and **4**, unresolvable), 0.83 (**2**), and 1.16 min (dicyclopentadiene) were observed. The product mixture contained 8.9% **2**, 84.2% a mixture of **3** and **4**, and 6.8% dicyclopentadiene. This 5.5% decrease in the relative amount of dicyclopentadiene is within the experimental error of the method (~10%) and indicated no loss of product. Thus excellent material balance was obtained in this reaction. Mass spectral analyses were made using ionizing potentials of 70 and 19 eV. At 19 eV, peaks due to (parent ion −1) mass unit were almost completely absent. After correction or ^{13}C content,[3] assignments corresponding to 50% C_8H_{10}, 47% C_8H_9D, and 3% $C_8H_8D_2$ for the fraction containing **3** and **4**, as well as 60% C_8H_{10}, 38% C_8H_9D, and 2% $C_8H_8D_2$ in the fraction containing **2**, were made. The fraction containing dicyclopentadiene had a parent ion of mass 132 corresponding to $C_{10}H_{12}$. On standing at room temperature the sample developed high-boiling components of mass 210–213 corresponding to Diels–Alder adducts involving protonated and deuterated **2**, **3**, and **4**, confirming our suspicions that the composition of the isomeric product mixture may change on standing due to adduct formation involving **2**, **3**, and **4**.

7-Isopropylidene-5,5,6,6-tetracyanorbornene (6).—Equimolar (0.10 mol) amounts of dimethylfulvene and tetracyanoethylene were dissolved in toluene and mixed in a three-necked flask equipped with a nitrogen bleed. A transient dark color was observed which faded quickly, and a solid product separated on standing. The product was recrystallized from acetone at 0° to yield white crystals: mp 133° (lit.[5] 138°); ir (KBr) 2250 cm^{-1} (C≡N); nmr (acetone-d_6) τ 3.10 (t, 2, vinyl), 5.04 (t, 2, bridgehead), 8.15 (s, 6, methyl).

Trapping of Isomers 2, 3, and 4 As Diels–Alder Adducts of TCNE.—The following procedure is typical for several repetitions of the trapping experiment. Some difficulty was encountered in separating the adducts **6**, **7**, and **8** by fractional crystallization. Material balance was not achieved on isolated adducts but relative amounts of **6**, **7**, and **8** were determined by integration of the nmr spectra of the total mixture of adducts. The absorptions used in these integrations were not complicated by overlap with other absorptions in the spectra. Peaks used in these estimated were the triplet at τ 3.10 due to the vinyl hydrogens of **6**, the multiplet centered at τ 3.95 due to the vinyl hydrogen H_b of **7**, and the broadened peak at τ 4.37 due to the downfield isopropenyl vinyl hydrogen of **8**.

The carbon tetrachloride solution of **2**, **3**, and **4** obtained from the protonation or deuteration of **1** was added with stirring to an equimolar amount (0.05 mol) of sublimed TCNE dissolved in 75 ml of acetone under N_2 at 0°. A fleeting dark color was observed to pass through the solution. The mixture was stirred for 10 min and solvent was removed under reduced pressure to give a greenish paste. Excess TCNE (mp 196°) was removed by crystallization from CH_2Cl_2 at 0°. Addition of petroleum ether (bp 60–90°) caused oiling of the product and solvents were again removed under reduced presssure. The residue was dissolved in refluxing toluene–petroleum ether (50:50). On standing several days at 0°, 0.4 g of 3a,4,5,6,6-pentahydro-4,4,5,5-tetracyano-7-methylindene (**7**), mp 92–93°, was collected: ir (KBr, in order of decreasing intensity) 762, 670, 1440, 680, 1430, 1105, 2920, 1260, 1380, 1125, 2890, 945, 920, 805, 325, 935, 2830, 1220, 780, 1155, 1250, 3060, 1350, 1045, 425, 1605, 1280, 1315, 610, 445, 840, 2245, 1065, 1065, 1080 cm^{-1}.

Anal. Calcd for $C_{14}H_{10}N_4$: C, 71.76; H, 4.31; N, 23.92. Found: C, 71.80; H, 4.33; N, 23.97.

The solvents from the remaining solution were allowed to evaporate at room temperature and, as the mixture became more concentrated, 0.2 g of 2-isopropenyl-5,5,6,6-tetracyanonorbornene (**8**) was deposited as white crystals: mp 156–157°; ir (KBr, in order of decreasing intensity) 915, 1380, 1280, 1270, 910, 1440, 830, 1570, 3080, 1430, 880, 610, 1620, 2955, 2990, 3005, 1245, 940, 745, 1010, 1030, 2245, 2920, 1180, 1230, 490, 555 cm^{-1}.

Anal. Calcd for $C_{14}H_{10}N_4$: C, 71.76; H, 4.31; N, 23.92. Found: C, 71.49; H, 4.30.

Registry No.—1, 26520-95-6; 2, 2175-91-9; 3, 26385-00-2; 4, 26385-01-3; 6, 33061-12-0; 7, 33061-13-1; 8, 33061-14-2.

Acknowledgment.—Receipt of support from the Research Council, University of North Carolina at Greensboro, is acknowledged. We thank Dr. Stephen Dale for 100-MHz nmr spectra and Dr. Martin Schulman for obtaining gc–ms data. It is a pleasure to acknowledge helpful discussions with Professor Jack Hine.

(19) Melting points are uncorrected. Infrared spectra were obtained using a Perkin-Elmer Model 521 spectrophotometer. Mass spectra were determined using a Varian Model CH-7 spectrometer, and proton nmr spectra were obtained using Varian Models T-60 and HA-100 spectrometers. Elemental analyses were made by Galbraith Laboratories, Knoxville, Tenn.

(20) W. Freiesleben, *Angew. Chem.*, **75**, 576 (1963).

(21) G. H. McCain, *J. Org. Chem.*, **23**, 632 (1958).

Reaction of 3,3-Diphenyl-1,2-*trans*-bis(*N*-nitrosourethano)cyclopropane with Methanolic Sodium Methoxide. Ring Opening between the Nitrogen Functions

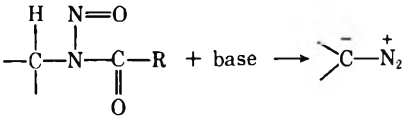
DEWEY J. NORTHINGTON[1] AND W. M. JONES*

Department of Chemistry, University of Florida, Gainesville, Florida 32601

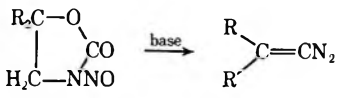
Received June 16, 1971

Reaction of 3,3-diphenyl-1,2-*trans*-bis(*N*-nitrosourethano)cyclopropane (2) with sodium methoxide in methanol has been found to give a mixture of 3,3-diphenyl-1-diazopropanone and 4,4-diphenyl-3-methoxy-1-pyrazoline 1-oxide. The structural assignment of the latter, which requires cleavage of the cyclopropane between the nitrogen functions, is based on spectral and chemical properties. The origin of the pyrazoline oxide is briefly discussed in terms of the diazabicyclo[2.1.0]pentene oxide **7**.

One of the more general methods of generating diazoalkanes is by the base-induced decomposition of *N*-nitrosoamine derivatives.[2] In our hands[3] this method has

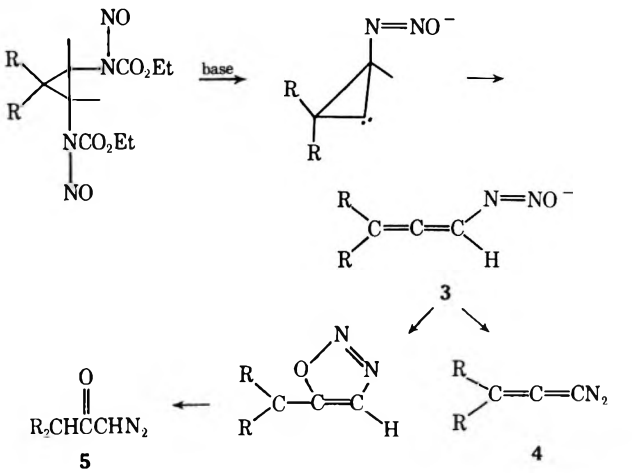


not been found generally useful for the generation of diazoalkenes because most vinyl amines exist primarily in the imine form,[4,5] thus precluding amine nitrosation. In a series of recent papers, Newman[6] has reported a method to generate diazoalkenes by allowing *N*-nitrosooxazolidones **1** to react with base. This method cleanly circumvents the problem mentioned above by generating the double bond after the amine function is nitrosated.



1

We have recently reported[7] our modestly successful attempts to generate a diazoallene by allowing 3,3-diphenyl-1,2-*trans*-bis(*N*-nitrosourethano)cyclopropane (**2**) to react with base, in this way attempting to generate the allene moiety *after* nitrosation of the amine function. Under many conditions, the reaction apparently proceeded well as far as the allenyl diazotate **3**, and, although a small portion gave the diazoallene **4**, most of the diazotate is believed to have undergone a unimolecular ring closure followed by opening to give diphenyldiazopropanone **5**. However, when the reaction was carried out in a dilute solution of sodium methoxide in methanol, in addition to the diazopropanone, a new material, 4,4-diphenyl-3-methoxy-1-pyrazoline 1-oxide (**8**), was formed as the major product. At this time we report a proof of structure of this material and some of its very interesting chemistry.



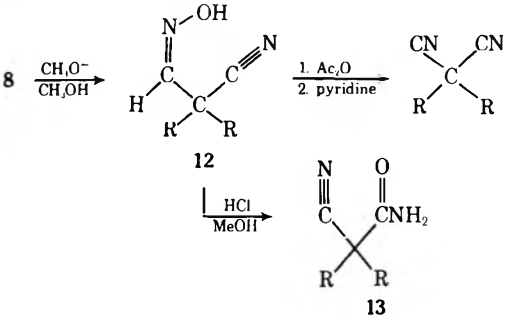
5 **4**

Results

3,3-Diphenyl-1,2-*trans*-bis(urethano)cyclopropane (**2**) was synthesized by conventional methods[8] from 3,3-diphenylcyclopropyl-1,2-*trans*-dicarboxylic acid *via* the bis acid chloride, acid azide, and isocyanate. Nitrosation was effected with N_2O_4 in ether.[9]

Treatment of the nitrosourethane **2** with a dilute solution of sodium methoxide in methanol gave as principal products 4,4-diphenyl-3-methoxy-1-pyrazoline 1-oxide (**8**) and diazopropanone **5** (several very minor unidentified products were formed). As reported previously,[7] reaction in a concentrated solution of sodium methoxide in methanol gave as the only identifiable product the diazopropanone **5** (*ca.* 70% yield).

The structure proof of **8** was difficult at best. Thus, although the nmr (see below) was completely consistent



12 **13**

(1) Support for this work by the National Science Foundation is gratefully acknowledged. Presented in part to the 1970 Meeting in Miniature of the Florida Section of the American Chemical Society. Taken from the Ph.D. Dissertation of D. J. Northington, University of Florida, 1970.

(2) *Cf.* A. Zollinger, "Azo and Diazo Chemistry," Interscience, New York, N. Y., 1961; P. A. S. Smith, "Open-Chain Nitrogen Compounds," W. A. Benjamin, New York, N. Y., 1966.

(3) Unpublished results of T. G. Squires.

(4) In cases where the vinyl amine is the more stable tautomer,[5] nitrosation of the amine function gives the vinylidene, presumably *via* the diazoalkene.

(5) *Cf.* D. Y. Curtin, J. A. Kampmeir, and B. R. O'Connor, *J. Amer. Chem. Soc.*, **87**, 863 (1965).

(6) M. S. Newman and T. B. Patrick, *ibid.*, **92**, 4312 (1970); M. S. Newman and C. D. Beard, *ibid.*, **92**, 4309 (1970); M. S. Newman and T. B. Patrick, *ibid.*, **91**, 6461 (1969); M. S. Newman and A. O. M. Okorodudu, *ibid.*, **90**, 4189 (1968); *J. Org. Chem.*, **34**, 1220 (1969).

(7) D. J. Northington and W. M. Jones, *Tetrahedron Lett.*, **No. 4**, 317 (1971).

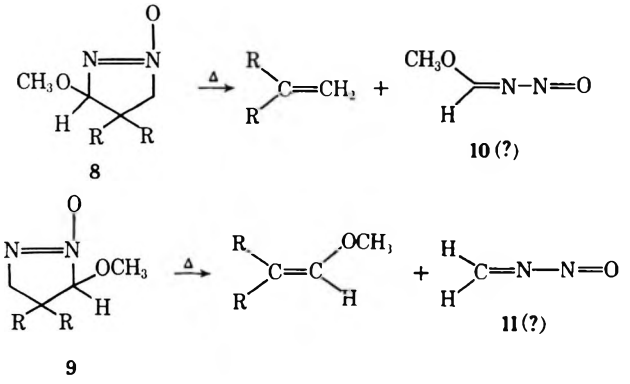
(8) For example, see J. M. Walbrick, J. W. Wilson, Jr., and W. M. Jones, *J. Amer. Chem. Soc.*, **90**, 2895 (1968).

(9) E. H. White and C. A. Aufdermarsh, Jr., *ibid.*, **83**, 1174, 1179, (1961).

with **8**, it neither identified the basic ring structure nor the position of the oxygen of the *N*-oxide. The carbon skeleton was ultimately determined by its chemistry. Isolation of diphenylmalonodinitrile[10] and its oxime precursor **12**[11] leave little doubt but that the cyclopropane opened between the two nitrogen functions. Strong ir absorption at 1525 cm^{-1}, an M − 16 peak in the mass spectrum, and strong end absorption in the uv indicate an azoxy function.[2,12] Finally, nmr absorptions at τ 4.25 (s, 1 H) for the methyne proton, 4.97 and 5.35 (AB quartet with J_{AB} = 13.5 cps) for nonequivalent geminal methylene protons, and 6.40 (s, 3 H) for the methoxy protons support the structural assignment of **8**. However, it should be noted that spectral data are no help in differentiating between the two possible oxide isomers (**8** *vs.* **9**).

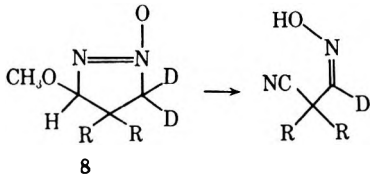
Two experiments, one of which may be generally applicable, led us to identify the pyrazoline oxide as **8**.

First, pyrolysis of **8** yielded 1,1-diphenylethylene and no detectable amount of 1,1-diphenyl-2-methoxyethylene, whereas its photoisomer[13] (the isomeric pyrazoline oxide **9**) gave 1,1-diphenyl-2-methoxyethylene and no trace of diphenylethylene. Thermal fragmentation of **8** to give diphenylethylene should give, in addition, a valence-satisfied nitrosoimine **10**. On the other hand, fragmentation of **8** to give diphenylmethoxyethylene requires initial formation of a diradical. The same arguments can, of course, also be made for the formation of 1,1-diphenyl-2-methoxy-



ethylene from **9**. These conclusions were further supported by the mass spectra of **8** and **9** in that the former showed a peak at *m/e* 180 with a relative intensity of 100 and none at 210, whereas the latter showed only a small peak at 180 (relative intensity 10) and a substantial peak (relative intensity 22) at *m/e* 210.

The assignment of structure **8** to the initial pyrazoline oxide was further supported by allowing it to react with sodium methoxide in MeOD. As noted above, reaction of **8** with base gives the aldoxime **12**. Assuming that the nitrogen bearing the oxide moiety in **8** becomes the aldoxime function in **12**, the following results are meaningful. When the reaction of sodium methoxide with **8** in MeOD was quenched with water at approximately the midpoint in the reaction, it was found that the starting material had incorporated deuterium into the methylene position to the extent that no absorptions in the nmr were noted for these protons, whereas no deuterium had been incorporated into the methyne position. Further, it was found that the product aldoxime had incorporated deuterium to the extent of 96% (nmr). Finally, undeuterated oxime did not exchange under the reaction conditions. Thus, unless some intermediate undergoes rapid and total deuterium exchange, these results point to structure **8** for the oxide.



8

Discussion

Of primary interest from these results is the origin of the pyrazoline oxide **8**. Although we do not have direct evidence, a number of arguments lend support to the series of reactions in Scheme I.

Certainly, the first step in the reaction must be conversion of one *N*-nitrosocarbamate group to a diazotate.[2] We further suggest that the second nitrosourethane is also converted to its diazotate prior to reactions leading to **8**.[14] The bisdiazotate would be expected to undergo two different types of reactions under our conditions. It could either react further with base and alcohol to ultimately give diazopropanone **5** (a reaction which should be favored by a high concentration of base[15]), or it could react with alcohol alone to give a cyclopropyldiazonium ion. This, in turn, would be expected to lose nitrogen to give a cyclopropyl cation,[15] which, in light of Moss and Landon's[16] recent work with diazotates, could give the azoxy compound **7**.

The steps in the conversion of **7** to **8** must, at this time, remain open. Recent work of Dolbier and Williams[17] on the photolysis of 4*H*-pyrazole oxides (analogous to **14** but highly substituted) led them to the conclusion that heterocycles analogous to **7** open thermally at temperatures as low as −30° to give two products, one of which is the starting 4*H*-pyrazole oxide. This suggests as one very real possibility ring opening to **14** followed by base-induced addition of MeOH.[18] On the other hand, direct attack of methoxide on the cyclopropane ring[19] of **7** cannot at this

(10) *Cf.* C. R. Hauser and E. Jordan, *J. Amer. Chem. Soc.*, **58**, 1772 (1936).

(11) Assignment of the anti configuration to the aldoxime is based on dehydration by acetic anhydride followed by pyridine as well as HCl in methanol. None of the Beckman rearrangement product predicted for the syn configuration was observed.

(12) V. T. Bandurco and J. P. Snyder, *Tetrahedron Lett.*, 4643 (1969); F. D. Greene and S. S. Hecht, *ibid.*, 575 (1969); W. R. Dolbier and W. M. Williams, *J. Amer. Chem. Soc.*, **91**, 2818 (1969).

(13) For a discussion on the photolysis of azoxy compounds, see F. D. Greene and S. S. Hecht, *J. Org. Chem.*, **35**, 2482 (1970).

(14) For convenience, the precursor to **5** is also pictured as the bisdiazotate. In fact, it could be a monodiazotate without changing the arguments. The bisdiazotate is the preferred precursor to **8**.

(15) W. Kirmse and H. Schutte, *J. Amer. Chem. Soc.*, **89**, 1284 (1967).

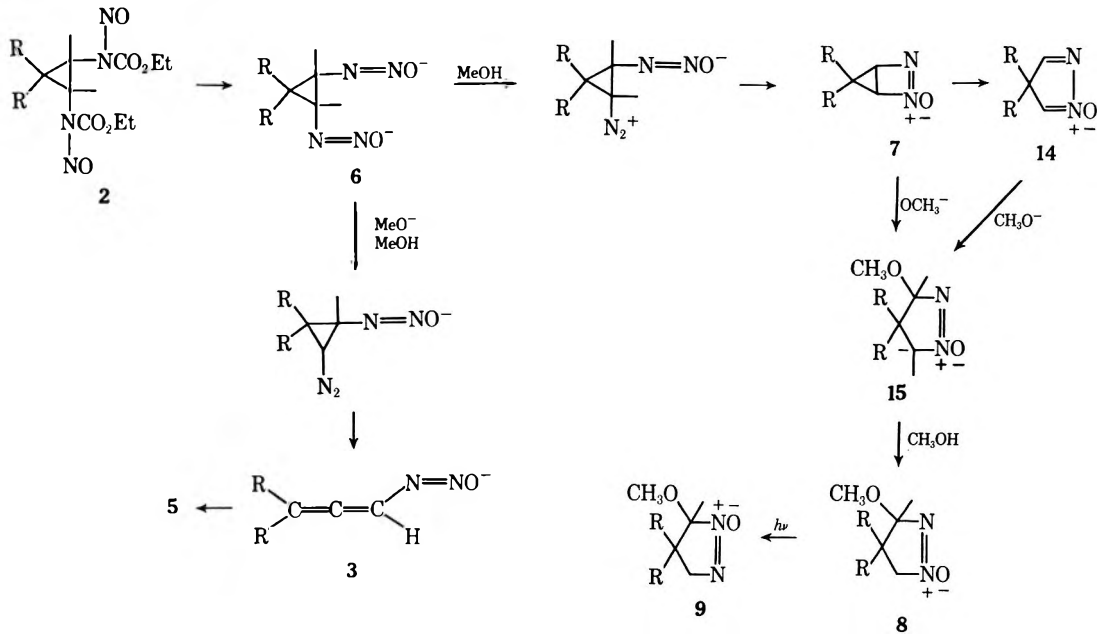
(16) R. A. Moss and M. J. Landon, *Tetrahedron Lett.*, 3897 (1969).

(17) W. R. Dolbier, Jr., University of Florida, private communication.

(18) To the best of our knowledge, the chemistry of 4*H*-pyrazole oxides with base has not been studied.

(19) Base-induced ring opening of cyclopropane, while rare, is not unknown in strained ring systems in which opening leads to a stable anion. For examples, see R. P. Blanchard, Jr., and A. Cairncross, *J. Amer. Chem. Soc.*, **88**, 587 (1966). The strain of the ring systems involved (bicyclobutane) and the probable sluggishness of the reaction (*e.g.*, 1-cyanobicyclobutane was opened by methoxide in methanol after 63 hr at room temperature) argues against direct attack on the cyclopropane ring.

SCHEME I



time be excluded. Preferential formation of **8** by either mechanism is certainly reasonable, since the observed facile and exclusive base-induced deuterium exchange at the methylene position in **8** leaves little question but that anion **15** is more stable than its counterpart which would lead to the isomeric oxide **9**.

Experimental Section

General.—Melting points were taken in a Thomas–Hoover capillary melting point apparatus and are uncorrected. A Beckman Model IR-10 was used to obtain infrared spectra. Nuclear magnetic resonance spectra were obtained on a Varian A-60 high resolution spectrometer. Chemical shifts are reported in units of τ using tetramethylsilane as an internal standard. Ultraviolet spectra were obtained from a Cary 15 spectrophotometer. The Hitachi Perkin-Elmer RMU-6E mass spectrometer was used to record mass spectra. The molecular ion peak, the base peak, and large significant fragments are reported. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

3,3-Diphenylcyclopropane-1,2-*trans*-dicarboxylic Acid—To a solution of 33 g of diethyl fumarate in 200 ml of ether was added 1 equiv of diphenyldiazomethane. The solution was stirred at room temperature for a few hours until the red color disappeared. The ether was removed under reduced pressure and the residue was pyrolyzed by slowly heating it to 180° until the gas evolution was complete (about 0.5 hr). The residue from the pyrolysis was saponified by refluxing it with 24 g of potassium hydroxide in 300 ml of water for 5 hr. The water solution was extracted twice with 100 ml of ether, warmed to 70°, and slowly acidified with dilute hydrochloric acid. The solution was allowed to cool for several hours and the precipitate was filtered and dried under vacuum. This yielded 46 g (80%) of the acid, mp 285–290° (lit.[20] mp 290°).

3,3-Diphenyl-1,2-*trans*-bis(urethano)cyclopropane (1).—3,3-Diphenylcyclopropane-1,2-*trans*-dicarboxylic acid was converted to the acid chloride by refluxing 21 g (0.74 mol) of the acid in excess thionyl chloride for 3 hr. The excess thionyl chloride was removed under reduced pressure; the last traces of thionyl chloride were removed by high vacuum overnight. The residue was dissolved in 120 ml of acetone and cooled in an ice bath. To this solution was added 38 g (4 equiv) of sodium azide in a minimum amount of water and the mixture was stirred at room temperature for 1.5 hr. This was poured into 300 ml of water and extracted with three 100-ml portions of ether. The combined ether solutions were washed with 50 ml of saturated brine and dried (Na_2SO_4). The ether was removed under reduced pressure and the residue was refluxed in 200 ml of benzene until nitrogen evolution ceased. The benzene solution of the isocyanate was cooled to room temperature and 35 ml of ethanol were added. This was refluxed for about 3 hr or until an ir spectrum showed complete loss of the isocyanate peak at 4.4 μ. The benzene solution was allowed to cool slowly to room temperature, and the solid product was filtered. The residue was washed with two small portions of benzene and recrystallized from benzene. This yielded 19 g (70%) of a white solid having needle-like crystals: mp 216–217°; ir (KBr) 3290, 1672, 1525, 1250–1290, 1075, 1045, 715 cm^{-1}; nmr ($CDCl_3$) τ 2.4–2.9 (10 H), 5.20 (broad s, 2 H), 5.90 (q, 4 H), 6.41 (d, 2 H), 8.82 (t, 6 H).

Anal. Calcd for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.60; H, 6.58; N, 7.80.

3,3-Diphenyl-1,2-*trans*-bis(*N*-nitrosourethano)cyclopropane (2).—The urethane was nitrosated in the following manner. 1 (1.0 g) was dissolved in 50 ml of ether, and 0.5 g of sodium sulfate and 1.3 g of sodium acetate were added. This mixture was cooled in a Dry Ice bath and stirred. To this was added 1.0 g of N_2O_4 in 10 ml of ether. The mixture was stirred for 10 min and then allowed to warm to room temperature by replacing the Dry Ice bath with a water bath. The excess N_2O_4 was removed under reduced pressure using an aspirator. This was then added to a stirred slurry of ice and saturated sodium bicarbonate solution. This mixture was transferred to a separatory funnel and the ether layer was collected. The ether solution was washed with cold saturated sodium bicarbonate solution and with saturated brine and dried (Na_2SO_4). In most cases **2** was used directly as the crude yellow oil obtained by removing the ether under reduced pressure. The ether solution could, however, be concentrated and pentane added to obtain crystalline **2** by placing the flask in the freezer compartment of the refrigerator overnight. This gave pale yellow crystals in 75–90% yield: mp 76–78° dec; ir (KBr) 2895, 1755, 1510, 1400, 1375, 1340, 1315, 1190, 1165, 1095, 1055, 970, 940, 900, 815, 760, 705, 610 cm^{-1}; nmr ($CDCl_3$) τ 2.4–3.0 (10 H), 5.40 (s, 2 H), 5.68 (q, 4 H), 8.78 (t, 6 H). This solid was unstable when left at room temperature, but a solution of **2** in ether could be kept in the freezer for a few weeks without noticeable decomposition.

Base-Induced Decomposition of 2 in Methanol.—Compound **2** was decomposed in methanol as follows. (1) Approximately 1.15 g (2.7 mmol) of **2** was dissolved in 60 ml of methanol. This was cooled in an ice bath, and 2.0 equiv of sodium methoxide was added. Gas evolution was complete after 20–30 min. The reaction was poured into approximately 200 ml of brine and extracted with two 50-ml portions of ether. This was dried (Na_2SO_4) and concentrated under reduced pressure. Nmr analysis of the residue showed about 20% of a compound identified as 3,3-diphenyl-1-diazopropanone (**5**) and 35% of a compound identified as 4,4-diphenyl-3-methoxy-1-pyrazoline 1-oxide

(20) J. van Alphen, *Recl. Trav. Chim. Pays-Bas*, **62**, 210 (1943).

(8).[21] In an experiment where 3 equiv of sodium methoxide was used, the results were the same.

The pyrazoline oxide was isolated by crystallization from the reaction mixture in ether or CCl_4. This gave 0.13 g (18%) of a white, crystalline solid: mp 126–127°; ir (KBr) 1525, 1335, 1205, 1130, 790, 730, 715, 700 cm^{-1}; nmr ($CDCl_3$) τ 2.5–3.2 (10 H), 4.25 (s, 1 H), 4.97 and 5.35 (J_{AB} = 13.5 cps, 2 H), 6.40 (s, 3 H); uv (EtOH) shoulder on end absorption 222 mμ (ϵ 19,000); mass spectrum (9 eV) *m/e* 268, 252, 238, 224, 180 (100), 121.

Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.42. Found: C, 71.62; H, 6.02; N, 10.44.

The diazopropanone was isolated by chromatographing the filtrate on silica gel eluting with pentane–ether mixtures. Crystallization from ether–pentane gave 0.078 g (11%) of a yellow solid: mp 67–68°; ir (KBr) 3070, 2090, 1625, 1485, 1440, 1335 and 1345 (doublet), 1280, 1130, 1060, 1030, 800, 745, 730, 710, 690 cm^{-1}; nmr (CCl_4) τ 2.81 (s, 10 H), 4.90 (s, 1, H), 5.20 (s, 1 H).

Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.39; H, 5.26; N, 11.78.

(2) Addition of 1.0 g of **2** in 60 ml of methanol to 27 ml of 25% sodium methoxide in methanol gave after work-up diazopropanone (*ca.* 70%) as the only identifiable product.

Reaction of 8 with Sodium Methoxide.—Compound **8** (0.136 g, 0.51 mmol) was dissolved in 10 ml of methanol, and 4 ml of 25% sodium methoxide in methanol was added. This was stirred for 40 min at room temperature, after which 50 ml of water was added. The excess base was neutralized with acetic acid, and crystallization commenced. This gave 0.103 g of a white crystalline solid (**12**) (86% yield), mp 145–147°. This was recrystallized from carbon tetrachloride: mp 151–152°; nmr ($CDCl_3$) τ 1.52 (s, 1 H), 2.20 (s, 1 H), 2.64 (s, 10 H); ir (KBr) 3330, 2250, 1590, 1480, 1440, 1420, 1280, 1180, 1140, 1070, 1030, 1010, 995, 965, 935, 910, 840, 782, 755, 740 cm^{-1}; uv λ_{max} (CH_3CN) 245, 251, 257 (ϵ 505), shoulder at 266, 375 mμ (ϵ 1.9); mass spectrum (70 eV) *m/e* (rel intensity) 236, 218 (100), 164.

Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.04; H, 5.14; N, 11.68.

Reaction of 8 with Sodium Methoxide in MeOD.—The pyrazoline oxide (35 mg) was dissolved in 1.5 ml of MeOD and a trace of NaOMe was added. Reaction was monitored by tlc. After 12 hr at room temperature (*ca.* half-life) the reaction mixture was poured into 50 ml of a mixture of dilute HCl and ether. The ether layer was washed with brine, dried, and evaporated to dryness. Preparative tlc of the residue yielded two fractions—starting material and oxime **12**. Analysis of recovered **8** by nmr showed no detectable retention of methylene protons with no detectable loss of the methyne proton. The spectrum of product **12** showed less than 5% aldehyde hydrogen.

In a parallel reaction, proteated oxime was exposed to the above reaction conditions. Recovered material showed no loss of aldehyde hydrogen.

Reaction of 12 with Acetic Anhydride and Pyridine.—Compound **12** (54 mg, 0.23 mmol) was heated with 1 ml of acetic anhydride overnight at 60°. Pyridine (5 ml) was then added and the mixture was heated for 20 hr at 100°. The reaction mixture was then added to ice. The crystals that were produced were filtered, washed with water, and dried under vacuum. This gave 32 mg (65%) of diphenylmalonodinitrile, a white, crystalline solid: mp 86–87° (lit.[22] mp 87.5°); ir (KBr) 3030 (m), 2920 (w), 2260 (w), 1950 (w), 1880 (w), 1800 (w), 1750 (w), 1590 (s), 1490 (s), 1450 (s), 770 (s), 745 (s), 702–691 cm^{-1} (doublet, s); mass spectrum (70 eV) *m/e* (rel intensity) 218 (100), 190, 165, 115.

Reaction of 12 with Hydrochloric Acid in Methanol.—Compound **12** (0.103 g, 0.44 mmol) was dissolved in 10 ml of methanol, and 2.0 ml of concentrated hydrochloric acid was added. This was refluxed for 1 hr, then poured into 50 ml of water and extracted with two 20-ml portions of chloroform. The chloroform was dried (Na_2SO_4) and concentrated. Ether was added to begin crystallization. This gave 0.045 g (45%) of the amide **13**, a white, crystalline solid: mp 159–160°; ir (KBr) 3390, 3320, 3200, 2260, 1960, 1350, 760, 700 cm^{-1}; nmr ($CDCl_3$) τ temperature dependent, at 35° 2.58 (s, 10 H), 4.30 (broad s, 2 H) (on cooling to −50° the broad singlet split into two broad singlets at τ 1.79 and 4.09); mass spectrum (70 eV) *m/e* (rel intensity) 194 (100), 166.

Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.35; H, 5.09; N, 11.69.

Pyrolysis of 8.—Compound **8** (0.109 g) was dissolved in 30 ml of chloroform and added to 1.5 g of Chromosorb P AW 60–80 mesh. The chloroform was removed under vacuum and the residue was pyrolyzed by dropping down a tube heated to 350° in a stream of nitrogen (0.1 l./min) under vacuum (2–3 mm) over a period of 30 min. The effluent gases were collected in a trap cooled in liquid nitrogen. The trapped material was dissolved in $CDCl_3$ and analyzed by nmr. The spectrum showed 55% starting material and 17% of a product identified as 1,1-diphenylethylene. Tlc on silica and glpc on 5 ft, 5% SE-30 and 150 ft, capillary Apiezon L columns showed retention times which were identical with that of a known sample of diphenylethylene. This indicates that **1** pyrolyzes in 38% yield to 1,1-diphenylethylene. No 2,2-diphenylvinyl methyl ether[23] could be detected by nmr or tlc.

Photolysis of 8.—Compound **8** (0.25 g) was irradiated with a 450-W Hanovia medium pressure mercury lamp in 130 ml of benzene in a water-cooled Pyrex apparatus for 12 hr (*ca.* 60% conversion). Concentration of the solution and chromatography of the residue on silica gel gave 50 mg of a new crystalline compound, mp 132–133°, identified as 4,4-diphenyl-3-methoxy-1-pyrazoline 1-oxide: ir (KBr) 1525 (s), 1370 (s), 1220 (s), 1150 (s), 705 cm^{-1} (s); nmr ($CDCl_3$) τ 2.5–3.2 (10 H), 4.53 (s, 1 H), 5.20 and 5.67 (J_{AB} = 16 cps, 2 H), 6.06 (s, 3 H); uv λ_{max} (EtOH) end absorption 225 mμ (ϵ 37,000); mass spectrum (70 eV) *m/e* (rel intensity) 268, 252, 238, 224, 210, 192, 121 (100).

Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.42. Found: C, 71.83; H, 5.94; N, 10.56.

Pyrolysis of 9.—Compound **9** was pyrolyzed using the same procedure that was used for **8**. Nmr analysis of the crude pyrolysate showed approximately 12% starting material and 33% 2,2-diphenylvinyl methyl ether (isolated by preparative tlc) identical in every way with a sample (except reported melting point) of authentic material prepared by the method of Wittig.[23] Both materials showed the following physical properties: nmr (CCl_4) τ 2.7–2.9 (m, 10 H), 3.67 (s, 1 H), 6.26 (s, 3 H); uv λ_{max} (EtOH) 264 mμ; mass spectrum (70 eV) *m/e* (rel intensity) 210 (100), 195, 167, 165, 152, 105.

Anal. Calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 84.50; H, 6.93.

Registry No.—**1**, 32640-76-9; **2**, 32640-77-0; **5**, 32640-78-1; **8**, 32640-79-2; **9**, 32640-81-6; **12**, 32670-71-6; **13**, 32640-80-5.

(21) Approximate yields based on total phenyl absorption as an internal standard.

(22) R. N. Bennett, *J. Chem. Soc.*, 2628 (1956).

(23) Wittig, *Chem. Ber.*, **94**, 1373 (1961). A crystalline material was reported. We were unable to induce crystallization and therefore carried out a complete characterization.

3-Isopropyl-1,3-diazabicyclo[3.3.1]nonan-2-one, a Simple Bicyclic Urea with a Bridgehead Nitrogen Atom

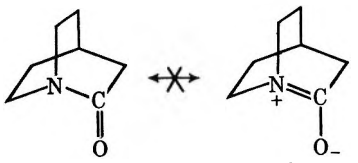
H. K. HALL, JR.,* AND R. C. JOHNSON

Department of Chemistry, University of Arizona, Tucson, Arizona 85721

Received June 25, 1971

Stabilization of a bicyclic compound containing the CO–N (bridgehead) unit, which formally violates Bredt's rule, was achieved by introduction of a second electron-donating atom (N) to give the N–CO–N (bridgehead) structure and by working with a conformationally strainless bicyclic ring system. 3-Isopropyl-1,3-diazabicyclo-[3.3.1]nonan-2-one (**9**), the first simple urea with a bridgehead N atom, was synthesized in two ways. Reaction of 3-(*N*-isopropylaminomethyl]piperidine with 1 equiv of phosgene in methylene chloride at 0° gave the desired urea directly. Alternatively, excess phosgene in ether at −75° gave biscarbamyl chloride **10**, which with silver carbonate in refluxing acetonitrile gave **9**. Once formed, **9** was stable to hydrolysis and ring-opening polymerization and is strainless by these criteria.

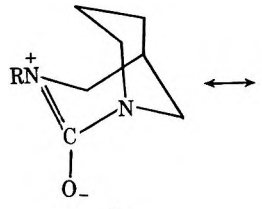
Lukes[1] proposed that bicyclic lactams such as 2-quinuclidone (**1**) should be incapable of existence



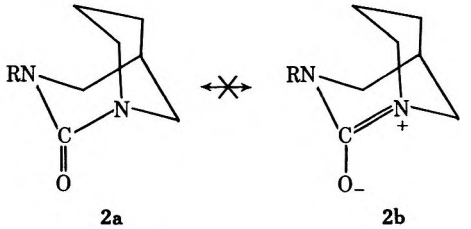
1a **1b**

because resonance form **1b** would be prohibited (Bredt's rule). However, ingenuity in synthesis has prevailed, and Pracejus[2,3] has prepared 2,2-dimethyl- and 2,2,6-trimethyl-2-quinuclidones. These lactams show unusual properties: their carbonyl infrared absorptions are found at anomalously high frequencies, they hydrolyze readily in water, and they appear to polymerize.[3]

To stabilize molecules containing N–C=O links at the bridgehead, introduction of a strongly electron-donating atom such as nitrogen adjacent to the carbonyl group would meet the demand of C=O for electrons *via* form **2c**.

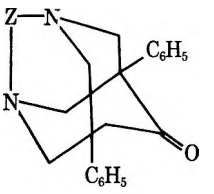


2c



2a **2b**

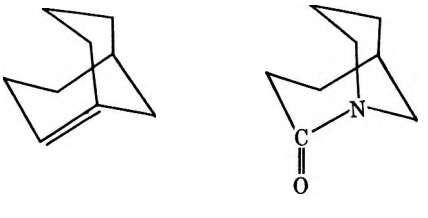
To our knowledge, no simple bridgehead urea has yet been reported. That the problem of synthesis of such compounds may not be trivial is shown by the work of Misito and Chiavarelli.[4] Although they readily obtained compounds **3a** and **3b** from the parent diamine,



3a, Z = SO
b, Z = SO_2

these investigators showed that the corresponding urea (**3**, Z = CO) was not formed under similar conditions.

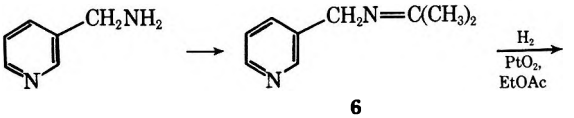
To avoid conformational strains such as those also present in **1**, we selected the strainless two-chair bicyclo[3.3.1]nonane structure shown in **2a–c**. Form **2b** may make a small contribution in this system, inasmuch as the homomorphic olefin **4** has been prepared as an unstable compound.[5,6] One attempt to synthesize lactam **5**, on the other hand, gave only polymer.[7]



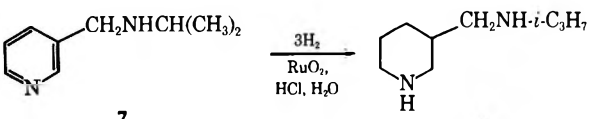
4 **5**

Results

3-Aminomethylpyridine was converted using acetone to 3-isopropylidenaminomethylpyridine (**6**), which on successive hydrogenations gave 3-(isopropylaminomethyl)piperidine (**8**). Reaction with di-*m*-tolyl carbonate failed to give the desired bicyclic urea **9**; so attention was given to the very reactive acyl chloride phos-



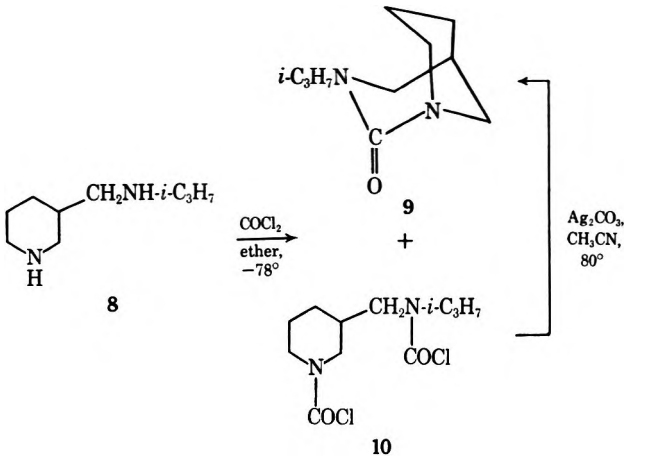
6



7 **8**

(1) R. Lukes, *Collect. Czech. Chem. Commun.*, **10**, 148 (1938).
(2) H. Pracejus, *Chem. Ber.*, **92**, 988 (1959).
(3) H. Pracejus, *ibid.*, **98**, 2897 (1965).
(4) D. Misito and S. Chiavarelli, *Gazz. Chim. Ital.*, **96**, 1696 (1966); *Chem. Abstr.*, **66**, 85777 (1966).
(5) J. A. Marshall and H. Faubl, *J. Amer. Chem. Soc.*, **92**, 948 (1970).
(6) J. R. Wiseman, *ibid.*, **92**, 956 (1970).
(7) H. K. Hall, Jr., *ibid.*, **82**, 1209 (1960).

gene. Reaction with phosgene in ether in the presence of various bases (triethylamine, cyclohexyldiethylamine, barium oxide, calcium carbonate), gave a mixture consisting largely of the *N,N'*-biscarbamoyl chloride **10** and a little urea **9**. Refluxing **10** with silver carbonate in acetonitrile converted it to **9**.



An alternate route was found by using dichloromethane at 0° as the reaction solvent.[8] Reaction of **8** with 1 equiv of phosgene, followed by addition of 2.2 equiv of triethylamine, was carried out. The reaction mixture remained homogenous and ~50% yields of cyclic urea **9** were obtained. At −40° a mixture with biscarbamoyl chloride **10** was obtained.

The urea **9**, bp 150° (0.2 mm), melted at 47–48°, had the proper elemental analysis, and was pure according to gas chromatography. The precision mass spectrum supported the assigned structure, giving a parent peak corresponding to $C_{10}H_{18}ON_2$. The nmr spectrum, other than that of the *N*-isopropyl group, was somewhat featureless, but was consistent with structure **9**.

Compound **9** was stable to boiling water for 20 hr but hydrolyzed slowly in hot sodium hydroxide solution. It showed no signs of polymerization after heating for extended periods with *p*-toluenesulfonic acid, phosphoric acid, or potassium *tert*-butoxide, and only starting material was recovered. Finally, the ir spectrum of urea **9** showed a carbonyl group at the normal frequency for a tetraalkylurea, 1650 cm^{-1}. All three criteria show that the molecule is not strained.

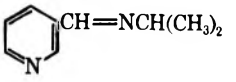
We have been able to synthesize the first bicyclic urea with a bridgehead nitrogen atom, owing to the fact that the demand of the carbonyl group for electrons has been satisfied by the other nitrogen atom and because conformational strain is absent from the 3-substituted bicyclo[3.3.1]nonane system. In fact, compound **9** represents the other extreme of stability from quinuclidone **1**. We anticipate that, by variation of electron-donating atom and of ring size, a variety of bicyclic nitrogen compounds of intermediate reactivity can be prepared. The synthesis methods developed in this investigation should apply to bridgehead urethanes, sulfonamides, and phosphonamides as well as to ureas, which, because of the widespread occurrence of such linkages in pharmaceutically active compounds, should be of interest in medicinal chemistry. Moreover, ring-opening polymerization of the more strained members should lead to novel polymers of possible biomedical utility. The synthesis of other bridgehead nitrogen compounds is currently underway in these laboratories.

(8) J. P. Li and J. H. Biel, *J. Org. Chem.*, **35**, 4100 (1970).

Experimental Section

Infrared spectra were taken on a PE 337 spectrometer. Gas chromatograms were taken on a 150 cm, 63 mm stainless steel column containing 30% SE-30 on 100/120 mesh Varaport 30. Melting points and boiling points are uncorrected.

3-Isopropylidenaminomethylpyridine (6).—3-Aminomethylpyridine (106.5 g, 0.99 mol, Research Organic and Inorganic Chemicals Co.), acetone (182 ml, 3 mol), and benzene (300 ml) were heated to reflux in a 1-l. round-bottom flask provided with Dean-Stark trap and water condenser. The reaction was discontinued when the rate of water collection became slow. Benzene and excess acetone were removed by distillation at atmospheric pressure using a heating mantle. The residual oil was distilled. Compound **6**, bp 68–80° (0.3 mm), 109.2 g, was obtained as a colorless liquid. It showed two peaks by vpc (ratio of peaks in order of increasing retention time, 1:1). The infrared spectrum of **6** showed a strong band at 1670 cm^{-1} (C=N). It appears that **6** may have been formed in a mixture with its tautomer **6a**.



6a

3-Isopropylaminomethylpyridine (7).—The above sample of **6** was taken up in ethyl acetate (350 ml) and placed under hydrogen (*ca.* 40 psi) at 20° using platinum oxide (500 mg) as catalyst. When hydrogen uptake became slow, the catalyst was separated by filtration and the filtrate was concentrated, leaving a yellow oil, 130 g. Vpc analysis showed two peaks in the ratio 15:85 (order of increasing retention time). The oil was distilled to give 95.4 g, bp 72–80° (1.6 mm). An infrared spectrum of **7** showed the absence of a band at 1670 cm^{-1} attributable to C=N, while absorption at >3000 cm^{-1} indicates the presence of the pyridine ring. Thus the hydrogenation of the C=N link seems to have been almost complete.

3-(Isopropylaminomethyl)piperidine (8).—The above product, **7**, 95.4 g, was taken up in water (200 ml) and the solution was acidified with concentrated hydrochloric acid (110 ml). The solution was placed under hydrogen (2000 psi) at 75° using ruthenium oxide as catalyst (*ca.* 1 g) and maintained under these conditions until gas absorption became slow. The catalyst was filtered. Excess water was removed by means of a rotary evaporator. The viscous residue was cooled in an ice bath and a concentrated aqueous solution of 40% sodium hydroxide was added slowly with swirling. The resulting aqueous slush was extracted with two portions of ether. The combined extract was dried over anhydrous sodium sulfate. Ether was removed by means of a rotary evaporator and the resulting oil was distilled, bp 56–61° (0.3–0.2 mm), yield 56 g (57%). In this experiment **8** was at least 93% pure by vpc, and in other runs approached 100%. An nmr spectrum of the material showed no signals attributable to aromatic hydrogens.

Anal. Calcd for $C_9H_{20}N_2$: C, 69.17; H, 12.90; N, 17.93. Found: C, 69.11; H, 12.90; N, 18.06.

Reaction of 3-(Isopropylaminomethyl)piperidine (8) with Excess Phosgene in Ether at −75° to Give the Biscarbamoyl Chloride 10.—A 1-l., three-necked Morton flask was fitted with a jacketed pressure-equalizing dropping funnel, cold-finger condenser, and three-way stopcock. The flask was provided with a magnetic stirrer. The apparatus was dried using a Bunsen flame and cooled under a stream of nitrogen. To the flask was added anhydrous ether (500 ml). Phosgene (4.20 ml, 0.0583 mol) was admitted by distillation from a calibrated trap in which it had been liquefied. The dropping funnel was charged with a solution of 3-(isopropylaminomethyl)piperidine (**8**, 3.0 g, 0.0192 mol) in 50 ml of ether. The reaction mixture was cooled to −75° using a Dry Ice–isopropyl alcohol bath. The solution in the addition funnel was cooled and the diamine solution was added by drops with efficient stirring. After addition was complete, the reaction mixture was allowed to warm to room temperature and stirring was continued for 4 hr. The solid was separated by filtration and the filtrate was concentrated using a

rotary evaporator, giving 10 as a colorless oil, 1.0 g. A strong infrared absorption band appeared at 1740 cm^{-1} (COCl), but none between 3600–3050 cm^{-1} (absence of NH). A weaker band at 1650 cm^{-1} (urea) was also present. That the above material was mainly the biscarbamoyl chloride **10** was supported by gravimetric analysis. A sample of this material (234 mg) was dissolved in acetone (2 ml) and treated with a solution of silver nitrate (307 mg) in water (10 ml). Mixing was accompanied by a fairly vigorous evolution of gas and rapid precipitation. After brief standing, the silver chloride was separated by filtration, washed with water, and dried to give 202 mg (theoretical mass 237 mg).

Reaction of Biscarbamoyl Chloride 10 with Silver Carbonate to Give Urea 9.—A sample which was largely biscarbamoyl chloride **10**, 844 mg, was dissolved in anhydrous acetonitrile (13 ml, from phosphorus pentoxide) in a 25-ml round-bottom flask provided with a magnetic stirring bar. Silver carbonate (1.65 g) was added to the solution and the mixture was stirred while being heated at reflux for 18 hr. The mixture was allowed to cool, filter, and evaporate. The crude dark oil (450 mg) was purified by molecular distillation, bp 220° (0.2–0.3 mm), to give **9** as a colorless oil (100–150 mg). The nmr spectrum and vpc retention time of this material were essentially identical with those of **9** prepared by the alternate route (below).

Reaction of 3-(*N*-Isopropylaminomethyl)piperidine (8) with Phosgene in Methylene Chloride at 0° to give 3-Isopropyl-1,3-diazabicyclo[3.3.1]nonan-2-one (9).—A 1-l. three-necked Morton flask was fitted with a mechanical stirrer, cold-finger, condenser, and three-way stopcock. The exit from the condenser was protected with a Drierite tube. The apparatus was dried with a Bunsen flame and cooled under a stream of nitrogen. To the flask was added dry methylene chloride (450 ml from 4-A molecular sieves) and 3-(*N*-isopropylaminomethyl)piperidine (**8**) (100% by vpc), yield 3.0 g, 0.0192 mol. Phosgene (1.36 ml, 0.0192 mol) was condensed in a graduated trap cooled in a Dry Ice–isopropyl alcohol bath. The reaction flask was cooled in an ice bath and the cold finger was charged with Dry Ice and isopropyl alcohol. The phosgene was transferred to the reaction flask by distillation at room temperature (10 min) using efficient stirring. Stirring was continued for 5 min after addition was complete and the reaction solution (colorless to slightly yellow) was allowed to come to room temperature.

The three-way stopcock was replaced with a pressure-equalizing addition funnel containing a solution of anhydrous triethylamine (5.2 ml) from barium oxide in 25 ml of methylene chloride. The solution was added by drops with stirring over 10 min at room temperature, and the final, almost colorless, solution was left at room temperature for 16 hr. It was washed with 3 ml of concentrated hydrochloric acid in 100 ml of water, with 3 g of sodium bicarbonate in 50 ml of water, and with 100 ml of water. After drying over anhydrous sodium sulfate, the solution was concentrated. The colorless residue, 3.35 g, was purified by molecular distillation, bp 150° (0.25 mm), bath 200°, to give **9** as a colorless oil, 1.02 g (28%). Vpc showed only a single peak (>98%) past solvent, retention time 4.5 min at 185° using a flow rate of 60 ml of He per minute.

Seeding the distillate with crystals obtained by preparative gas chromatography induced crystallization.

An nmr spectrum of the distillate (CCl_4) showed a pentuplet (septuplet?) at δ 4.3, a series of multiplets at 4.2–0.9, and a doublet at 1.18. The mass spectrum (sample by preparative gas chromatography) showed the parent ion at *m/e* 182.1433, corresponding to $C_{10}H_{18}ON_2$. The analytical sample of **9** was recrystallized twice from ethyl acetate at −45° and resublimed under N_2, mp 48.2–49.2°. *Anal.* Calcd for $C_{10}H_{18}N_2O$: C, 65.90; H, 9.95; N, 15.37. Found: C, 65.68; H, 9.84; N, 15.23.

When the reaction was performed under identical conditions, but at −40°, the product contained approximately equal amounts of **9** and **10**. The latter could be destroyed by excess $AgNO_3$ in acetone–water, and urea **9** could be recovered in 29% yield.

Stability of 3-Isopropyl-1,3-diazabicyclo[3.3.1]nonan-2-one to Water, Acid, and Base.—The title material was soluble in water. A solution was monitored by gas chromatography in order to detect changes due to possible hydrolysis. No change was observed, however, after 24 hr at room temperature. Another sample (71 mg) as a solution in water (2.0 ml) was heated under reflux for 20 hr. Chromatograms following standard injections showed no change over this period. The material was completely stable toward water.

Sodium Hydroxide Solution.—A solution of 30 mg of **9** and 57 mg of sodium hydroxide in 0.5 ml of water and 0.36 g of tetrahydrofuran was refluxed. After 2 hr about 80% of **9** had disappeared (by vpc) and after 6 hr almost none remained. No other peaks were detected. Slow hydrolysis occurs under these conditions.

Potassium *tert*-Butoxide.—A sample of **9** (30 mg) was mixed with a small quantity of potassium *tert*-butoxide (~0.1 mg). The mixture was allowed to stand at room temperature for 22.5 hr under nitrogen. There was no change in the composition of the material as determined by infrared analyses. The mixture was heated at 120–125° (under nitrogen) for 22 hr. The infrared spectrum recorded after this time was essentially identical with that of starting material.

***p*-Toluenesulfonic Acid Monohydrate.**—Another sample of **9** (92 mg) was placed in contact with a few small crystals of *p*-toluenesulfonic acid monohydrate (under nitrogen). The infrared spectrum recorded after standing for 10 hr at room temperature showed no change from starting material. The mixture was heated at 105–120° for 24 hr. An infrared spectrum recorded after this time was essentially identical with one of starting material.

85% Phosphoric Acid.—A mixture of **9** (96 mg) and 85% phosphoric acid (2.5 mg) was heated for 17 hr at 200° in a Wood's metal bath (sealed tube under vacuum). At the end of this time, the tube was opened and a sample was examined by infrared. The spectrum was essentially identical with one of starting material.

Registry No.—**6**, 33037-67-1; **7**, 19730-12-2; **8**, 33037-69-3; **9**, 33037-70-6; **10**, 33037-71-7.

Acknowledgment.—We are grateful to the National Science Foundation for the support of this work through its Science Development Program Grant to the University of Arizona. We are also deeply indebted to Dr. James Berry of the High Pressure Laboratory, University of Arizona, for many hydrogenations.

Ring Expansion of Bicyclo[2.1.1.]hexan-2-one and Related Compounds

THOMAS GIBSON

The Procter & Gamble Company, Miami Valley Laboratories, Cincinnati, Ohio 45239

Received August 4, 1971

The diazomethane ring-expansion reaction of bicyclo[2.1.1]hexan-2-one and related compounds has been investigated as a method for the synthesis of bicyclo[3.1.1]heptanones. The reaction, while sluggish, provides a convenient procedure for the synthesis of bicycloheptanones **6–14** from the bicyclohexanones **1–5**. The lack of epoxide formation, the preference for C_2–C_3 over C_1–C_2 bond migration, and the lack of reactivity of the products **6–14** is discussed in terms of the influence of ring strain and steric effects on the zwitterionic intermediate in the reaction.

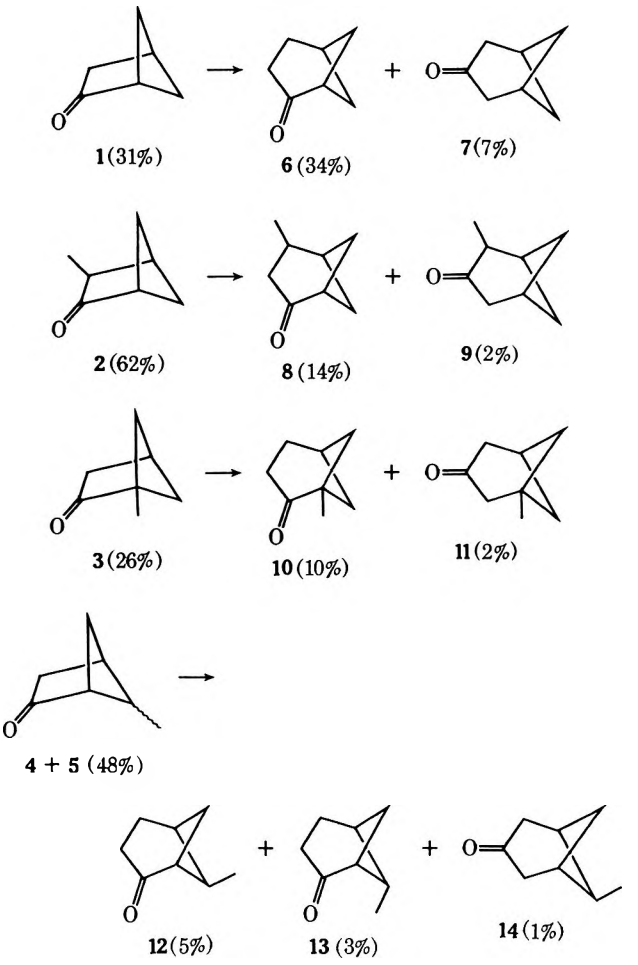
Various approaches to the construction of compounds of the bicyclo[3.1.1]heptane series are possible. Four of these, involving ring formation in 1,3-disubstituted cyclobutanes, ring closure of 2-tosyloxymethylcyclohexanones,[1] photocycloaddition of 1,6-heptadienes, and ring contraction of bicyclo[3.2.1]octanes, have been discussed at some length by Musso, *et al.*[2] For some time we have been engaged in attempts to utilize the photocycloaddition method for this purpose.[3] Since it appears from this work that direct cycloaddition to the bicyclo[3.1.1]heptane system from acyclic dienone precursors is not feasible, we have examined a variation of this approach. This involves initial cycloaddition to the bicyclo[2.1.1]hexan-2-one system,[4] followed by a ring-expansion reaction. The availability of compounds **1–5** by the photocycloaddition process[4] provided a source of materials suitable for a thorough study of the ring expansion reaction, the results of which are presented in this paper.

Results

Synthesis of Bicyclo[2.1.1]hexanones.—Compounds **1–5** (Chart I) were prepared by the method previously described.[4] The isomers **4** and **5** were used as the 1:3 *exo–endo* mixture obtained from the irradiation of *trans*-1,5-heptadien-3-one.[4b]

Ring-Expansion Reactions.—The ring expansion reactions were carried out in methanol by generation *in situ* of diazomethane from *N*-methyl-*N*-nitrosourethane.[5,6] The results shown in Chart I, which gives yields of products and recovery of starting material as determined by gas–liquid partition chromatography (glpc), were obtained with the use of approximately 2 molar equiv of urethane per mol of ketone. The use of a larger excess of diazomethane did not lead to an improvement in yields, although a thorough study of this point has not been carried out. All reactions gave varying amounts of *N*-methylurethane, which interfered with analysis and isolation of products on polar glpc columns. The most convenient isolation procedure found involved basic hydrolysis to remove urethane followed by preparative glpc using a nonpolar liquid phase such as SE-30.

CHART I



Some difficulty was encountered in isolation of products from the reaction of **4** and **5**, and therefore complete characterization was not possible. Compounds **6** and **7** were identified by direct comparison of their infrared spectra and glpc behavior with those of authentic samples.[7] Ketones **6–14** displayed the expected infrared carbonyl maxima for this system, as well as nmr spectra consistent with the assigned structures. The details of these spectra are recorded in the Experimental Section.

We found high-resolution mass spectrometry to be a most useful tool for the purpose of establishing the position of the carbonyl group in the isomers formed in a reaction. Thus, the ketone **6**, in which the carbonyl group is adjacent to the bridgehead position, showed a base peak at *m/e* 67, corresponding to a composition of

(1) E. Wenkert and D. P. Strike, *J. Org. Chem.*, **27**, 1883 (1962); F. Nerdel, D. Frank, and H. Marschall, *Angew. Chem.*, **74**, 587 (1962); K. B. Wiberg and G. W. Klein, *Tetrahedron Lett.*, 1043 (1963).

(2) H. Musso, K. Naumann, and K. Grychtol, *Chem. Ber.*, **100**, 3614 (1967).

(3) T. W. Gibson and W. F. Erman, unpublished results.

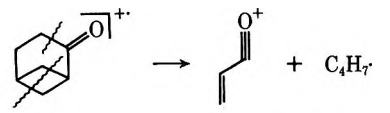
(4) (a) F. T. Bond, H. L. Jones, and L. Scerbo, *Tetrahedron Lett.*, 4685 (1965); (b) T. W. Gibson and W. F. Erman, 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970.

(5) C. D. Gutsche, *Org. React.*, **8**, 364 (1954).

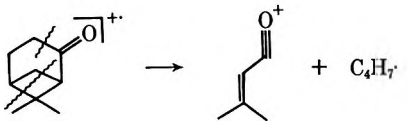
(6) E. P. Kohler, M. Tishler, H. Potter, and H. T. Thompson, *J. Amer. Chem. Soc.*, **61**, 1057 (1939).

(7) We express our thanks to Professor H. Musso for kindly providing us with samples of these two compounds.

C_5H_7. The most abundant oxygen-containing fragment appeared at *m/e* 55, corresponding to a composition of C_3H_3O. The process leading to this fragment can be rationalized as shown and is supported by the observation of the analogous fragmentation in nopinone (**15**) which generates the ion C_5H_7O as the most abun-



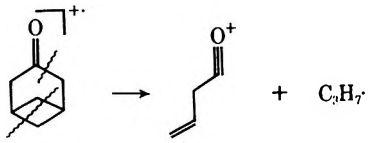
6



15

dant oxygen-containing fragment, along with the C_3H_3O ion at lower intensity.

Ketone **7**, on the other hand, shows as the base peak an oxygen-containing fragment corresponding to a



7

composition of C_4H_5O, probably arising from the process shown.

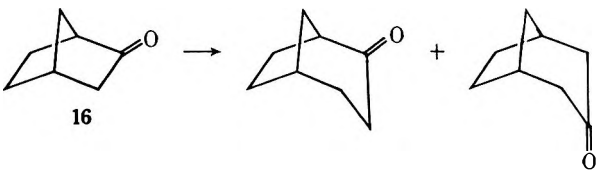
The observation of analogous data from the other product sets allowed unambiguous assignment of structures (*cf.* Experimental Section).

Discussion

In addition to the synthetic utility of this process, there are a number of mechanistic questions of interest. We wished to know what effect placing the carbonyl group in a rigid bicyclic framework would have on three relationships: competition between ring expansion and epoxide formation, the relative migratory aptitudes of bridgehead *vs.* bridge carbon atoms, and the relative reactivities toward ring expansion of bicyclo[2.1.1]hexanones and bicyclo[3.1.1]heptanones. It has been generally accepted that the reaction involves nucleophilic addition of diazomethane to the carbonyl group, generating a zwitterionic intermediate, which is then partitioned between epoxide formation and alkyl shift.[8] The following discussion will be based on the assumption that this mechanism is operating.

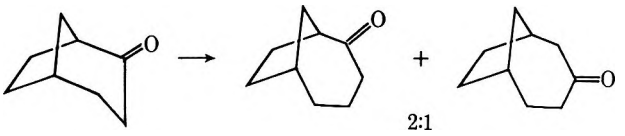
Epoxide Formation.—The non-Lewis acid catalyzed reaction of diazomethane with alicyclic ketones generally results in some epoxide formation.[8] We were unable however, to isolate any epoxides from the reactions of **1**–**5** with diazomethane, nor did we obtain any evidence for their presence in crude reaction products by examination of ir and nmr spectra. This parallels the behavior shown by norcamphor (**16**) in the ring-expansion reaction[9] in which no epoxide formation was observed. The absence of epoxide formation in that system was rationalized on the basis of ring strain in the zwitterionic intermediate, which would favor partition toward ring expansion rather than closure to spiro epoxide. This effect would be expected to be even more pronounced in the more highly strained bicyclohexane system, and it is therefore not surprising that epoxide formation was not observed.

Migratory Aptitudes.—The results shown in Chart I reveal that there is a ratio of approximately 5–7:1 in favor of bridge migration (C_3) over bridgehead migration (C_1). This behavior is similar to that shown by both norcamphor (**16**) and bicyclo[3.2.1]octan-2-one (**17**), which are reported to give 2:1 ratios in favor of



16

2:1

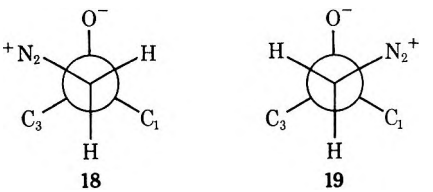


17

2:1

bridge migration in the presence of 0.1 equiv of diazomethane.[9] This preference for 2,3- over 1,2-bond shift was attributed to nonbonded interactions in the zwitterion intermediate, in which eclipsing with the hydrogens in the 3 position occurs, weakening the 2,3 bond. The same would be true in the bicyclo[2.1.1]-hexanones, and, in fact, studies of molecular models show that this effect should be somewhat accentuated in this system. In the bicyclo[2.1.1]hexane system, the bridgehead hydrogen is situated in a perfectly staggered orientation to the two C_2 substituents, while appreciable eclipsing occurs at this position in the bicyclo[2.2.1]heptane system. Thus the difference in relief of strain brought about by stretching of the C_2–C_3 bond in preference to stretching of the C_1–C_2 bond would be greater in the bicyclohexane system, leading to the larger ratio observed.

The steric situation around C_2 in the zwitterion intermediate should also have an effect on the relative energies of the rotational conformers (**18** and **19**)



18 **19**

(8) C. D. Gutsche and D. Redmore, "Carbocyclic Ring Expansion Reactions," Academic Press, New York, N. Y., 1968, pp 81–99.

(9) G. Fachinetti, F. Pietra, and A. Marsili, *Tetrahedron Lett.*, 393 (1971).

leading to the transition states for bond migration. Turro and Gagosian,[10] attempting to explain migration preferences in the reaction of diazoethane with substituted cyclopropanes, considered energy differences in the rotational conformers leading to products to be an important factor. Comparison of Dreiding models of the rotational conformers **18** and **19** reveals a decidedly greater interaction between the diazo group (which with its accompanying solvent shell should be of considerably greater steric bulk than a hydrogen atom) and the syn C_3 hydrogen in **18** than with the bridgehead hydrogen in **19**. This occurs as a result of the eclipsed arrangement of the tetrahedral C_2 substituents with the C_3 hydrogens, in contrast to their staggered relationship with the C_1 hydrogen, as mentioned above. This would favor somewhat conformer **19**, which leads to C_2–C_3 bond migration. This effect does not appear to be significantly altered by the presence of a methyl group at C_1. In **2**, with a methyl group at C_3, which would presumably lead to trans approach of nucleophile, the effect is slightly accentuated, leading to a slightly greater preference for C_2–C_3 bond migration. The data obtained for **4** and **5** are not sufficiently accurate to use with any confidence, but it would not be expected that the methyl group at C_5 would have any significant effect on rotational energy differences. Thus, steric effects in the intermediate zwitterion provide two arguments for rationalizing the preference for C_2–C_3 bond shift in the bicyclohexane system.

Relative Reactivities.—In view of the known greater reactivity of cyclohexanone over cyclopentanone toward ring expansion,[8] we anticipated some difficulty in stopping the reaction of the bicyclohexanones at the bicycloheptanone stage. In fact, this situation exists in the norcamphor series, in which reactivity of the bicyclo[3.2.1]octanone **17** is much greater than that of **16**.[9] To get some information on this point, we carried out the attempted ring expansion of nopinone (**15**) under the same conditions used for the bicyclohexanones. Reaction with diazomethane produced from 2 equiv of urethane was carried out for 2 days, after which time glpc analysis revealed no loss of starting material and no detectable ring-expansion products. This result appeared promising with respect to the planned use of the ring-expansion reaction for synthesis of the bicyclo[3.1.1]heptanone system, but we felt that the unreactivity of nopinone might be due to the presence of the *gem*-dimethyl group. This grouping would be expected to hinder formation of a tetrahedral center at the carbonyl carbon, irrespective of the route of approach of the nucleophile to the carbonyl group. However, this unreactive behavior appears to be characteristic of the bicyclo[3.1.1]heptanone system, since in no instance could we obtain any glpc evidence for the formation of bicyclo[4.1.1]octanones in the ring-expansion reactions shown in Chart I, even in the presence of a large excess of diazomethane. Study of models of the three ring systems does not provide any ready explanation for the low reactivity of the bicyclo[3.1.1]heptanones. However, their stability to diazomethane serves to make the ring expansion reaction convenient for their synthesis.

(10) N. J. Turro and R. B. Gagosian, *J. Amer. Chem. Soc.*, **92**, 2036 (1970).

Experimental Section[11]

Attempted Ring Expansion of Nopinone (15).—To an ice-cooled solution of 0.50 g (3.6 mmol) of nopinone[12] in 16 ml of methanol was added 0.25 g of anhydrous Na_2CO_3. A solution of 0.97 g (7.4 mmol) of *N*-methyl-*N*-nitrosourethane in 9 ml of methanol was then added over 25 min. After addition was complete, the ice bath was removed and the solution was allowed to warm to ambient temperature and stirred for 2 days. Filtration followed by distillation gave an oily residue composed mainly of nopinone and *N*-methylurethane. The latter impurity was removed by treatment with 10 ml of 1 *N* NaOH at 60° for 4 hr. The 0.530 g of neutral material recovered showed an infrared spectrum and glc analysis nearly identical with those of starting material. No peaks were observed in the glpc analysis in the area in which ring expansion products would be expected to appear.

Ring Expansion of 1.—To a solution of 0.30 g of **1** in 20 ml of methanol over 0.40 g of Na_2CO_3 was added 1.20 g of nitrosomethylurethane in methanol solution.[6] The solution was stirred overnight at room temperature, the excess diazomethane was destroyed with 1 ml of 3% HCl, the solution was neutralized with NaOH, and the solvent was removed by distillation. The residue was taken up in water, the aqueous solution was extracted with ether, and the ether solution was dried over $MgSO_4$. Distillation gave 0.457 g of colorless oil, bp 85–95° (20 mm). A glpc analysis on two columns[11] showed four major peaks in the ratio of 31:5:38:25, which were collected and identified spectroscopically. Yields were calculated on the basis of the areas under the glpc peaks, assuming equivalent response of the TC detector to the different compounds.

Peak 1 (31%) was identified as recovered **1**.

Peak 2 (**7**, 7% yield) had sublimed, mp 60–62° (lit.[2] 59°). The ir spectrum was identical with that of an authentic sample, as was the glpc retention time on an SE-30 column.[7] The nmr spectrum showed signals at τ 8.65 (2 H, dd, J = 7 and 2 Hz), 7.7 (2 H, m), and 7.55 (6 H, s). The high-resolution mass spectrum showed a moleclar ion at m/e 110 ($C_7H_{10}O$) and a base peak at m/e 69 (C_4H_5O).

Peak 3 was identified by spectroscopic means as *N*-methylurethane.

Peak 4 (**6**, 34% yield) was semicrystalline. The ir spectrum and glpc retention time on an SE-30 column were identical with those of an authentic sample.[7] The nmr spectrum showed signals at τ 8.41 (2 H, dd, J = 7 and 3 Hz), 8.00 (2 H, m), 7.46 (4 H, m), and 7.20 (2 H, q, J = 5 Hz). The high resolution mass spectrum showed a molecular ion at m/e 110 ($C_7H_{10}O$), the base peak at m/e 67 (C_5H_7), and the most intense oxygen-containing fragment at m/e 55 (C_3H_3O).

The *p*-toluenesulfonylhydrazone had mp 209–210° (lit.[2] 206–208°).

The reaction was repeated using 8 equiv of urethane added in two batches over a 4-day period. The *N*-methylurethane was removed by hydrolysis and the neutral product was distilled to give a 40% yield of a mixture composed mainly of **6** and **7**, with some starting material and other impurities present. No evidence was seen for further ring-expanded materials.[13]

Ring Expansion of 2.—A solution of 0.502 g of **2** in methanol

(11) Melting points were determined on a micro hot stage and are corrected; boiling points are uncorrected. Infrared spectra were recorded on Perkin-Elmer 257 and 137 spectrophotometers as neat films or 5% solutions in CCl_4. Nuclear magnetic resonance spectra were obtained on a Varian Associates HA-100 spectrometer using TMS as an internal reference in $CDCl_3$. Nmr data are recorded in this order: chemical shift (integration, multiplicity where s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and coupling constant in hertz). Mass spectra were determined with an Atlas CH-4 spectrometer, or, where noted, high-resolution spectra were obtained with an Atlas SM-1 spectrometer. Glpc analyses were carried out on a Varian Aerograph Model 202B instrument using thermal conductivity detectors. Columns used were 5 ft × 0.25 in. stainless steel packed with 15% FFAP polyester or 15% SE-30 silicone oil on HMDS-treated 60–80 mesh Chromosorb W support. Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich.

(12) J. Meinwald and P. G. Gassman, *J. Amer. Chem. Soc.*, **82**, 5445 (1960).

(13) The low material balances observed in these reactions are partially due to loss of the starting bicyclohexanones by codistillation with solvent, a fact which led to some difficulty in their synthesis. Glpc examination of the methanol obtained from reaction of **1** with diazomethane showed the presence of considerable amounts of **1** with no evidence for **6** or **7**. The yields of bicycloheptanone products are based on starting bicyclohexanone, and are probably reasonably accurate.

over 0.20 g of Na_2CO_3 was treated with 1.359 g of nitrosomethylurethane,[6] and the resulting mixture was stirred overnight at room temperature. Work-up followed by distillation gave 0.569 g of colorless oil, bp 60–70° (20 mm), which showed four major peaks on glpc analysis. Isolation and analysis identified these as *N*-methylurethane (30%), starting material (62%), and two ring-expanded products in yields of 2 and 14%. Pure materials were isolated by preparative glpc on a 10-ft SE-30 column. The minor product, **9**, showed λ_{max} 5.84 μ and nmr signals at τ 8.87 (3 H, d, J = 7 Hz), 8.64 (2 H, m), 7.2–8.0 (5 H), and 7.47 (2 H, s). The high-resolution mass spectrum showed a molecular ion at m/e 124 ($C_8H_{12}O$), the base peak at m/e 67 (C_5H_7), and major oxygen-containing fragments at m/e 69 (C_4H_5O) (68% of base peak) and 83 (C_5H_7O), corresponding to the two modes of the fragmentation pattern observed for **7**.

The major product, **8**, showed λ_{max} 5.80 μ and nmr signals at τ 8.95 (3 H, d, J = 6.5 Hz), 8.42 (2 H, m), 7.3–8.1 (6 H), and 7.20 (1 H, m). The high-resolution mass spectrum showed a strong molecular ion at m/e 124 ($C_8H_{12}O$), the base peak at m/e 68 (C_5H_8), and the major oxygen-containing fragment at m/e 70 (C_4H_6O) (44% of base peak).

The *p*-toluenesulfonylhydrazone had mp 162–164°.

Anal. Calcd for $C_{15}H_{20}N_2O_2S$: C, 61.63; H, 6.90; N, 9.58. Found: C, 61.59; H, 6.85; N, 9.62.

Ring Expansion of 3.—A solution of 0.284 g of **3** in methanol over 0.20 g of Na_2CO_3 was treated with 0.821 g of nitrosomethylurethane,[6] and stirred overnight at room temperature. Distillation gave a mixture which contained 26% of recovered starting material and two ring-expansion products in 2 and 10% yields, both of which were isolated by preparative glpc.

The minor product, **11**, showed λ_{max} 5.80 μ and nmr signals at τ 8.92 (3 H, s), 8.58 (2 H, dd, J = 8 and 2 Hz), 8.08 (2 H, m), 7.73 (2 H, s), 7.63 (2 H, s), and 7.6 (1 H, m). The high-resolution mass spectrum showed a molecular ion at m/e 124 ($C_8H_{12}O$), the base peak at m/e 55 (C_4H_7), and major oxygen-containing fragments at m/e 83 (C_5H_7O) (99% of base peak) and 69 (C_4H_5O) (83% of base peak) resulting from the two possible modes of fragmentation of **11** corresponding to that of **7**.

The major product, **10**, showed λ_{max} 5.82 μ and nmr signals at τ 8.93 (3 H, s), 8.29 (2 H, dd, J = 7.0 and 2.5 Hz), 7.96 (4 H, m), 7.52 (2 H, t, J = 7 Hz), and 7.5 (1 H, m). The high-resolution mass spectrum showed a molecular ion at m/e 124 ($C_8H_{12}O$), the base peak at m/e 81 (C_6H_9), and the major oxygen-containing fragment at m/e 69 (C_4H_5O) (94% of base peak), establishing the presence of the carbonyl group at the 2 position.

The *p*-toluenesulfonylhydrazone had mp 159–161°.

Anal. Calcd for $C_{15}H_{20}N_2O_2S$: C, 61.63; H, 6.90; N, 9.58. Found: C, 61.64; H, 6.86; N, 9.60.

Ring Expansion of 4 and 5.—A solution of 0.250 g of a 3:1 endo:exo mixture of **4** and **5** in methanol over 0.20 g of Na_2CO_3 was treated with 0.692 g of nitrosomethylurethane,[6] and the mixture was stirred overnight at room temperature. Work-up followed by distillation gave 0.222 g of colorless oil, bp 60–80° (20 mm), which showed the presence of starting material (42%; 3:1), and two product peaks in yields of 1 and 9%. The minor product was identified as **14** on the basis of λ_{max} 5.82 μ, nmr signals at τ 8.72 (3 H, d, J = 6.8 Hz), 8.26 (1 H, br d, J = 7 Hz), 7.86 (2 H, m), 7.42 (4 H, s), and *ca.* 7.4 (2 H). The high-resolution mass spectrum showed a molecular ion at m/e 124 ($C_8H_{12}O$), the base peak at m/e 67 (C_5H_7), and the major oxygen-containing fragments in nearly equal intensity at m/e 83 (C_5H_7O) and 69 (C_4H_5O).

The nmr spectrum of the material corresponding to the major peak showed signals for two methyl groups at τ 9.15 (d, J = 6 Hz) and 8.67 (d, J = 6.8 Hz) in a ratio of 3:5. The high-resolution mass spectrum showed a molecular ion at m/e 124 ($C_8H_{12}O$) and a base peak at m/e 69 (C_4H_5O), while the ir spectrum showed a single carbonyl band at 5.82 μ. These data suggest the presence of a mixture of the two isomers **12** and **13** in a ratio of 5:3. The stereochemistry of the methyl groups in these compounds, as well as that of **14**, are assigned on the basis of their chemical shifts, in analogy with the chemical shift positions of methyl groups in other bicyclo[3.1.1]heptanes.[14]

Registry No.—**6**, 17159-87-4; **7**, 17159-75-0; **8**, 33122-17-7; **8** *p*-toluenesulfonylhydrazone, 33122-18-8; **9**, 33061-07-3; **10**, 33122-19-9; **10** *p*-toluenesulfonylhydrazone, 33122-20-2; **11**, 33061-08-4; **12**, 33066-01-2; **13**, 33066-02-3; **14**, 33061-09-5.

Acknowledgment.—The able technical assistance of R. L. Munyon, Sr., is gratefully acknowledged.

(14) T. W. Gibson and W. F. Erman, *J. Amer. Chem. Soc.*, **91**, 4771 (1969).

The Crystal Structure of 1-(*p*-Bromophenyl)-1,2-epoxycyclohexane. Evidence for Three-Ring Phenyl Pseudoconjugation[1]

Stefano Merlino

Istituto di Mineralogia, Università di Pisa, 56100 Pisa, Italy

Giovanni Lami, Bruno Macchia,* Franco Macchia, and Luigi Monti

Istituti di Chimica Farmaceutica e di Chimica Organica, Università di Pisa, 56100 Pisa, Italy

Received June 1, 1971

1-(*p*-Bromophenyl)-1,2-epoxycyclohexane crystallizes in space group $P2_1/c$, with unit cell dimensions a = 9.91, b = 5.72, c = 19.41 Å; β = 102° 20 min. The structure was solved by single-crystal X-ray diffraction methods. Least-squares refinement led to a final agreement factor for the observed reflections, R = 0.072. In the molecular structure the cyclohexane ring has a half-chair conformation. The epoxydic ring (C–C bond length 1.48 Å with estimated standard deviation 0.02 Å, C–O bond lengths with mean value 1.47 Å, estimated standard deviation 0.02 Å) makes an angle of 83° with the phenyl ring, as the result of pseudoconjugative interaction. This interaction is also indirectly responsible for the particular conformation assumed by the cyclohexane ring.

The geometry of the variously substituted cyclohexane rings has been extensively studied by means of electron diffraction, X-ray, and microwave spectroscopy.[2] The structural determinations on 1,2-epoxycyclohexanes are largely limited[3,4] to the classical electron diffraction studies of Ottar[5] who measured the skeletal geometry and the various interatomic distances in this system. In particular, the 1,2-epoxycyclohexane

(1) This work was supported by Consiglio Nazionale delle Ricerche, Roma.

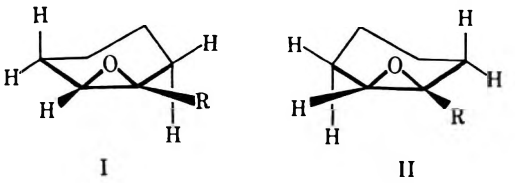
(2) (a) C. Altona and M. Sundaralingam, *Tetrahedron*, **26**, 925 (1970); (b) H. Booth, *Progr. Nucl. Magn. Resonance Spectrosc.*, **5**, 231 (1969), and references cited therein.

(3) R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959).

(4) A. Rosowsky in "Heterocyclic Compounds with Three- and Four-Membered Rings," Part 1, A. Weissberger, Ed., Interscience, New York, N. Y., 1964, p. 1.

(5) B. Ottar, *Acta Chem. Scand.*, **1**, 283 (1947).

molecule can exist in two enantiomeric "half-chair" conformations (I, II) which readily undergo chair inversion.



I II

These two conformations are no longer equivalent when a substituent is present in the ring. It has been demonstrated by nmr spectrometry that, when the cyclohexane ring is incorporated into a rigid system, for example, steroids, or when there are bulky substituents such as a *tert*-butyl group present in the 4 position, the ring is constrained in one particular half-chair conformation.[6] However, this approach to the study of the ring conformations fails in assessing the subtle conformational effects arising when there are substituents at the 1 or 2 positions.

While the geometry of a molecule in the solid state does not necessarily reflect its conformations in solution, we have considered it worthwhile, in relation to the behavior of 1-phenyl-1,2-epoxycyclohexanes,[7] to investigate the geometry of the 1-(*p*-bromophenyl)-1,2-epoxycyclohexane by X-ray diffraction. This investigation should allow, at least in the solid state, to establish the exact conformational situation of the phenyl ring, with regard to its possible conjugation with the epoxide ring.[8-10] This problem is of some importance since it can be very useful in connection with the physical and chemical properties of these epoxides and, more generally, can be of significance in connection with the electronic structure of the epoxide ring which at the present time is still a subject of much discussion.[3,4]

Experimental Section

Preparation of the Compound. 1-(*p*-Bromophenyl)cyclohexene.—A solution of 1-(*p*-bromophenyl)cyclohexanol[11] (10.0 g) in acetic acid (10 ml) was treated with sulfuric acid (2 ml). The resulting mixture was swirled for 30 sec and then poured into water. After cooling the precipitate was collected, washed with water, and crystallized from ethanol to give the pure product (7.60 g), mp (Kofler hot stage) 72–73° (lit.[12] mp 73.5–74°).

1-(*p*-Bromophenyl)-1,2-epoxycyclohexane.—A solution of 1-(*p*-bromophenyl)cyclohexene (5.0 g, 0.021 mol) in 75% aqueous dioxane (100 ml) was treated with *N*-bromoacetamide (3.30 g, 0.024 mol) in 50% aqueous dioxane (50 ml). This suspension was warmed on a steam bath for 10 min, cooled, treated with potassium hydroxide (10.0 g) in water (50 ml), stirred for 15 min, poured in water, and extracted with ether. The ether layer was washed with water, dried ($MgSO_4$), and evaporated to yield a residue (5.10 g) which was dissolved in petroleum ether and chromatographed through a 1.5 × 25 cm column of neutral alumina (grade II) collecting 10-ml fractions. Elution with petroleum ether (bp 30–50°) yielded in succession small quantities of unreacted starting material and pure 1-(*p*-bromophenyl)-1,2-epoxycyclohexane (3.20 g), which crystallized from petroleum ether (bp 30–50°), mp 57–57.5° (lit.[13] mp 48.5°).

X-Ray Data.—The crystal data were determined by means of rotation and Weissenberg photographs obtained with Cu Kα radiation and precession spectra taken with Mo Kα radiation. 1-(*p*-Bromophenyl)-1,2-epoxycyclohexane: mol wt 253.1; monoclinic space group $P2_1/c$, from systematic absences ($h0l$ absent for $l = 2n + 1$, $0k0$ absent for $k = 2n + 1$); $a = 9.91 \pm 0.02$ Å, $b = 5.72 \pm 0.01$ Å, $c = 19.41 \pm 0.03$ Å; $\beta = 102° 20 \pm 10$ min; unit cell volume $U = 1075.4$ Å^3; $D_c = 1.57$ g cm^{-3} with $Z = 4$; F(000) = 512; μ (Cu Kα) = 50 cm^{-1}.

The intensity data were recorded with Ni-filtered Cu Kα radiation (λ 1.5418 Å), by means of Weissenberg photographs, with the multiple films technique and integration process. A crystal elongated in the *b* direction was reduced to cylindrical shape with a diameter of 0.017 cm ($\mu R = 0.425$ for Cu Kα radiation). Four layers with *b* as rotation axis (k = 0–3) were taken. A total of 753 independent reflexions were observed. The intensities, measured with a Nonius microdensitometer, have been corrected for Lorentz and polarization factors and for the absorption factor using the three-constants formula proposed by Palm[14] for cylindrical crystals.

Determination and Refinement of the Structure.—The structure determination was carried out by means of a three-dimensional Patterson synthesis. The bromine position was determined and a successive three-dimensional Fourier synthesis, calculated with the signs determined by the bromine atom, revealed all the heavy atoms of the structure; the agreement index $R_1 = \Sigma \, ||F_o| - |F_c| \, |/\Sigma|F_o|$ calculated at this stage resulted in 0.27.

Three cycles of full-matrix least-squares refinement were computed; positional coordinates, isotropic temperature factors, and the scale factors were introduced among the refined parameters. Unit weights were given to all the reflections. The R_1 value was calculated as 0.14.

At this point anisotropic temperature factor for the bromine atom was introduced and the following weighting scheme was used: $\sqrt{w} = 0$ for unobserved reflexions; $\sqrt{w} = 1$ for observed reflexions with $|F_o| \leq 8$; $\sqrt{w} = 1/(0.06\,|F_o| + 0.5)$ for observed reflexions with $|F_o| > 8$. Two further refinement cycles reduced R_1 to 0.082.

Then hydrogen atoms were introduced in calculated positions with isotropic temperature factors of 5.0 Å^2. One further least-squares cycle in which the hydrogen parameters were not varied led the agreement index to $R_1 = 0.072$.

The scattering factors used in the structure factor calculations were taken from International Tables for X-ray Crystallography[15] for all atoms.

The observed and the calculated factors and the final positional and thermal parameters with their standard deviations appear in the microfilm edition of this journal.[16]

Description and Discussion of the Structure.—Interatomic distances and bond angles (Table I and II) have been calculated by means of the ORFFE program of Busing, Martin, and Levy and the least-squares plane by means of the program LSQPL, incorporated in the Crystal Structures Calculations System X-RAY 63.[17]

(6) G. Berti, B. Macchia, and F. Macchia, *Tetrahedron*, **24**, 1755 (1968); *Gazz. Chim. Ital.*, **100**, 334 (1970).

(7) P. L. Barili, G. Berti, B. Macchia, F. Macchia, and L. Monti, *J. Chem. Soc. C*, 1168 (1970), and other papers in this series.

(8) N. H. Cromwell and G. V. Hudson, *J. Amer. Chem. Soc.*, **75**, 872 (1953).

(9) L. A. Strait, D. Jambotkar, R. Ketcham, and M. Hrenoff, *J. Org. Chem.*, **31**, 3976 (1966).

(10) W. A. Bernett, *J. Chem. Educ.*, **44**, 17 (1967).

(11) D. Y. Chang and R.-J. Yu, *J. Chin. Chem. Soc. (Taipei)*, **6**, 68 (1959); *Chem. Abstr.*, **54**, 13058 (1960).

(12) D. Y. Chang and N. Shieh, *J. Chin. Chem. Soc. (Taipei)*, **1**, 64 (1954); *Chem. Abstr.*, **49**, 6888 (1955).

(13) N. V. Meiya and A. F. Nikolaev, *Zh. Org. Khim.*, **1**, 296 (1965); *Chem. Abstr.*, **62**, 16167 (1965).

(14) J. H. Palm, *Acta Crystallogr.*, **17**, 1326 (1964).

(15) "International Tables for X-Ray Crystallography," Vol. III, Kynoch Press, Birmingham, England, 1962, p 202.

(16) Listing of structure factors, coordinates, and anisotropic temperature factors 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 St., N.W., Washington, D. C. 20036, by referring to author, title of article, volume, and page number. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

(17) J. M. Stewart, "Crystal Structure Calculations System for the IBM 709/7090/7094," Technical Report TR-64-6, Computer Science Center, University of Maryland, and Research Computer Laboratory, University of Washington, 1964.

Table I

Bond Lengths and Their Standard Deviations

Atoms	Distances, Å	Esd, Å
C(1)–O	1.45	0.02
C(2)–O	1.48	0.02
C(1)–C(2)	1.48	0.02
C(2)–C(3)	1.51	0.02
C(3)–C(4)	1.51	0.03
C(4)–C(5)	1.55	0.02
C(5)–C(6)	1.51	0.02
C(6)–C(1)	1.51	0.02
C(1)–C(7)	1.49	0.02
C(7)–C(8)	1.36	0.02
C(8)–C(9)	1.40	0.02
C(9)–C(10)	1.35	0.02
C(10)–C(11)	1.43	0.02
C(11)–C(12)	1.40	0.02
C(12)–C(7)	1.39	0.02
Br–C(10)	1.926	0.015

Table II

Bond Angles and Their Standard Deviations

	Angle, deg	Esd, deg
C(1)–O–C(2)	60.7	1.0
C(1)–C(2)–O	58.9	1.0
C(2)–C(1)–O	60.5	1.0
C(3)–C(2)–O	113.4	1.3
C(6)–C(1)–O	111.5	1.3
C(7)–C(1)–O	113.7	1.4
C(7)–C(1)–C(2)	119.2	1.3
C(6)–C(1)–C(2)	117.9	1.3
C(1)–C(2)–C(3)	122.4	1.4
C(2)–C(3)–C(4)	114.7	1.3
C(3)–C(4)–C(5)	108.3	1.7
C(4)–C(5)–C(6)	110.4	1.4
C(5)–C(6)–C(1)	112.4	1.4
C(6)–C(1)–C(7)	119.0	1.3
C(1)–C(7)–C(8)	122.8	1.5
C(1)–C(7)–C(12)	119.4	1.3
C(12)–C(7)–C(8)	117.7	1.4
C(7)–C(8)–C(9)	123.4	1.6
C(8)–C(9)–C(10)	117.7	1.5
C(9)–C(10)–C(11)	122.8	1.4
C(10)–C(11)–C(12)	116.0	1.6
C(11)–C(12)–C(7)	122.3	1.5
C(9)–C(10)–Br	120.6	1.2
C(11)–C(10)–Br	116.5	1.3

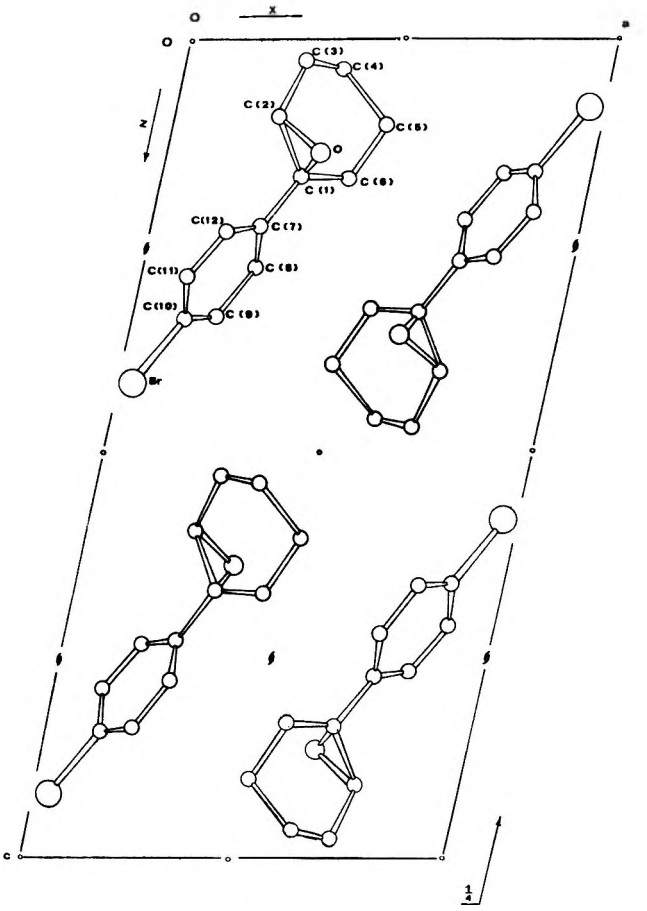


Figure 1.—The molecular structure of 1-(*p*-bromophenyl)-1,2-epoxycyclohexane, viewed along the direction normal to the epoxydic ring.

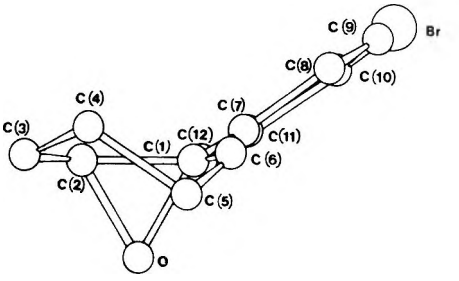


Figure 2.—Crystal structure as viewed along the *b* axis.

In what follows we shall examine the different aspects of the molecular structure: (a) bond lengths and angles in the system 1,2-epoxycyclohexane, (b) the geometry of the bromophenyl group, (c) the stereochemistry of the system made up by the epoxydic and phenyl rings, and (d) the conformation of the epoxycyclohexane ring.

(a) The structure of the 1,2-epoxycyclohexane group is very similar to that determined by an electron diffraction study[5] for 1,2-epoxycyclohexane, with the four carbon atoms C(1)–C(2)–C(3)–C(6) almost in a plane (the least-squares plane and the deviations from planarity are given in Table III); the angle between this plane and the plane of epoxydic ring is 80°. As regards bond lengths in the epoxydic ring, Ottar[5] determined a distance equal to 1.42 Å for the C–O bond; the values found in this work (1.48 Å for C–C bond and the mean value 1.47 Å for C–O bond) agree with the values determined by Erlandsson[18] in a microwave spectroscopic investigation of 1,2-epoxycyclopentane (1.52 Å for C–C and 1.47 Å for C–O bond lengths).

(b) In Table III we report two least-squares planes relative to the phenyl ring and the deviations from the calculated plane. The C–C bond lengths (mean value 1.39 Å) and the bond angles are normal.

(c) The conjugative properties of the three-membered rings have been amply documented and are clearly explained by the bent bond model developed for cyclopropane. The theory[10] shows that the geometry for maximum pseudoconjugative interaction between a three-membered ring and an adjacent π system is that where the plane of the ring and the axis of the π-orbital's system are parallel. This situation is satisfied in the molecular structure of 1-(*p*-bromophenyl)-1,2-epoxycyclohexane (Figure 1) where the dihedral angle between the epoxy ring and the phenyl ring is of 83°. This point is also relevant for the conformation assumed by the epoxycyclohexane group.

(d) In fact, once the pseudoconjugative interaction induces the phenyl ring to dispose its plane normal to the three-membered ring, the conformation I is preferred over II, because of more

(18) G. Erlandsson, *Ark. Fys.*, **9**, 341 (1955); *Chem. Abstr.*, **49**, 11421 (1955).

TABLE III
LEAST-SQUARES PLANES[a]

	Atoms defining the plane	A	B	C	D
Plane I	C(7), C(8), C(9), C(10), C(11), C(12)	7.1773	2.4574	7.2735	3.4945
Plane II	Br, C(7), C(8), C(9), C(10), C(11), C(12), C(1)	7.2141	2.4532	7.1623	3.4674
Plane III	C(1), C(2), C(3), C(6)	6.7074	4.2102	−2.5713	1.6003

	Deviations from the plane (in Å)		
Atoms	Plane I	Plane II	Plane III
Br		0.002	
C(1)		0.016	−0.003
C(2)			0.003
C(3)			0.001
C(6)			−0.003
C(7)	−0.004	−0.016	
C(8)	0.005	−0.002	
C(9)	−0.006	−0.005	
C(10)	0.005	0.011	
C(11)	−0.003	−0.002	
C(12)	0.003	−0.005	

[a] The equations, in the form $Ax + By + Cz = D$, where x, y, and z are fractional coordinates, were calculated [V. Schomaker, J. Waser, R. E. Marsh, and G. Bergman, *Acta Crystallogr.*, 12, 600 (1959)] with all weights equal to 1.

TABLE IV
SHORTEST INTERMOLECULAR DISTANCES[a]

Br···Br^{v}	3.52
Br···C(3^{iii})	3.90
Br···C(2^{iv})	3.79
C(7)···C(6^{ii})	3.66
C(11)···C(8^{i})	3.75
C(11)···C(8^{iv})	3.73
C(11)···C(9^{i})	3.70
C(11)···C(9^{iv})	3.60
C(11)···C(10^{iv})	3.59
C(11)···C(11^{iv})	3.78
C(12)···Br^{iv}	3.98
C(12)···C(8^{i})	3.76
C(12)···C(10^{iv})	3.68
O···C(4^{iii})	3.74
O···C(5^{iii})	3.78
O···C(6^{iii})	3.54

[a] C···C and C···O contacts are below 3.80 Å; C···Br and Br···Br contacts are below 4.00 Å.

favorable steric interaction between the hydrogen atom linked to C(8) atom at one hand and the two hydrogen atoms linked to C(6) at the other hand; the distances between H(8) and H(6a) (pseudoequatorial) and between H(8) and H(6b) (pseudoaxial) are 2.6 and 2.2 Å, respectively.

Crystal Packing.—The packing of the molecules in the crystal is described by Figure 2. In Table IV we report the short intermolecular distances. In this table the atoms of the different asymmetric units are related to the atoms of the fundamental unit as follows: i, atom at x, $1 + y$, and z; ii, atom at $1 - x$, $1/2 + y$, and $1/2 - z$; iii, atom at x, $1/2 - y$, and $1/2 + z$; iv, atom at $-x$, $1/2 + y$, and $1/2 - z$; v, atom at $-x$, $-y$, and $1 - z$.

As the values reported in Table IV clearly show, the intermolecular interactions are exclusively of the van der Waals type.

All the calculations were performed on the IBM 7090 computer of Centro Nazionale Universitario di Calcolo Elettronico (CNUCE), Pisa.

Registry No.—1-(*p*-Bromophenyl)-1,2-epoxycyclohexane, 1605-15-8.

Photochemical Rearrangements of Bicyclic 6/5-Fused Cross-Conjugated Cyclohexadienones and Related Compounds[1a]

DRURY CAINE,* ANA M. ALEJANDE,[1b] KO MING, AND WILLIAM J. POWERS, III

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

Received August 5, 1971

The ring A unsubstituted bicyclic 6/5-fused cross-conjugated cyclohexadienone **7a** and its 4-methyl (**7b**) and 6-methyl (**7c**) derivatives have been prepared and irradiated at 2537 Å in dry dioxane. The major product in each case was the corresponding bicyclo[3.1.0]hex-3-en-2-one (**8**); **7a** and **7b** also gave small amounts of linearly conjugated dienones (**9**). The bicyclo[3.1.0]hex-3-en-2-one **8b**, which has similar substitution to lumisantonin **12**, was irradiated with light of wavelength greater than 3000 Å in both dioxane and ethanol. In the former solvent it gave mainly the homoannular dienone **14**, while in the latter it afforded the 5/6-fused ethoxy ketone **19**. The photochemistry of these compounds is compared with that of related substances and possible mechanistic pathways are discussed.

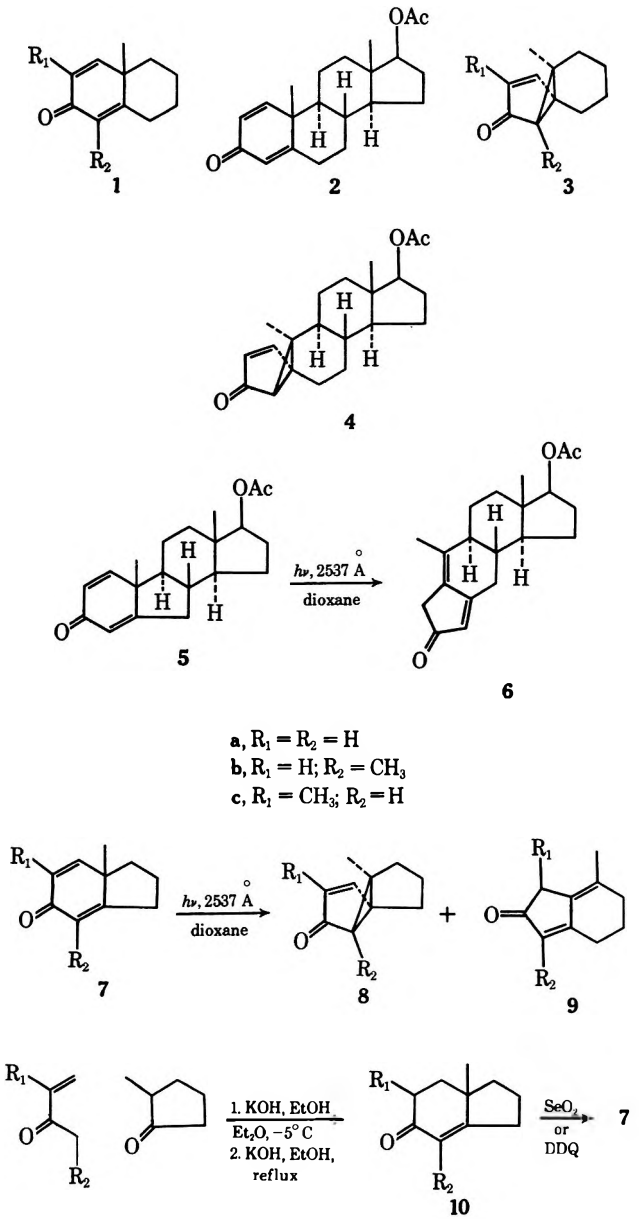
It is well known that on irradiation at 2537 Å in inert solvents such as dioxane 6/6-fused bicyclic (**1**) and steroidal cross-conjugated cyclohexadienones, for example, **2**, undergo facile rearrangements into the corresponding bicyclo[3.1.0]hex-3-en-2-ones **3** and **4**, respectively, termed lumiproducts.[2] In contrast, Jeger, Schaffner, and coworkers[3] have reported that *B*-nor-1-dehydrotestosterone acetate (**5**), having a five-mem-

(1) (a) This investigation was supported by Public Health Service Grant No. 15044 from the National Institute of General Medicine and by a NASA Institutional Grant (NsG-657). (b) National Science Foundation Undergraduate Research Participant, summer 1968.

(2) For reviews see (a) P. J. Kropp, *Org. Photo. Chem.*, **1**, 1 (1967); (b) K. Schaffner, *Advan. Photochem.*, **4**, 81 (1966).

(3) G. Bozzato, H. P. Throndsen, K. Schaffner, and O. Jeger, *J. Amer. Chem. Soc.*, **86**, 2073 (1964).

bered ring fused to the dienone chromophore, is converted directly into the linearly conjugated dienone **6** under similar conditions. In view of these results it appeared of interest to determine the behavior of model bicyclic 6/5-fused dienones such as **7**. Thus we have prepared the ring A unsubstituted indanone **7a**[4] and its 4-methyl (**7b**) and 6-methyl (**7c**) derivatives and have investigated the photochemistry of these compounds in dioxane.[5] In addition, a study of the photochemistry of the bicyclo[3.1.0]hex-3-en-2-one **8b**, the major product of irradiation of **7b**, has been carried out. From mechanistic considerations it appeared that **8b** should exhibit similar photochemical behavior to that of lumisantonin (**12**), which has been studied extensively.[2,6,7] Thus we wished to compare the photochemical behavior of **8b** with that of **12** as well as that of the model lumiproduct **3b** derived from the 6/6-fused dienone **1b**.[2a]



Dienones **7a–c** were obtained from the corresponding enones **10a–c** by dehydrogenation with either 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) or selenium dioxide. Michael addition of 2-methylcyclopentanone to the appropriate vinyl ketone was carried out using potassium hydroxide in ethanol–ether at −5°.[8] These conditions led to the isolation of mixtures of the enones and the corresponding diketone and ketol precursors, and refluxing with potassium hydroxide in ethanol was carried out to complete the aldol cyclization and dehydration reactions. The 4-methyl enone **10b** was readily converted into **7b** on treatment with DDQ in dioxane.[9] However, similar treatment of both **10a** and **10c** gave mixtures of the desired cross-conjugated dienones and the related heteroannular compounds which were difficult to separate. Dienone **7a** was obtained in low yield by treating **10a** with selenium dioxide in *tert*-butyl alcohol according to the procedure of Bloom,[4] and **7c** was obtained from **10c** in a similar manner. The three enones and dienones in this series exhibited the expected physical and spectral properties (see Experimental Section).

Irradiations of dilute solutions of **7a–c** in dry dioxane were conducted at room temperature using a Hanau NK6/20 low pressure mercury lamp which emits *ca.* 90% of its ultraviolet irradiation at 2537 Å. After removal of the solvent under reduced pressure, the photolysis mixtures were subjected to chromatography on silica gel and when necessary the products were further purified by preparative glc.[10] Lumiproducts of the type **8** were the major products of irradiation of each of the dienones, and irradiation periods which led to the optimum yields of these substances were determined by glc analysis[10] of aliquots of the photolysis mixtures taken at various time intervals. In addition to the lumiproducts, linearly conjugated dienones **9a** and **9b** were produced on irradiation of **7a** and **7b**, respectively. No product of the type **9c** could be detected from runs using **7c**. These results are summarized in Table I. The dienones **9a** and **9b** apparently

Table I

Products of Irradiation of 6/5-Fused Cross-Conjugated Cyclohexadienones in Dioxane at 2537 Å

Dienone 7	Irradiation time, min	Yield of products, % 8	9
a	75	55	21
b	120	50	~5
c	90	67	

were derived directly from **7a** and **7b** rather than being produced from the lumiproducts in a secondary process. When **8a** and **8b** were isolated and subjected to extended irradiation in dioxane at 2537 Å, products of the type **9** were not formed in significant amounts.

The lumiproducts **8a**, **8b**, and **8c** were identified readily on the basis of their uv, ir, and nmr spectral properties, which were quite close to those reported

(4) S. M. Bloom, *J. Amer. Chem. Soc.*, **81**, 4728 (1959).

(5) A preliminary account of this work has been published: D. Caine, W. J. Powers, III, and A. M. Alejandre, *Tetrahedron Lett.*, 6071 (1968).

(6) M. H. Fisch and J. H. Richards, *J. Amer. Chem. Soc.*, **90**, 1547, 1553 (1968); **85**, 3029 (1963).

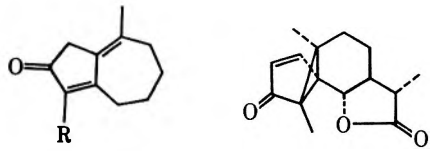
(7) (a) O. L. Chapman and L. F. Englert, *ibid.*, **85**, 3028 (1963); (b) L. Barber, O. L. Chapman, and J. D. Lassila, *ibid.*, **90**, 5933 (1968).

(8) Conditions similar to those described by Ross and Levine [N. C. Ross and R. Levine, *J. Org. Chem.*, **29**, 2341 (1964)] for the synthesis of $\Delta^{1,9}$-octalone and derivatives were employed.

(9) D. Burn, R. Kirk, and V. Petrow, *Proc. Chem. Soc.*, 14 (1960).

(10) A 10 ft × 0.25 in. column containing 15% silicone SE-30 on Chromosorb W was employed.

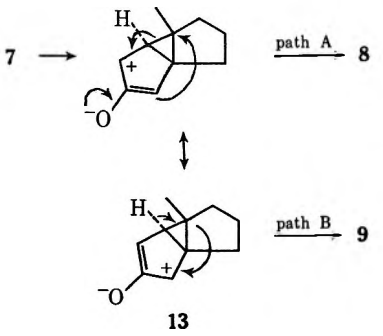
for the related homologs, **3a**,[11a] **3b**,[11b] and **3c**[11c] The linearly conjugated dienones **9a** and **9b** exhibited absorption maxima at 296 and 302 mμ, respectively, in 95% ethanol which were indicative of the structures. The uv, ir, and nmr spectra of **9a** were quite similar to those of the related 5/7-fused dienone **11** (R = H)[12] and the steroidal dienone **6**[3] having analogous structures, while those of **9b** resembled closely those of **11** (R = CH_3) which can be obtained by dehydration[13] of the 5/7-fused hydroxy ketone produced on irradiation of **1b** in aqueous acetic acid.[14]



11 **12**

The formation of lumiproducts of the type **8** presumably occurs *via* 1,4-sigmatropic rearrangements (path A, Scheme I) in dipolar cyclopropyl intermediates

SCHEME I



13

of the type **13**, generally accepted to be involved in dienone photolysis.[2] Jeger, Schaffner, and coworkers[3] have proposed that the formation of **6** from **5** involves the collapse of an intermediate analogous to **13** *via* path B, Scheme I. Since the normal steroidal dienone **2** gave only **4** under similar conditions, they suggested that because of the five-membered B ring an excessive amount of stain would be involved in the formation of a lumiproduct from **5**, and that this accounts for the intervention of the new pathway.[3] In the case of the unsubstituted model dienone **7a**, it appears that the two possible modes of rearrangement compete is indicated by the formation of both **8a** and **9a** in a 5:2 ratio. The exclusive reaction of **5** *via* a path B type process must result from the added strain due to the *trans* fusion of the C ring to the five-membered B ring in the steroidal system.[15]

The ratio of the tricyclic product to the linearly conjugated one was higher for the 4-methyl substituted dienone **7b** than for the unsubstituted case, and no linearly conjugated dienone product was observed in the irradiation of **7c**. It is possible that products of the type **9** were produced in greater amounts from the methyl-substituted compounds, but that these were rapidly converted into nonvolatile materials. It is also possible that if methyl substituents are present at either position the sigmatropic rearrangement pathway (path A) from **13** to **8** is favored relative to the unsubstituted case. However, the nature of such an effect is not immediately obvious.

While lumiproducts are relatively stable to irradiation at 2537 Å compared with their dienone precursors,[11c] previous work has shown that compounds such as **3**, **4**, and **12** undergo facile rearrangement on irradiation with light of wavelength greater than 3000 Å.[2] Thus a dilute solution of **8b** in dry dioxane was irradiated at room temperature for 90 min using a 450-W Hanovia high-pressure mercury lamp fitted with a Pyrex filter. Analysis of the photolysis mixture by glc[16] revealed the presence of one major product comprising 88% of the volatile components and *ca.* 6% each of the starting material and a minor product. Chromatography of the mixture on silica gel led to the isolation of the major product, which was identified as the homoannular dienone (**14**), in *ca.* 50% yield.

The ir and nmr spectral properties of **14** were consistent with the structure and it exhibited a uv absorption maximum at 335 mμ in 95% ethanol.[17] Catalytic hydrogenation of **14** using 10% palladium on carbon in 95% ethanol led to the isolation of its known tetrahydro derivative having a *cis* ring fusion.[18]

The minor product of irradiation of **8b** proved to be the dienone **7b**. In a separate run, **8b** was irradiated for 30 min and the photolysis mixture was analyzed by glc.[16] The mixture was found to contain **8b**, **14**, and **7b** in an approximately 2:2:1 ratio. Direct irradiation of **7b** under the same conditions as described for **8b** also led to **14**. Monitoring of the reactions by glc[16] revealed that **8b** was formed as an intermediate.

Lumisantonin **12** yields mainly a homoannular dienone **15** when irradiated at wavelengths greater than 3000 Å, and **8b** having the same substitution on the bicyclo[3.1.0]hex-3-en-2-one moiety yields a similar product. Fisch and Richards[6] have proposed that **15** is formed *via* a 1,2-methyl migration in the dipolar intermediate **16** and have presented evidence for the intervention of such a species. However, using infrared spectroscopy Chapman and coworkers[7b] have observed that the ketene **17** is formed on irradiation of **12** at 77°K and that **17** is converted into **15** thermally. These workers have suggested that the ketene pathway is likely to be involved to some degree in the photochemical conversion of **12** into **15** at room temperature.

A ketene intermediate, presumably **18**, believed to be a precursor of **14**, has been observed by infrared spectroscopy when **8b** was irradiated as the neat glass and in hydrocarbon glasses at 77°K.[19] In view of this it appeared possible that **18** might be formed and trapped

(11) (a) P. J. Kropp and W. F. Erman, *J. Amer. Chem. Soc.*, **85**, 2456 (1963); (b) P. J. Kropp, *ibid.*, **87**, 3914 (1965); (c) P. J. Kropp, *ibid.*, 4055 (1964).

(12) D. Caine and J. F. DeBardeleben, *Tetrahedron Lett.*, 4585 (1965).

(13) D. Caine and J. B. Dawson, unpublished work.

(14) (a) D. Caine and J. B. Dawson, *J. Org. Chem.*, **29**, 3108 (1964); (b) P. J. Kropp, *ibid.*, **29**, 3110 (1964).

(15) We are grateful to Dr. K. Schaffner for a private communication on this point.

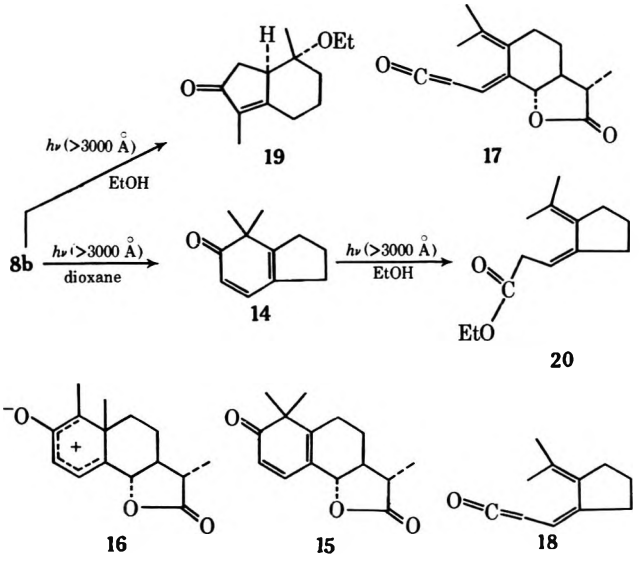
(16) A 10 ft × 0.25 in. column containing Carbowax K-20M on Chromosorb W was employed.

(17) The uv maximum for **14** is close to the predicted value of 338 mμ using the Woodward–Fieser rules. The related homoannular dienones derived from **12** and 6-epilumisantonin show uv absorption maxima at significantly shorter wavelengths.[6] Lack of planarity of the conjugated system and/or electron-withdrawing effects associated with the presence of the lactone rings in the latter compounds may account for this.

(18) J. A. Marshall, N. H. Andersen, and P. C. Johnson, *J. Amer. Chem. Soc.*, **89**, 2748 (1967).

(19) We are indeed grateful to Professor O. L. Chapman for carrying out this experiment and interpreting the results.

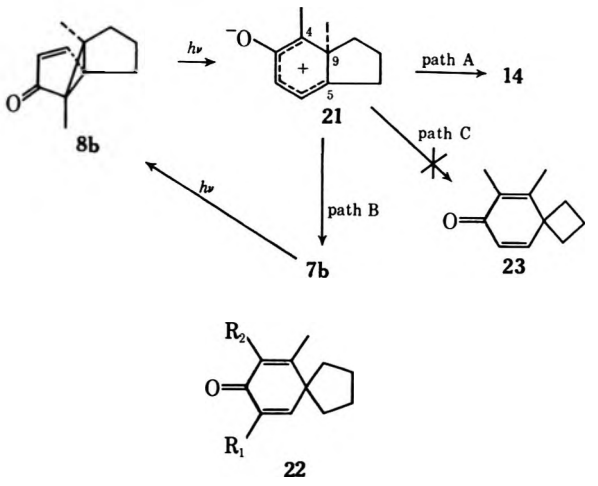
at room temperature if **8b** were irradiated in a nucleophilic solvent such as ethanol. However, when **8b** was irradiated under the conditions described above except substituting absolute ethanol for dioxane, the only photoproduct that could be isolated proved to be the ethoxy ketone **19** which was identified on the basis of its spectral properties. The ethanol adduct of the proposed ketene **18**, *i.e.*, **20**, could not be detected in this run. For reference purposes a sample of **20** was prepared by irradiation of **14** in absolute ethanol using the light source described above. The diene ester exhibited the expected nmr spectral properties which in the appropriate regions were very similar to those reported for photosantonic acid.[20] Also, compound **19** was obtained when **7b** was irradiated under the conditions described for **8b**. Apparently, in ethanol **8b** rearranges essentially completely into **7b** which is further converted into **19** *via* attack of the solvent on an intermediate analogous to **13**. Additional work on the photochemical behavior of dienones **7a–c** in nucleophilic solvents is in progress and will be reported later.



The behavior observed for **8b** in dioxane appears to be most readily explained by considering that light excitation leads to cleavage of the 4,5 bond to produce, after electron demotion, the dipolar species **21** (Scheme II). As pointed out above, this type of pathway has been proposed in the conversion of **12** into **15**[6] and analogous pathways have been invoked to explain the photochemistry of number to bicyclo[3.1.0]hex-3-en-2-ones derived from fused ring cross-conjugated cyclohexadienones.[2] In **21** a 1,2-methyl shift from C-9 to C-4 (path A) would give rise of **14**, while a similar shift from C-9 to C-5 (path B) would give **7b**. A minor rearrangement product of **12** which could have arisen *via* a path B type process has been tentatively identified,[6] and the exclusive formation of a cross-conjugated dienone, considered to arise by this type of pathway, has been reported[21] for the irradiation of the lumiproduct derived from 17β-hydroxy-1,4,9(11)-androstrien-3-one.

The results after short irradiation time can be explained by considering that the path A and

Scheme II



path B modes of reaction of **21** compete, with the former being somewhat favored. On extended irradiation **14** greatly predominates, since **7b** is photochemically labile, being reconverted into **8b** (Scheme II).

The behavior of **8b** in ethanol also can be explained in terms of **21**, if one considers that in going from the aprotic solvent dioxane to the protic one path B becomes greatly favored. Some rather striking solvent effects have been observed in other lumiproduct rearrangements.[2a] In **21** path A rearrangement may be favored in dioxane because in the nonpolar solvent charge separation must be minimized in the dipolar species. However, in ethanol **21** may be protonated on oxygen, giving a mesoionic species in which other factors could favor path B rearrangement.[22]

No significant amounts of products which could be considered to be derived from 1,2-methylene migration (path C) in **21** were observed. Kropp[2a,11] has reported that irradiation of lumiproducts (**3**) in various media leads to photoproducts which are presumably formed by way of spirodienones (**22**). A path C type rearrangement in a species analogous to **21** would lead to **23**. However, path C products are apparently completely eliminated as the size of the ring attached to the bicyclo[3.1.0]hex-3-en-2-one moiety is reduced from six to five members. Kropp[2a,11] has suggested that a methylene shift does not take place in the rearrangement of **12**, because a spirodienone having two trans-fused five-membered rings would be highly strained. The work of Schuster and Fabian,[23] which showed that path A and path C products arise on irradiation of 6-epilumisantonin, supports this suggestion. A spiro[5.3]nonane derivative such as **23** would be expected to be more strained than **22**. Thus the photochemical behavior of **8b** appears to provide excellent additional support for Kropp's hypothesis.

Although a ketene intermediate appears to be ruled out in the irradiation of **8b** in ethanol at room temperature, the results obtained when **8b** was irradiated at 77°K make it necessary to consider the possibility that the ketene pathway is involved in the formation of **14** in the inert solvent, dioxane, at room temperature. Indeed, as has been suggested for the case of lumisantonin,[7b] pathways involving the dipolar intermediate

(20) E. E. vanTamelen, S. H. Levin, G. Brenner, J. Wolinsky, and P. E. Aldrich, *J. Amer. Chem. Soc.*, **81**, 1666 (1959).

(21) I.j. Lorenc, M. Miljkovic, K. Schaffner, and O. Jeger, *Helv. Chim. Acta.*, **49**, 1183 (1966).

(22) H. E. Zimmerman, R. Keese, J. Nasielski, and J. S. Swenton, *J. Amer. Chem. Soc.*, **88**, 4895 (1966).

(23) D. I. Schuster and A. C. Fabian, *Tetrahedron Lett.*, 4093 (1966).

21 and the ketene 18 may compete when the photolysis is carried out in the inert medium. Also, the possibility exists that a cyclopropanone[24] precursor to 21 intervenes, although the irradiation at 77°K did not provide evidence on this point.[19]

Experimental Section[25]

7,7a-Dihydro-7a-methyl-5(6*H*)-indanone (10a).—Compound 10a was prepared by a method similar to that reported by Ross and Levine.[8] A dried 500-ml three-necked round-bottom flask equipped with a thermometer, dropping funnel and magnetic stirring bar was placed under positive nitrogen flow. Anhydrous ether (200 ml) was added to the flask and a solution of 2.8 g (0.05 mol) of potassium hydroxide in 20 ml of absolute ethanol was added. The mixture was cooled to −7° with an ice–salt bath and 27.40 g (0.28 mol) of 2-methylcyelopentanone was added. A solution of 9.0 g (0.129 mol) of methyl vinyl ketone in *ca.* 50 ml of anhydrous ether was added at a rate sufficiently slow to keep the reaction temperature at or below −5°. When the addition was complete, the mixture was stirred for 45 min at −5°, then for 45 min with the ice–salt bath removed. The mixture was poured into 200 ml of 10% hydrochloric acid and the layers were separated. The aqueous layer was saturated with salt and extracted with two 50-ml portions of ether. The combined organic layers were dried over magnesium sulfate and the solvents were removed under reduced pressure. Distillation of the residue gave 7.1 g of 2-methylcyclopentanone (26% recovery), bp 41–42° (15 mm), and 14.04 g of a mixture, bp 68–105° (0.25 mm), which appeared by ir and glc[10] to consist of 10a plus its precursor diketone and ketol. This material was dissolved in 200 ml of 10% ethanolic potassium hydroxide and refluxed under nitrogen for 30 min. The mixture was cooled to room temperature and neutralized with glacial acetic acid. The solvents were removed under reduced pressure, water was added to dissolve the potassium acetate formed in the neutralization, and the layers were separated. The aqueous layer was extracted with two 25-ml portions of ether and the combined organic layers were dried over magnesium sulfate. The solvents were removed under reduced pressure and the product was distilled through a short path distilling head to give 10.9 g (57%) of 10a, bp 65–67° (0.30 mm) [lit.[4] 112° (4 mm)].

6,7a-Dimethyl-7,7a-dihydro-5(6*H*)-indanone (10c).—In a dried 500-ml three-necked round-bottom flask, fitted with a magnetic stirring bar, dropping funnel, and thermometer and under positive nitrogen flow, a solution of 2.8 g (0.02 mol) of potassium hydroxide in 20 ml of absolute ethanol was dissolved in *ca.* 200 ml of anhydrous ether. The reaction mixture was cooled to −5° with an ice–salt bath and 29.4 g (0.334 mol) of 2-methylcyclopentanone was added. Methyl isopropenyl ketone (14 g, 0.167 mol) in *ca.* 50 ml of anhydrous ether was added dropwise with stirring, while the reaction mixture temperature was maintained at −5°. The ice bath was removed and the mixture was stirred for 45 min. The mixture was poured into 200 ml of 10% hydrochloric acid. The layers were separated and the aqueous layer was extracted with two 25-ml portions of ether. The combined organic layers were dred with magnesium sulfate and the solvents were removed under reduced pressure. Distillation of the residue gave 5.1 g of 2-methylcyclopentanone (17%), bp 41–43° (15 mm). Further distillation gave 18.0 g of tractable material, bp 72–95° (0.07 mm). This was dissolved in 200 of 10% ethanolic potassium hydroxide and refluxed with stirring under nitrogen for 75 min. The mixture was cooled and neutralized with glacial acetic acid, and the solvents were removed under reduced pressure. Water was added to dissolve the potassium acetate formed, the layers were separated, and the aqueous layer was extracted with two 25-ml portions of ether. The combined organic layers were dried over magnesium sulfate. The solvents were removed at reduced pressure and the resulting yellow oil was distilled to yield 12.7 g (46%) of 10c, bp 61° (0.05 mm). Compound 10c exhibited the following spectral properties: uv max (95% EtOH) 238 mμ (ε 10,700); ir (CCl_4) 5.97 (conjugated C=O) and 6.32 μ (C=C); nmr (CCl_4) δ 5.65 (m, 1 H), 1.25–2.87 (broad absorption, 9 H), 1.19 (s, 3 H), 1.07 (d, 3 H, J = 7.0 Hz). *Anal.* Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.20; H, 9.84.

4,7a-Dimethyl-7,7a-dihydro-5(6*H*)-indanone (10b).—A dried 1000-ml three-necked round-bottom flask equipped with a dropping funnel, magnetic stirring bar, and thermometer was placed under positive nitrogen flow. Anhydrous ether (400 ml) was added to the flask and a solution of 4.5 g (0.08 mol) of potassium hydroxide in 30 ml of absolute ethanol was added. The mixture was cooled, with stirring to −5° by means of an ice–salt bath, and 52.0 g (0.53 mol) of 2-methylcyclopentanone was added. A solution of 20.5 g (0.244 mol) of ethyl vinyl ketone in *ca.* 150 ml of anhydrous ether was added dropwise while the temperature of the reaction mixture was maintained at −5° or below. Then stirring was continued for an additional 1 hr with the cooling bath removed. The mixture was poured into 300 ml of 10% hydrochloric acid, and the layers were separated. The aqueous layer was extracted with two 25-ml portions of ether, and the combined organic layers were dried over magnesium sulfate. The solvents were removed under reduced pressure. Distillation using a short-path head gave 2-methylcyclopentanone, 25.8 g (49%), bp 43–44° (21 mm), followed by 20.1 g of 10b and its diketone and ketol precursor, bp 99–113° (1.0 mm). This material was dissolved in 300 ml of 10% ethanolic potassium hydroxide and refluxed for 30 min under nitrogen. The mixture was cooled to room temperature and neutralized with glacial acetic acid, and the solvents were removed under nitrogen pressure. Water was added to dissolve the potassium acetate, the layers were separated, and the aqueous layer was extracted with two 25-ml portions of ether. The combined organic layers were dried over magnesium sulfate and the solvents were removed under reduced pressure. Distillation of the resulting yellow oil through a short path head gave 12.7 g (33%) of 10b, bp 87° (0.85 mm), which exhibited the following properties: uv max (95% EtOH) 247 mμ (ε 13,700); ir (CCl_4) 5.99 (unsaturated C=O), 6.20 μ (C=C); nmr (CCl_4) δ 1.7–2.91 (broad absorption, 10 H), 1.59 (s, 3 H). *Anal.* Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.84. Found: C, 80.21; H, 10.00.

7a-Methyl-5(7a*H*)-indanone (7a).—Compound 7a was prepared by the method of Bloom.[4] A dried 1000-ml three-necked round-bottom flask equipped with a reflux condenser and magnetic stirring bar was placed under positive nitrogen flow and 750 ml of freshly distilled *tert*-butyl alcohol and 7 ml of glacial acetic acid were introduced. Freshly sublimed selenium dioxide, 8.4 g (0.076 mol), was added and the mixture was stirred until the selenium dioxide dissolved. Enone 10a, 11.3 g (0.075 mol), was added and the mixture was refluxed, with stirring, for 46 hr. The mixture was concentrated to *ca.* 200 ml by distillation of solvents under nitrogen. Selenium metal was removed by several filtrations, with suction, and the remaining solvents were removed under nitrogen pressure. The resulting black viscous mass was taken up in 250 ml of ether and filtered with suction. The ethereal solution was washed with five 50-ml portions of 5% sodium hydroxide and dried with magnesium sulfate, and the solvents were removed under nitrogen pressure. Distillation through a short path head gave 2.3 g (21%) of 7a, bp 70–71° (0.3 mm) [lit.[4] 69–70° (0.65 mm)]. The nmr spectrum of this compound had not been previously reported. It showed absorptions at δ (CCl_4) 7.02 (d, 1 H, J_{AB} = 9.5 Hz), 5.99 (d of d, 1 H, J_{AB} = 9.5 Hz, J_{BX} = 2.0 Hz), 5.89 (m, 1 H), 1.32–3.08 (broad absorption, 6 H), 1.21 (s, 3 H).

6,7a-Dimethyl-5(7a*H*)-indanone (7c).—Dienone 7c was prepared by a modification of the method of Bloom.[4] A dried 100-ml three-necked round-bottom flask equipped with a reflux condenser and magnetic stirring bar was placed under positive nitrogen flow. Dried, freshly distilled *tert*-butyl alcohol (75 ml) was introduced and 2.45 g (0.022 mol) of freshly sublimed selenium dioxide and 7 ml of glacial acetic acid was added. The mixture was stirred until the selenium dioxide dissolved and 3.2 g (0.02 mol) of 10c was added. The mixture was refluxed with stirring for 30 hr. The mixture was cooled to room temperature, and the selenium metal was removed by filtration with suction. The solvents were removed under reduced pressure, leaving a viscous black mass that was distilled through a short path head to

(24) L. Barber, O. L. Chapman, and J. P. Lassila, *J. Amer. Chem. Soc.*, **91**, 3664 (1969).

(25) Melting and boiling points are uncorrected. Infrared spectra were obtained using a Perkin-Elmer Model 457 or 137 infrared spectrophotometer. Ultraviolet spectra were determined using a Cary Model 14 recording spectrophotometer using 1-cm matched quartz cells. Nmr spectra were determined at 60 MHz with a Varian A-60 spectrometer. Signals are reported in parts per million (δ), downfield from internal tetramethylsilane. All compounds gave appropriate parent ions in their mass spectra at 70 eV using a Varian M-66 spectrometer. Vapor phase chromatography was performed using an Aerograph A-90-P3 with helium as the carried gas. Microanalyses were obtained by Galbreath Laboratories, Inc., Knoxville, Tenn.

give 1 g of a brown oil, bp 65–69° (0.65 mm). Analysis by glc[10] showed that the oil consisted of *ca.* 60% **10c** and 40% unreacted **7c**. The mixture was chromatographed on silica gel. Elution with 300 ml of hexane and 450 ml of 5% ether–hexane gave recovered **10c** mixed with a small amount of the desired compound **7c**. Further elution with 100 ml of 5% ether–hexane and 100 ml of ether gave 519 mg (16%) of **7c** which exhibited the following spectral properties: uv max (95% EtOH) 244 mμ (ε 12,900); ir (CCl_4) 5.97 (conjugated C=O) and 6.14 μ (C=C); nmr (CCl_4) δ 6.72 (q, 1 H, J = 1.5 Hz), 5.88 (t, 1 H, J = 1.8 Hz), 1.41–2.92 (broad absorption, 6 H), 1.79 (d, 3 H, J = 1.5 Hz), and 1.18 (s, 3 H). *Anal.* Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.54; H, 8.91.

4,7a-Dimethyl-5(7a*H*)-indanone (7b).—Compound **7b** was prepared by a modification of the method of Burn, Kirk, and Petrow.[9] A 1000-ml three-necked round-bottom flask equipped with a reflux condenser and magnetic stirring bar was placed under positive nitrogen flow. Freshly distilled anhydrous *p*-dioxane (500 ml) was charged into the flask and 9.35 g (0.0413 mol) of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) was added. The mixture was stirred until the DDQ dissolved, and 6.60 g (0.0403 mol) of **10b** was added. The mixture was refluxed with stirring for 30 hr. The solution was cooled to room temperature, and the solid 2,3-dichloro-5,6-dicyanohydroquinone (DDHQ) was collected by filtration with suction. The mixture was concentrated to *ca.* 50 ml by removal of solvents under reduced pressure. The mixture was cooled to room temperature and filtered with suction to remove the remaining DDHQ. It was then poured onto a loosely packed solumn of 70 g of alumina and eluted under pressure with 500 ml of benzene. The solvents were removed under reduced pressure and the resulting yellow oil was distilled through a short path head to give 3.92 (60%) of **7b**, bp 88° (0.5 mm), which exhibited the following spectral properties: uv max (95% EtOH) 243 mμ (ε 11,900); ir (CCl_4) 6.01 (conjugated C=O), 6.21 μ (C=C); nmr (CCl_4) δ 6.99 (d, 1 H, J = 9.5 Hz), 6.02 (d, 1 H, J = 9.5 Hz), 1.15–2.83 (broad absorption, 6 H), 1.72 (s, 3 H), and 1.17 (s, 3 H). *Anal.* Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.29; H, 8.66.

Irradiation of 7a-methyl-5(7a*H*)-indanone (7a) in Dioxane.—The dienone **7a**, 570 mg (0.0038 mol), was dissolved in 300 ml of anhydrous dioxane and irradiated with a Hanau NK 6/20 lamp for 75 min. Using a stream of dry nitrogen, the solution was agitated constantly for 10 min prior to and during the irradiated period. The solvents were removed under reduced pressure, and the crude mixture was chromatographed on silica gel. Elution with 5% ether–hexane (1500 ml) gave 312 g (55%) of 7a-methyl-3,7a-dihydro-3a,7-cyclo-6(7a*H*)-indanone (**8a**) which was greater than 90% pure by glc.[10] The analytical sample was collected by preparative glc[10] and showed uv max (95% EtOH) 236 mμ (ε 6300) and 271 (4200); ir (CCl_4) 5.86 μ (C=O); nmr (CCl_4) δ 7.28 (d, 1 H, J_{AB} = 5.5 Hz, C-7 H), 5.77 (d of d, 1 H, J_{AB} = 5.5, J_{BX} = 0.8 Hz, C-6 H), 1.47–2.27 (broad absorption, 7 H), and 1.68 (s, 3 H, C-7a CH_3). *Anal.* Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found; C, 80.99; H, 8.23.

Further elution with 10% ether–hexane (1000 ml) gave a small amount of starting material, and elution with ether (200 ml) gave 120 mg (21%) of the linearly conjugated dienone **9a** which was greater than 90% one component by glc.[10] The analytical sample was collected by preparative glc[10] and showed uv max (95% EtOH) 296 mμ (ε 19,000); ir (CCl_4) 5.86 (C=O), 5.97 (C=C), and 6.30 μ (C=C); nmr (CCl_4) δ 5.69 (s, 1 H, C-1 H, 2.72 (s, 2 H, C-3 CH_2), 1.53–2.90 (broad absorption, 6 H), and 1.81 (s, 3 H, C-4 CH_3). *Anal.* Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 80.71; H, 8.47.

Irradiation of 4,7a-Dimethyl-5(7a*H*)-indanone (7b) in Dioxane.—The dienone **7b**, 222 mg (0.0013 mol), was dissolved in freshy distilled dioxane and irradiated for 120 min using a Hanau NK 6/20 lamp. Using a stream of dry nitrogen, the solution was agitated constantly for 10 min prior to and during the irradiation period. Analysis of the mixture by glc[10] showed the presence of starting material and two other volatile components in a *ca.* 2:7:1 ratio. The mixture was subjected to chromatography on silica gel. Elution with hexane (900 ml) gave 110 mg (50%) of **8b**, bp 75–80° (bath temperature) (0.2 mm), which showed uv max (95% EtOH) 247 mμ (ε 4820) and 274 (2900); ir ($CHCl_3$) 5.88 (C=O) and 6.36 μ (C=C); nmr (CCl_4) δ 7.28 (d, 1 H, J_{AB} = 5.5 Hz, C-7 H), 5.74 (d, 1 H, J_{AB} = 5.5 Hz, C-6 H), 1.56–2.80 (broad absorption, 6 H), 1.18 (s, 3 H, C-4 CH_3), and 1.08 (s, 3 H, C-7a CH_3). *Anal.* Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.24; H, 8.40.

Further elution with 10% ether–hexane (200 ml) gave a small amount of starting material, and elution with more 10% ether–hexane gave *ca.* 12 mg (*ca.* 5%) of a solid material having an identical glc[10] retention time with the minor component of the photolysis mixture. This quantity of material was insufficient for complete characterization, but in a separate larger scale run, this component was collected directly by preparative glc.[10] The product identified as **9b** showed mp 85–88°; uv max (95% EtOH) 302 mμ (ε 14,000); ir (CCl_4) 5.99 (C=O) and 6.22 μ (C=C); nmr ($CDCl_3$) δ 2.80 (s, 2 H, C-3 CH_2), 2.6–1.9 (broad absorption, 6 H), 1.80 (s, 3 H, C-1 CH_3), and 1.72 (s, 3 H, C-4 CH_3). *Anal.* Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.28; H, 8.78.

Irradiation of 6,7a-Dimethyl-5(7a*H*)-indanone (7c) in Dioxane.—The dienone **7c**, 427 mg (0.0026 mol), was dissolved in 250 ml of anhydrous dioxane and irradiated with a Hanau NK 6/20 lamp for 90 min. Using a stream of dry nitrogen, the solution was agitated constantly for 15 min prior to and during the irradiation period. The reaction was monitored by glc[10] and **7c** had been converted into a single volatile photoproduct after this time. The solvent was removed under reduced pressure, and the crude product was subjected to chromatography on silica gel. Elution of the column with hexane (275 ml) followed by 25% ether–hexane (250 ml) gave 286 mg (67%) of 5,7a-dimethyl-3a,7-cyclo-6(7a*H*)-indanone (**8c**), bp 70–80° (bath temperature) (0.2 mm). The analytical sample was purified by preparative glc[10] and showed the following properties: uv max (95% EtOH) max 235 mμ (ε 4630) and 283 (2120); ir (CCl_4) 5.86 (C=O) and 6.18 μ (weak shoulder, C=C), nmr (CCl_4) δ 6.84 (m, 1 H, C-7 H), 1.45–2.33 (broad absorption, 7 H), 1.66 (d, J = 1.5 Hz, 3 H, C-6 CH_3), and 1.11 (s, 3 H, C-7a CH_3). *Anal.* Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.16; H, 8.90.

Irradiation of 7,7a-Dimethyl-3a,7a-dihydro-3a,7-cyclo-6(7*H*)-indanone (8b) in Dioxane.—A solution prepared from 300 mg of the bicyclo[3.1.0]hex-3-en-2-one **8b** in 200 ml of anhydrous dioxane was irradiated for 90 min using a 450-W Hanovia high-pressure lamp fitted with a Pyrex filter. Using a stream of dry nitrogen the solution was constantly agitated for 15 min prior to and during the irradiation period. Removal of the solvent under reduced pressure yielded a mixture which by glc analysis[16] was shown to contain one major component and two minor components in an approximately 88:6:6 ratio. The retention time of one of the minor components was identical with that of the starting material. Chromatography of the mixture on silica gel using hexane as the eluting solvent led to the isolation of 151 mg (50%) of the major photoproduct, 4,4-dimethyl-5(4*H*)-indanone (**14**), as a light yellow oil. Compound **14** showed uv max (95% EtOH) 335 mμ (ε 3800); ir (CCl_4) 6.00 (C=O) and 6.12 μ (C=C); nmr (CCl_4) 6.86 (d, 1 H, J_{AB} = 10 Hz), 5.79 (d, 1 H, J_{AB} = 10 Hz), 1.76–2.75 (broad absorption, 6 H), and 1.16 (s, 6 H). *Anal.* Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.52; H, 8.68.

A solution of 102 mg of **14** in 60 ml of 95% ethanol was shaken with 17 mg of 10% palladium on carbon in a hydrogen atmosphere for 16 hr. Removal of the catalyst by filtration and removal of the solvent under reduced pressure gave the cis-fused tetrahydro derivative of **14** as a colorless oil, ir (CCl_4) 5.86 μ. This material was not purified, but ws converted directly into its semicarbazone derivative, mp 203–206° (lit.[18] 207–208°).

The second minor product showed a glc[16] retention time identical with that of **7b**. In a run identical with that described above, **8b** was irradiated for 30 min. After vaporization of the solvents, glc analysis[16] of the photolysis mixture showed that it contained **8b**, **14**, and **7b** in an approximately 2:2:1 ratio. Samples of **8b**, **14**, and **7b** were collected by preparative glc[16] and showed spectral properties identical with those of authentic materials.

Irradiation of 4,7a-Dimethyl-5(7a*H*)-indanone (7b).—A solution of 650 mg of **7b** was irradiated under identical conditions with those described for **8b**. The reaction progress was monitored by glc analysis[16] of aliquots of the photolysis mixture taken at various time intervals. After a short irradiation time **8b** was the major product, but on continued irradiation a peak corresponding to **14** began to develop. After a total irradiation period of 1.5 hr, **14** was the major volatile component in the photolysis mixture.

Irradiation of 8b and 7b in Absolute Ethanol.—A solution of 420 mg (0.0026 mol) of **8b** in 250 ml of absolute ethanol was irradiated for 1 hr using a 450-W Hanovia high-pressure mercury lamp in a Pyrex probe. During the photolysis the mixture was

agitated with a stream of dry nitrogen. Removal of the solvents under reduced pressure and glc analysis[16] of the crude mixture showed the presence of the starting material and a major product in a *ca.* 23:77 ratio. Only traces of other volatile products were observed. Distillation of the mixture gave a fraction, bp 75–85° (bath temperature) (0.2 mm), which proved to be mainly starting material. A higher boiling fraction, bp 100–110° (bath temperature) (0.2 mm), weighing 300 mg (55%), was collected. This fraction contained essentially one component, which was identified as the 5/6-fused ethoxy ketone **19**: uv max (95% EtOH) 242 mμ (ε 10,600); ir (CCl_4) 5.91 (C=C) and 6.08 μ (C=C); nmr (CCl_4) δ 3.45 (q, 2 H, J_{AX} = 7 Hz, OCH_2CH_3), 2.9–1.6 (broad absorption, 9 H), 1.63 (broad s, 3 H, C-1 CH_3), 1.10 (t, 3 H, J = 7 Hz, OCH_2CH_3), and 0.88 (s, 3 H, C-4 CH_3). *Anal.* Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.72; H, 9.79.

Irradiation of **7b** under identical conditions with those described above gave **19** as the sole photoproduct.

Irradiation of **14** in Absolute Ethanol.—Dienone **14** (380 mg) in 250 ml of absolute ethanol ws irradiated under identical conditions with those described above for **8b**. Removal of the solvent under reduced pressure gave 400 mg of crude liquid which on the basis of its spectral properties appeared to be largely the unconjugated diene ester **20**. Attempted purification of the compound by preparative glc[16] led to extensive isomerization to a mixture of **20** and the corresponding cis- and trans-conjugated diene esters. However, an analytical sample of **20** could be collected from the mixture. The sample showed ir (CCl_4) 5.74 (ester C=O) and 6.06 μ (conjugated diene); nmr (CCl_4) δ 5.42 (broadened t, J = 6 Hz, 1 H, vinyl H), 4.17 (q, J = 7 Hz, 2 H, $OCHCH_3$), 2.97 (broadened d, J = 6 Hz, 2 H, O=CCH_2CH=), 1.70 (s, 3 H, CH_3C=), 1.65 (s, 3 H, CH_3C=), and 1.25 (t, 3 H, OCH_2CH_3). *Anal.* Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, C, 75.00; H, 9.45.

Registry No.—**7a**, 22416-99-5; **7b**, 22417-00-1; **7c**, 22417-01-2; **8a**, 22417-02-3; **8b**, 22417-03-4; **8c**, 22417-04-5; **9a**, 22417-05-6; **9b**, 33070-69-8; **10a**, 17299-55-7; **10b**, 33070-71-2; **10c**, 33070-72-3; **14**, 33070-73-4; **19**, 33065-85-9; *cis*-**20**, 33065-86-0; *trans*-**20**, 33065-87-1; 2-methylcyclopentanone, 1120-72-5.

Photocyclizations. II. Synthesis of Iminoethanophenanthridine (Seven-Membered Ring) Homologs[1]

HELEN H. ONG AND EVERETTE L. MAY*

National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland 20014

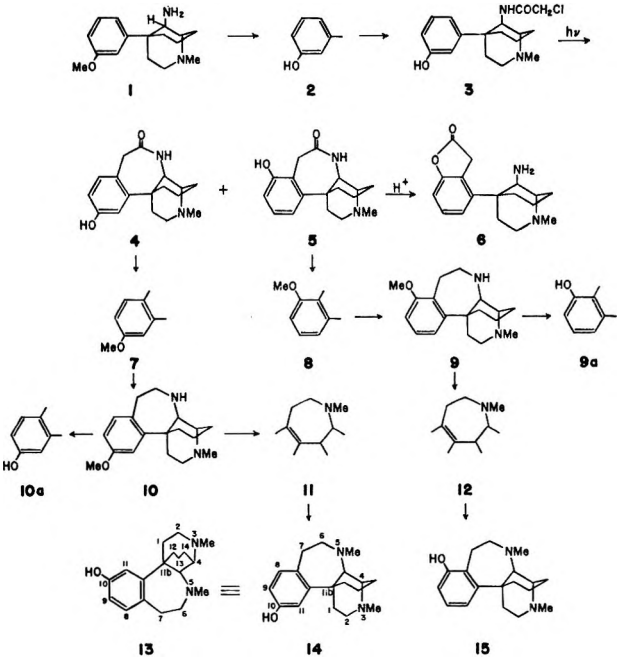
Received August 18, 1971

Photolysis of 9-*cis*-chloroacetamino-5-(*m*-hydroxyphenyl)-2-methyl-2-azabicyclo[3.3.1]nonane (**3**) has given both ortho and para ring closure to propanopyridobenzazepinones, **5** and **4**, whose structures were deduced from mass and nmr spectral data and by chemical evidence. The *O*-acetyl derivative of *o*-hydroxy compound **5** formed more slowly than that of **4**. Furthermore, acid treatment of **5** caused lactam ring opening with the formation of a new lactone ring (*cf.* **6**), in effect N → O acyl migration. Methylation of **4** and **5** followed by diborane reduction gave homophenanthridines **10** and **9**, respectively, which were N-methylated then O-demethylated to **14** and **15**.

In paper I of this series[2] we reported the synthesis of 4,5-dihydro-1*H*-naphth[1,8-de]azocin-2(3*H*)-one by irradiation of 1-(2-chloroacetamino)naphthalene. This communication is concerned with the photocyclization of a chloroacetamino group attached to a rigid azabicyclononane system with attack at both the ortho and para positions of a neighboring phenolic ring.[3] The results described here indicate a broadened scope and utility for this reaction especially toward the synthesis of complex heterocyclic systems.

The starting amine **1**[4] was hydrolyzed to **2** with boiling 48% hydrobromic acid. Conversion of **2** to the chloroacetamino compound **3** was effected in high yield by N,O dichloroacetylation with choroacetic anhydride in an aprotic solvent (potassium carbonate) and selective saponification.[5]

Amide **3**, irradiated in dilute aqueous solution, was completely consumed during 90 min to give two products. Preliminary mass spectral data (*m/e* 286 and 243[6] and no higher peaks) and proximate R_f values (for the sublimed mixture) in several solvent systems[7] were



(1) These compounds are named benzazepines in the Experimental Section in accord with Chemical Abstracts recommendations.

(2) H. H. Ong and E. L. May, *J. Org. Chem.*, **35**, 2544 (1970).

(3) Previously reported photocyclizations of *N*-chloroacetyl compounds (see ref 2 and papers cited therein) have included no examples of alicyclic amines. Furthermore, this appears to be the first record of closure to the ortho position in a monophenolic compound.

(4) H. H. Ong and E. L. May, *J. Heterocycl. Chem.*, **8**, 1007 (1971).

(5) Low yields of **3** (1 mol of chloroacetic anhydride) or extensive quaternization of **2** (with excess reagent) were obtained when the procedure of O. Yonemitzu, T. Tokuyama, M. Chaykovsky, and B. Witkop, *J. Amer. Chem. Soc.*, **90**, 776 (1968), was used.

(6) This is probably due mainly to loss of CH_2NCH_3, but loss of –NHCO– may also contribute; *cf.* A. M. Duffield, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, **86**, 5536 (1964).

(7) Silica gel GF plates: system I, $MeNO_2$–AcOH–H_2O (90:28:12), R_f 0.41, 0.35; II, $CHCl_3$–Et_3N (5:1), R_f 0.07, 0.18, for example.

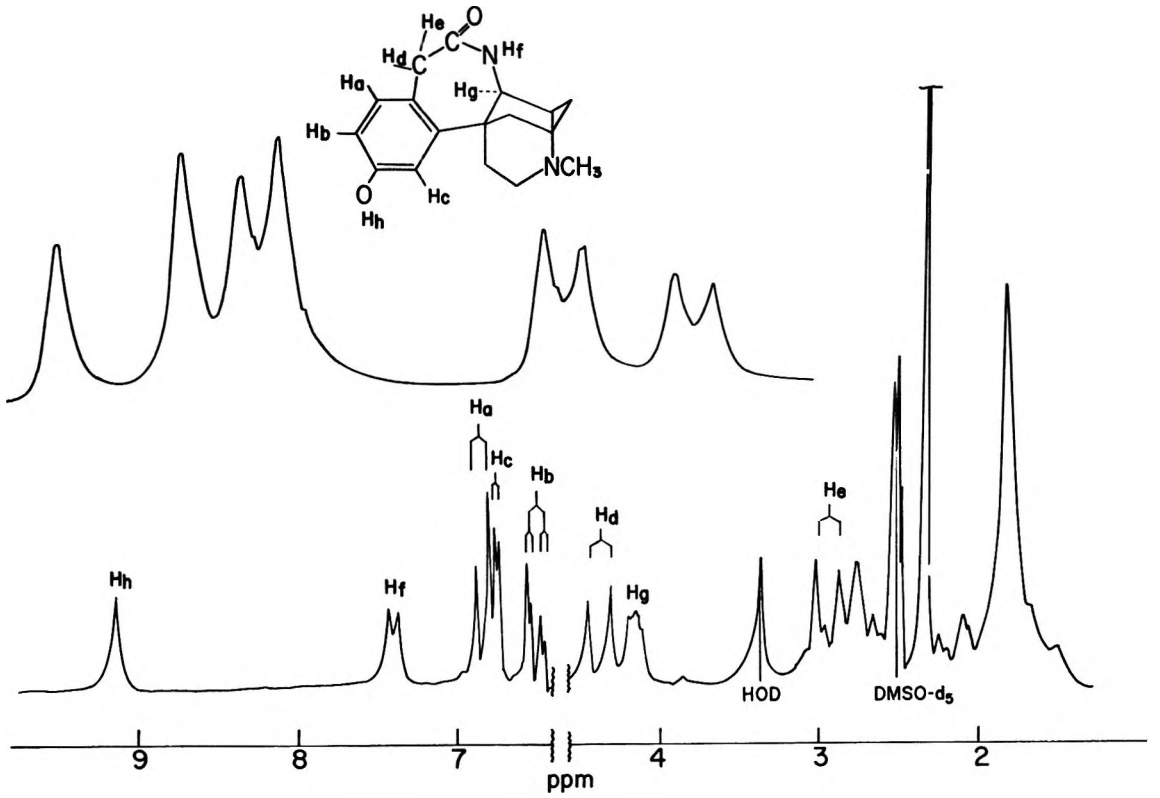
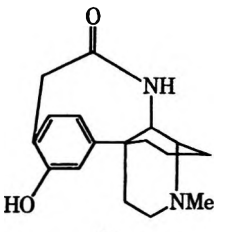


Figure 1.—Nmr spectrum of 4 measured at 100 MHz in DMSO-d_6. Multiplets arising from the aromatic protons are shown amplified and expanded (ten times) just above the main spectrum.

consistent with isomeric structures **5** and **4** (ortho and para ring closure through loss of hydrogen chloride) as the principal products.

Separation of **4** from **5** was effected by fractional crystallization in ethanol. Compound **4**, the more soluble of the two, was assigned the empirical formula $C_{17}H_{22}N_2O_2$ based on its elementary and mass spectral analyses. Its ir spectrum exhibited a carbonyl stretching frequency at 1655 cm^{-1}, expected for a medium-sized lactam, and its nmr spectrum established the site of cyclization as para to the phenolic hydroxyl group. A 100-MHz pattern of **4** taken in DMSO-d_6 (Figure 1) showed the presence of three aromatic protons: a doublet centered at δ 6.82 (J_{ab} = 8.0 Hz), a second doublet centered at δ 6.74 (J_{bc} = 2.5 Hz), and a quartet centered at δ 6.51. The splitting pattern and coupling constants are such that they are reconcilable only with structure(s) incorporating a 1,2,4-trisubstituted benzene, as in **4**. The only other possible structure consistent with the foregoing spectral data is **16**, which was ruled out on steric considerations. The nonequivalent nature of the two methylene protons adjacent to the carbonyl group (H_d at δ 4.36 and H_e at δ 2.96, doublets, $|J|$ = 14 Hz)[8] should not be too surprising in view of the rigidity and lack of symmetry of **4**. The considerable difference in chemical shift between H_d and H_e could be partly due to the anisotropic effect exerted by the nearby aromatic system; H_d is deshielded by being in or near the aromatic ring, whereas H_e is shielded by being above or under the π plane.[9,10] Effects of other magnetically anisotropic groups, such as the carbonyl double bond and the alicyclic ring, are also not to be excluded.



16

Compound **4** was readily converted to its *O*-acetyl derivative, the nmr spectrum of which (100 MHz, $CDCl_3$) further confirmed the 1,2,4 pattern of the aromatic protons: two doublets at δ 7.06 (J = 8.5 Hz) and 7.02 (J = 2.4 Hz) and a quartet at δ 6.85. In addition, the phenolic proton signal at δ 9.12 vanished while a sharp singlet due to the acetyl group appeared at δ 2.44.

The less soluble photoproduct, **5**, is also assigned the empirical formula $C_{17}H_{22}N_2O_2$ on the basis of elemental analyses and mass spectral data. Its ir spectrum exhibited a carbonyl frequency of 1665 cm^{-1}, somewhat higher than the corresponding band observed with **4**. The position of ring closure was likewise established by nmr spectroscopy to be ortho to the phenolic hydroxyl group and the alicyclic substituent.

A 100-MHz spectrum of **5** taken in DMSO-d_6 showed a pseudo-AMX pattern for the three aromatic protons, each appearing as a quartet (see Figure 2), indicative of three adjacent protons each of which is coupled unevenly to two others. The "double doublet" at lowest field (δ 6.91) showed the two largest splittings (J_{ortho} = 7.6 and 8.4 Hz), and hence must be the signal from the

(8) A negative value is assumed for the geminal coupling constant.

(9) The methylene protons adjacent to the carbonyl group in 7-hydroxy-1,2,4,5-tetrahydro-3*H*-3-benzazepin-2-one gave a singlet at δ 3.55; *cf.* reference in footnote 5.

(10) F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy," Academic Press, New York, N. Y., 1969, p 67.

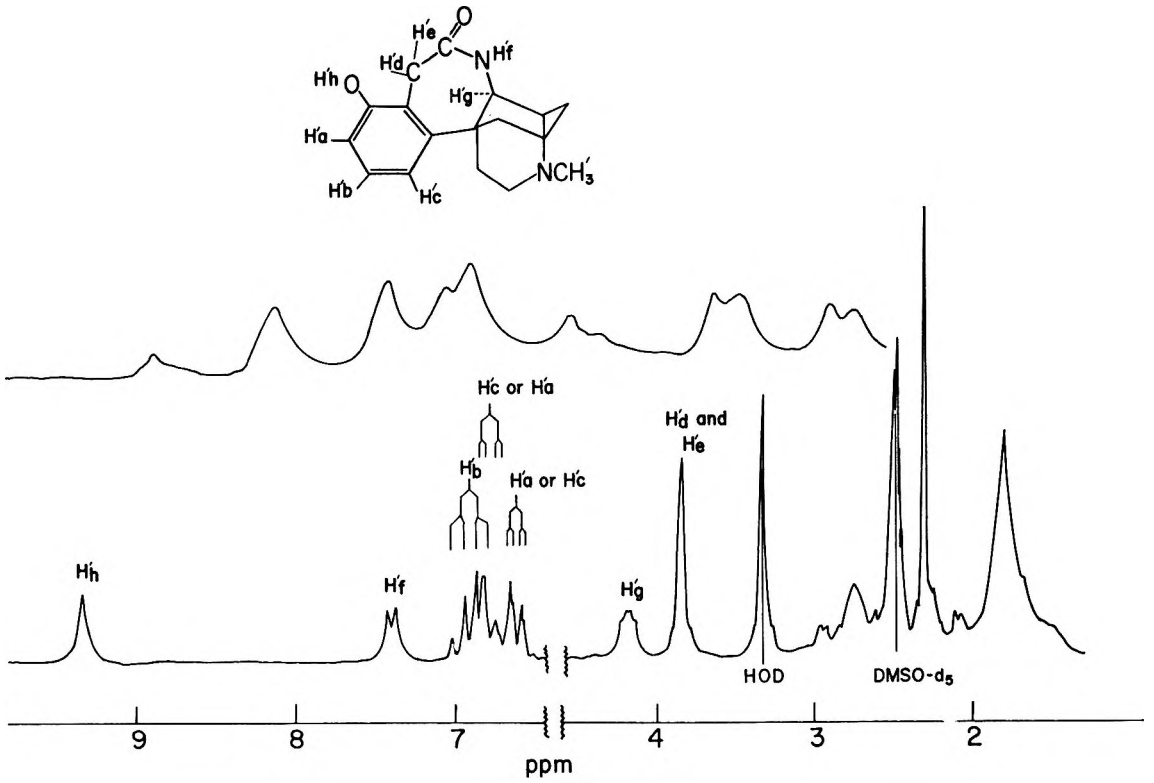


Figure 2.—Nmr spectrum of **5** measured at 100 MH_z in DMSO-d_6. Multiplets arising from the aromatic protons are shown amplified and expanded (ten times) just above the main spectrum.

middle proton, H'_b. Although it seems reasonable that the quartet at the highest field (δ 6.62) can be attributed to H'_a, an unambiguous assignment could not be made without data from the appropriate double resonance experiments. It is interesting to note that the two methylene protons, H'_d and H'_e, in **5** now coalesced to a single peak at δ 3.80; this possibly reflects a different conformation adopted (preferentially) by the seven-membered azepine ring in **5**, as compared to that in **4**, because of crowding by the ortho hydroxyl group.

Compound **5** reacted less readily with acetic anhydride to give a mono-*O*-acetyl derivative, whose nmr spectrum showed the aromatic protons in a degenerate ABX pattern, the X part (the multiplet at higher field) being attributed to the proton para[11] to the acetoxy group. A well-separated AB quartet (δ 3.92 and 3.72) was now observed for the two methylene protons in the azepine ring.

The structure of **5** was further confirmed by chemical evidence. The hydrochloride, despite its thermal stability, underwent a facile acid rearrangement to give an amino lactone, **6** (ν_{max} 1800 cm^{-1}), which can be formed only when the lactam bridge is ortho to the phenolic hydroxyl group. The presence of a primary amino group was apparent from the mass spectrum of **6**, which showed a moderate peak at *m/e* 269 and a prominent peak at *m/e* 256 due to the loss of NH_3 and $CHNH_3$, respectively, in addition to the molecular ion at *m/e* 286.[12] The *O*-acetyl derivative of **5** underwent a similar acid rearrangement to give **6** in good yield, but, under identical conditions, **4** was resistant to acid hydrolysis.

(11) D. W. Mathieson, "Nuclear Magnetic Resonance for Organic Chemists," Academic Press, London, 1967, p 184.

(12) The peaks at *m/e* 269 and 256 were totally absent in the spectrum of **5**. Peaks corresponding to $M^+ - NH_3$ and $M^+ - CHNH_3$ were also observed in the mass spectra of **1** and **2**.

Methylation of **4** with excess diazomethane gave **7** in 90% yield, along with a trace of the O,N-dimethylated product. Reduction of **7** with diborane in THF gave **10**, which was converted to **11** by reductive methylation with formaldehyde and formic acid. Refluxing **10** and **11** with 48% HBr afforded **10a** and **14**, respectively.

Compound **5** was subjected to the same reaction sequences to give **9a** and **15** *via* intermediates **8**, **9**, and **12**. The ease of reaction and the yield of each step corresponded well with those observed for photoproduct **4**.

The effect of pH on the photolysis of **3** was also studied. There was apparently no change in the course of reaction when the pH of the irradiation mixture was increased from 3 to 9. The relative as well as total yields of **4** and **5** remained virtually unchanged.

Experimental Section

All melting points were determined on a Kofler hot-stage and are uncorrected; ir spectra were recorded with a Perkin-Elmer grating spectrophotomer, model 257. Mass spectral data were obtained with a Hitachi RMR-6E double-focusing spectrometer at 80 eV, and nmr spectra were measured on a Varian HA-100 or HA-60 spectrometer using tetramethylsilane (δ 0) as internal standard.

9-*cis*-Amino-5-(*m*-hydroxyphenyl)-2-methyl-2-azabicyclo-[3.3.1]nonane (2) Dihydrodromide.—A mixture of 0.4 g (1.5 mmol) of **1**[4] and 3 ml of 48% HBr was refluxed under N_2 for 30 min. The cooled solution was concentrated *in vacuo* to give 510 mg (83%) of **2** 2HBr, mp 263–265°.

Anal. Calcd for $C_{15}H_{24}Br_2N_2O$: C, 44.14; H, 5.92; N, 6.86. Found: C, 43.86; H, 5.69; N, 6.90.

The free base was precipitated when an aqueous solution of **2** dihydrobromide was treated with 40% K_2CO_3. Recrystallization from ether–petroleum ether (bp 30–60°) gave colorless prisms: mp 164–165°; ν_{max}^{KBr} 3160, 1590 cm^{-1}; mass spectrum *m/e* 246 (M^+), 229, 216, 203 (base).

Anal. Calcd for $C_{15}H_{22}N_2O$: C, 73.16; H, 9.00; N, 11.37. Found: C, 73.29; H, 8.88; N, 11.12.

9-*cis*-Chloroacetamino-5-(*m*-hydroxyphenyl)-2-methyl-2-azabicyclo[3.3.1]nonane (3).—A solution of 320 mg (1.3 mmol) of **2** in 20 ml of $CHCl_3$ with 720 mg of anhydrous K_2CO_3 was stirred while 480 mg (2.8 mmol) of chloroacetic anhydride in 5 ml of $CHCl_3$ was added dropwise during 5–10 min. Stirring was continued for an additional 2 hr, and water was added to decompose the unreacted anhydride. The chloroform layer was separated and evaporated *in vacuo* to a sirup which by its ir spectrum (Nujol) was shown to be the dichloroacetylated derivative of **2** (1780 and 1670 cm^{-1}). NaOH (1 *N*, 10 ml) was then added to the residue to effect saponification of the ester group. After 30 min, the clear, aqueous solution was washed once with ether, acidified to pH 4 with 12 *M* HCl, and basified again with solid K_2CO_3. The precipitate was filtered (405 mg, 96%); silky needles from ether–petroleum ether, ν_{max}^{KBr} 3270, 2700, 1675 cm^{-1}. It decomposed and polymerized slowly above 120° without melting.

Anal. Calcd for $C_{17}H_{23}ClN_2O_2$: C, 63.26; H, 7.18; N, 8.68. Found: C, 63.80; H, 7.36; N, 8.78.

The hydrochloride gave (methanol–ether) microscopic granules. It darkened without melting at *ca.* 300°: nmr (D_2O, 60 MHz) δ 6.70–6.30 (m, 4, aromatic protons), 3.95 (s, 2, $ClCH_2$–), 3.00 (s, 3, $-N^+CH_3$), the remaining alicyclic protons were not resolved.

Anal. Calcd for $C_{17}H_{24}Cl_2N_2O_2$: C, 56.83; H, 6.70; N, 7.79 Found: C, 56.61; H, 6.57; N, 8.01.

Photolysis of 3. 1,2,3,4,4a,5-Hexahydro-8-hydroxy-3-methyl-4,11b-propano-11b*H*-pyrido[4,3-*a*][3]benzazepin-6(7*H*)-one (5) and 1,2,3,4,4a,5-Hexahydro-10-hydroxy-3-methyl-4,11b-propano-11b*H*-pyrido[4,3-a][3]benzazepin-6(7*H*)-one (4).—A solution of 360 mg (1 mmol) of **3** HCl in 500 ml of oxygen-free water was irradiated with a 200-W Hanovia high-pressure mercury-immersion lamp equipped with a Vycor filter. Nitrogen was bubbled through the solution during the irradiation and the quartz well was kept water-cooled. After neutralization with 152 mg (1.1 mmol) of K_2CO_3, the solution was concentrated to dryness at 30°. Trituration of the residue with water gave 256 mg (87%) of a precipitate which was approximately a 50:50 mixture of **4** and **5**, as indicated by tlc in several systems.[7] A preliminary purification of the mixed photoproducts was carried out by sublimation (10^{-4} mm) at 240°. A mass spectrum of the mixture showed the base peak (also the highest in mass number) at *m/e* 286, corresponding to molecular ion(s) of the dehydrohalogenated photoproducts.

When the photolysis of **3** was carried out in neutral (pH 7 phosphate buffer) or alkaline medium (K_2CO_3 added prior to irradiation), similar results were obtained. The relative as well as total yields of **4** and **5** were essentially unchanged.

Separation and Identification of Photoisomers (4 and 5).—The photoproducts obtained from irradiation of **3** were almost insoluble in all organic solvents, with the exception of DMSO and alcohols. In general, **5** was less soluble than **4**. A small amount of pure **5** was obtained by five recrystallizations of the sublimed mixture from a minimum of boiling ethanol. For a larger scale separation, 2 g of the sublimed mixture was dissolved in 50 ml of boiling ethanol. The solution was slightly cooled, seeded with a few crystals of pure **5**, and left undisturbed for 24 hr. The crystals which separated contained approximately 70% of **5** and 30% of **4**, and two more recrystallizations with seeding afforded 650 mg (28%) of pure **5**, colorless prisms from ethanol. The homogeneity of **5** could be shown by tlc, which revealed only one spot, R_f 0.41 in system I and 0.07 in system II;[7] it darkened without melting above 300°; ν_{max}^{KBr} 3260, 3100, 1665 cm^{-1}; mass spectrum *m/e* 286 (M^+), 243; nmr (DMSO-d_6, 100 MHz) δ 9.34 (s, 1, ArOH), 7.40 (d, 1, NHCO, J_{NHCH} = 6 Hz), 6.91 (q, 1, aromatic H, $J \cong 7.6$ and 8.4 Hz), 6.79 (q, 1, aromatic H, $J \cong 1.5$ and 8.4 Hz), 6.62 (q, 1, aromatic H, $J \cong 1.5$ and 7.6 Hz), 4.15 (q, 1, –CHNHCO–), 3.80 (s, 2, $ArCH_2$–), 2.29 (s, 3, NCH_3).

Anal. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.29; H, 7.74; N, 9.78. Found: C, 71.37; H, 7.97; N, 9.76.

Compound **5** gave a positive color test with ferric chloride. Its hydrochloride salt was prepared in ether; recrystallization from methanol–ether gave colorless prisms, mp >300°.

Anal. Calcd for $C_{17}H_{23}ClN_2O_2$: C, 63.26; H, 7.18; N, 8.68. Found: C, 63.06; H, 7.34; N, 8.53.

The filtrates from the recrystallizations of **5** were combined and concentrated to dryness. Two recrystallizations of the residue from a minimum of boiling methanol gave 570 mg (25%) of virtually pure **4**: fine needles; mp 285–288° dec; ν_{max}^{KBr} 3260, 1655 cm^{-1}; mass spectrum *m/e* 286 (M^+), 243; nmr (DMSO-d_6, 100 MHz) δ 9.12 (s, 1, ArOH), 7.39 (d, 1, NHCO–, J_{NHCH} = 6 Hz), 6.82 (d, 1, aromatic H, J = 8.0 Hz), 6.74 (d, 1, aromatic H, J = 2.5 Hz), 6.51 (q, 1, aromatic H, J = 2.5 and 8.0 Hz), 4.36 and 2.96 [q, 2, ArCH(H′)–, $|J|$ = 14 H], 4.15 (q, 1, –CHNHCO–), 2.32 (s, 3, NCH_3).

Anal. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.29; H, 7.74; N, 9.28. Found: C, 71.44; H, 7.46; N, 9.57.

Compound **4** gave a positive phenol test with $FeCl_3$ solution. It was shown to be free of **5** by tlc in two sysems (one spot; R_f 0.35 in system I, 0.18 in system II).[7]

***O*-Acetyl Derivative of 5.**—A suspension of 100 mg (0.35 mmol) of **5** in 2 ml of acetic anhydride was warmed at 90° until a clear solution was formed (24 hr). Evaporation of the solution *in vacuo* gave an oily residue which was taken up in methylene chloride, washed with $NaHCO_3$, and dried (Na_2SO_4). Removal of the solvent gave 85 mg (74%) of a precipitate which was recrystallized from acetone to give hexagonal plates: mp 235–238°; ν_{max}^{KBr} 3230, 1770, 1680 cm^{-1}; mass spectrum *m/e* 328 (M^+), 300, 286, 285; nmr ($CDCl_3$, 100 Hz) δ 7.15–7.25 (m, 2, aromatic protons, AB part of an ABX), 6.92 (m, 1, aromatic H, X part of an ABX), 6.40 (d, 1, NHCO–, J_{NHCH} = 6 Hz), 4.26 (q, 1, –CHNH–), 3.92 and 3.70 [q, 2, ArCH(H′)–, $|J|$ = 15 Hz], 2.45 (s, 3, CH_3CO–), 2.34 (s, 3, NCH_3).

Anal. Calcd for $C_{19}H_{24}N_2O_3$: C, 69.48; H, 7.36; N, 8.53. Found: C, 69.49; H, 7.65; N, 8.83.

***O*-Acetyl Derivative of 4.**—A mixture of 120 mg (0.35 mmol) of **4** in 2 ml of acetic anhydride was kept at 90° for 2 hr, during which time a clear solution was gradually formed. After isolation as described above, 91 mg (77%) was obtained. Recrystallization from acetone–hexane gave prisms: mp 232–235° dec; ν_{max}^{Nujol} 3200, 1770, 1670 cm^{-1}; mass spectrum *m/e* 328 (M^+), 300, 286, 285; nmr ($CDCl_3$, 100 MHz) δ 7.06 (d, 1, aromatic H, J = 8.5 Hz), 7.02 (d, 1, aromatic H, J = 2.4 Hz), 6.85 (q, 1, aromatic H, J = 8.5 and 2.4 Hz), 4.39 and 3.27 [q, 2, ArCH(H′)–, $|J|$ = 15 Hz], 4.26 (q, 1, –CHNHCO–), 2.44 (s, 3, CH_3CO–), 2.35 (s, 3, NCH_3).

Anal. Calcd for $C_{19}H_{24}N_2O_3$: C, 69.48; H, 7.36; N, 8.53. Found: C, 69.68; H, 7.31; N, 8.67.

Acid Rearrangement of 5 HCl to 9-*cis*-Amino-5-(2′-oxo-2′,3′-dihydrobenzofuryl)-2-methyl-2-azabicyclo[3.3.1]nonane (6) 2HCl.—A solution of 161 mg (0.5 mmol) of **5** HCl in 4 ml of 4 *N* HCl was refluxed under N_2 for 24 hr. The course of the reaction was followed by tlc[7] which showed a gradual change from R_f 0.41 to 0.33. Evaporation of the excess acid, followed by reprecipitation from ethanol–ethyl acetate, gave 125 mg of a very hygroscopic powder. It decomposed gradually above 150–160°: ν_{max}^{Nujol} 3180, 1800 cm^{-1}; mass spectrum *m/e* 286 (M^+), 269, 256.

Anal. Calcd for $C_{17}H_{24}Cl_2N_2O_2$: N, 7.79. Found: N, 8.04.

1,2,3,4,4a,5-Hexahydro-8-methoxy-3-methyl-4,11b-propano-11b*H*-pyrido-[4,3-a][3]benzazepin-6(7*H*)-one (8).—A solution of 134 mg (0.5 mmol) of **5** in 10 ml of methanol was allowed to stand overnight with an excess of diazomethane prepared from 1.2 g of *N*-methyl-*N*′-nitrosoguanidine. Evaporation of the reaction mixture, followed by vacuum sublimation (10^{-4} mm, 170°), gave 110 mg (74%) of virtually pure **8**. Recrystallization from acetone–hexane afforded colorless plates: mp 228–231°; ν_{max}^{Nujol} 1675 cm^{-1}; mass spectrum *m/e* 300 (M^+), 257 (base).

Anal. Calcd for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.06; N, 9.32. Found: C, 71.48; H, 7.68; N, 9.25.

1,2,3,4,4a,5,6,7-Octahydro-8-methoxy-3-methyl-4,11b-propano-11b*H*-pyrido[4,3-a][3]benzazepine (9) 2HBr.—To a solution of 300 mg (1 mmol) of **8** was added 6 ml of 1 *M* borane[13] in THF and the mixture was refluxed for 4 hr. The slightly cooled solution was treated with 12 ml of 6 *N* HCl and refluxing was continued for an additional 2 hr. Evaporation *in vacuo* left a semisolid mass which was basified with 1 *N* NaOH. The liberated oil was taken up in ether, dried over K_2CO_3, and converted to 285 mg (64%) of **9** 2HBr in ether. Recrystallization from ethanol–ether gave fine needles: mp 265–268°; mass spectrum *m/e* 286 (M^+), 271, 243 (base).

Anal. Calcd for $C_{18}H_{28}Br_2N_2O$: C, 48.22; H, 6.29; N, 6.24. Found: C, 48.13; H, 6.48; N, 6.58.

1,2,3,4,4a,5,6,7-Octahydro-3-methyl-4,11b-propano-11b*H*-pyrido[4,3-*a*]-[3]benzazepin-8-ol (9a) 2HBr.—A solution of 150

(13) Purchased from Alpha Inorganics, Inc.

mg (0.52 mmol) of **9** in 3 ml of 48% HBr was refluxed under N_2 for 30 min. Evaporation of the excess acid *in vacuo* left an oily residue which was crystallized from ethanol–acetone–ether to give 191 mg (84%) of irregular prisms, mp 283–286°, mass spectrum *m/e* 272 (M^+), 229 (base).

Anal. Calcd for $C_{17}H_{26}Br_2N_2O$: C, 47.01; H, 6.03; N, 6.45. Found: C, 46.91; H, 6.26; N, 6.36.

1,2,3,4,4a,5,6,7-Octahydro-3,5-dimethyl-8-methoxy-4,11b-propano-11b*H*-pyrido[4,3-a][3]benzazepine (12) 2HBr.—A mixture of 400 mg (1.4 mmol) of **9** and 2 ml of formic acid was refluxed for 2 hr before 1.8 ml of 38% formaldehyde solution was added. Refluxing was continued for 18 hr. Evaporation of the mixture *in vacuo*, followed by basification with 1 *N* NaOH, afforded 390 mg of **12** as a viscous oil. It was converted to its dihydrobromide in anhydrous ether, yield 605 mg (93%). Recrystallization from 90% ethanol–ether gave colorless rods, mp 275–277°, mass spectrum *m/e* 300 (M^+), 285, 270, 269, 257 (base).

Anal. Calcd for $C_{19}H_{30}Br_2N_2O$: C, 49.36; H, 6.54; N, 6.06. Found: C, 49.20; H, 6.69; N, 6.28.

1,2,3,4,4a,5,6,7-Octahydro-3,5-dimethyl-4,11b-propano-11b*H*-pyrido[4,3-a]-[3]benzazepin-8-ol (15) 2HBr.—A mixture of 320 mg (0.7 mmol) of **12**·2HBr in 3 ml of 48% HBr was refluxed under N_2 for 30 min. Evaporation *in vacuo* left a crystalline residue which was recrystallized from 90% ethanol–ether to give 300 mg (96%) of **15** 2HBr, mp 230–235° dec, *m/e* 286 (M^+), 243 (base).

Anal. Calcd for $C_{18}H_{28}Br_2N_2O$: C, 48.22; H, 6.29; N, 6.24. Found: C, 48.31; H, 6.54; N, 6.08.

1,2,3,4,4a,5-Hexahydro-10-methoxy-3-methyl-4,11b-propano-11b*H*-pyrido-[4,3-a][3]benzazepin-6(7*H*)-one (7).—A solution of 240 mg (0.84 mmol) of **4** in 50 ml of methanol was methylated with an excess of diazomethane in the same manner as described for **5**. The course of reaction was followed by tlc (system I) which showed a gradual disappearance of the spot at R_f 0.35 while a new spot emerged at R_f 0.56. Evaporation of the solution followed by sublimation (10^{-4} mm, 180°) gave 223 mg (88%) of **7**, rectangular plates from acetone: mp 246–249° dec; ν_{max}^{Nujol} 3200, 1675 cm^{-1}; *m/e* 300 (M^+), 257 (base).

Anal. Calcd for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.06; N, 9.32. Found: C, 72.22; H, 7.86; N, 9.55.

1,2,3,4,4a,5,6,7-Octahydro-10-methoxy-3-methyl-4,11b-propano-11b*H*-pyrido[4,3-a][3]befinazepine (10) 2HBr.—A solution of 240 mg (0.8 mmol) of **7** in 50 ml of THF was reduced with 5 ml of 1 *M* borane in THF. After 4 hr, the mixture was treated with 12 ml of 6 *N* HCl and refluxing was continued for an additional 2 hr. Evaporation of the mixture *in vacuo* left an oily residue which was basified with 2 *N* NaOH and extracted with ether. After drying briefly over K_2CO_3, the amine was converted to **10** 2HBr by passing through anhydrous HBr, yield 225 mg (63%). Recrystallization from 90% ethanol–ether gave irregular prisms, mp 269–272°, mass spectrum *m/e* 286 (M^+), 271, 243 (base).

Anal. Calcd for $C_{18}H_{28}Br_2N_2O$: C, 48.22; H, 6.29; N, 6.24. Found: C, 47.98; H, 6.52; N, 6.18.

1,2,3,4,4a,5,6,7-Octahydro-3-methyl-4,11b-propano-11b*H*-pyrido[4,3-a][3]benzazepin-10-ol (10a) 2HBr.—A mixture of 224 mg (0.5 mmol) of **10**·2HBr in 4 ml of 48% HBr was refluxed for 30 min. Evaporation of the excess acid *in vacuo* left a sirup which, upon trituration with acetone, crystallized to yield 196 mg (90%) of **10a**·2HBr. Recrystallization from 95% ethanol–ether gave fine needles, mp 279–282° dec, mass spectrum *m/e* 272 (M^+), 229 (base).

Anal. Calcd for $C_{17}H_{26}Br_2N_2O$: C, 47.02; H, 6.03; N, 6.45. Found: C, 47.26; H, 6.32; N, 6.31.

1,2,3,4,4a,5,6,7-Octahydro-3,5-dimethyl-10-methoxy-4,11b-propano-11b*H*-pyrido[4,3-a][3]benzazepine (11) 2HBr.—Compound **10**, 286 mg (1 mmol, purified through its dihydrobromide), was methylated with formic acid (90%) and formalin in the same manner as described for **9** to give 431 mg (93%) of **11** 2HBr, mp 243–246° dec, prisms from 90% ethanol–ether, mass spectrum *m/e* 300 (M^+), 285, 270, 269, 257 (base).

Anal. Calcd for $C_{19}H_{30}Br_2N_2O$: C, 49.36; H, 6.54; N, 6.06. Found: C, 49.44; H, 6.61; N, 6.25.

1,2,3,4,4a,5,6,7-Octahydro-3,5-dimethyl-4,11b-propano-11b*H*-pyrido-[4,3-a][3]benzazepin-10-ol (14) 2HBr.—A mixture of 462 mg (1 mmol) of **11**·2HBr in 3 ml of 48% HBr was refluxed gently for 1 hr. Evaporation of the excess acid *in vacuo* left an oily residue which crystallized upon trituration with acetone, yield 350 mg (78%). Recrystallization from 80% ethanol–ether gave elongated plates, mp 238–241° dec, mass spectrum *m/e* 286 (M^+), 243 (base).

Anal. Calcd for $C_{18}H_{28}Br_2N_2O$: C, 48.22; H, 6.29; N, 6.24. Found: C, 48.20; H, 6.53; N, 6.39.

When the refluxing time was prolonged to more than 1 hr, extensive decomposition and polymerization took place.

Registry No.—**2**, 32969-96-3; 2 diHBr, 32969-97-4; **3**, 32969-98-5; **3** HCl, 33068-03-0; **4**, 33020-81-4; **4** *O*-acetyl derivative, 33020-82-5; **5**, 33068-04-1; **5** HCl, 33020-83-6; **5** *O*-acetyl derivative, 33020-84-7; **6** diHCl, 33068-05-2; **7**, 33020-85-8; **8**, 33020-86-9; **9** diHBr, 33020-87-0; **9a** diHBr, 33020-88-1; **10** diHBr, 33020-89-2; **10a** diHBr, 33020-90-5; **11** diHBr, 33020-91-6; **12** diHBr, 33020-92-7, **14** diHBr, 33020-93-8; **15** diHBr, 33020-89-2.

Strained Heterocyclic Systems. VI. Basicities of Some Quinoxalines[1]

J. HODGE MARKGRAF* AND ROBERT J. KATT

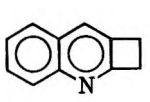
Department of Chemistry, Williams College, Williamstown, Massachusetts 01267

Reeeived August 17, 1971

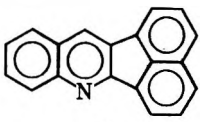
The basicities of a series of 2,3-disubstituted quinoxalines were determined by potentiometric titration in acetic anhydride. A decrease in basicity was observed for those compounds containing a fused, strained ring adjacent to the heteroatoms. Such an effect was consistent with previous interpretations based on orbital rehybridization. In conjunction with the present study, J (^{13}C–H) values were determined for the benzylic protons of acenaphthene and pyracene.

It has recently been established that a fused strained ring adjacent to the nitrogen atom in a quinoline ring causes a marked decrease in the basicity of such heterocyclic compounds.[2-4] These observations are in accord with the concept of orbital rehybridization developed by Streitwieser and coworkers to account for the changes in kinetic acidity and reactivity toward electrophilic substitution observed with strained carbocyclic systems.[5] This interpretation has gained support from a variety of studies: J (^{13}C–H) nmr data,[6,7] esr data,[8,9] rates of protodesilylation,[10] polarographic reduction potentials,[11] and molecular orbital calculations.[12]

In our earlier studies of 1,2-dihydrocyclobuta[*b*]quinoline (**1**) and acenaphtho[1,2-*b*]quinoline (**2**) de-

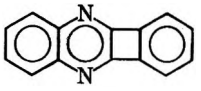


1



2

creases in basicity of ten- and fivefold, respectively, were observed relative to model compounds. Since there is greater strain in biphenylene than in benzocyclobutene,[13] it was anticipated that pK_a data for an azabiphenylene would exhibit a further substantial decrease in basicity. Although no monoazabiphenylenes have been reported in the literature, the diazabiphenylene, benzo[3,4]cyclobuta[1,2-*b*]quinoxaline (**3**), has been known for some time.[14] This report, therefore, presents the synthesis and basicity measurements of a series of strained quinoxaline derivatives.



3

Results and Discussion

The compounds selected for this study are listed in Table I. Basicities were determined as half-neutralization potentials (HNP) at 25° in acetic anhydride by titration with perchloric acid in acetic acid. The apparent acid dissociation constants (pK_a) were calculated from the known values of selected quinoxalines and the assumption that HNP (Ac_2O) and pK_a (H_2O) are linearly related.[15] Structures **4**, **5**, and **7** of known aqueous acidities[16] were used to calibrate the above extrapolation. Compounds **8** and **10** were model compounds of previously unknown basicity. Compounds **3**, **6**, and **9** were the desired quinoxalines containing strained fused rings adjacent to the heteroatoms. Those compounds, not commercially available, were prepared by condensation of *o*-phenylenediamine with the appropriate α diketone.

TABLE I

BASICITIES OF 2,3-DISUBSTITUTED QUINOXALINES

Compound	HNP,[a] mV	pK_a
2,3-Dimethylquinoxaline (**4**)	468	2.08[c]
Phenazine (**5**)	536	1.23[d]
1,2-Dihydrocyclopent[5,6]acenaphtho-[1,2-*b*]quinoxaline (**6**)	536[b]	1.23
Quinoxaline (**7**)	548	1.03[d]
2,3-Diphenylquinoxaline (**8**)	564	0.85
Acenaphtho[1,2-*b*]quinoxaline (**9**)	573	0.72
Benzo[3,4]cyclobuta[1,2-*b*]quinoxaline (**3**)	581[b]	0.62
Dibenzo[*a*,*c*]phenazine (**10**)	607	0.30

[a] Duplicate runs, ±2 mV, at 25° unless otherwise stated. [b] At 30°. [c] Reference 16a. [d] Reference 16b.

The basicity data are presented in Table I. The sequence of relative base strengths (**7** > **8** > **9** > **3**) was in accord with prediction. The diphenyl (**8**) and acenaphtho (**9**) derivatives exhibited the same relative effects in the quinoline series.[3] The fact that **3** was the least basic in the above series confirmed our expectations, although the decrease in basicity relative to **8** (*ca.* twofold) was less than that anticipated. This discrepancy may be attributed to the effect of the second nitrogen atom, which is the dominant influence. The difference between the basicities of

(1) Part V: C. W. Koch and J. H. Markgraf, *J. Heterocycl. Chem.*, **7**, 235 (1970).

(2) J. H. Markgraf and W. L. Scott, *Chem. Commun.*, 296 (1967).

(3) J. H. Markgraf and R. J. Katt, *Tetrahedron Lett.*, 6067 (1968).

(4) E. Spinner and G. B. Yeoh, *J. Chem. Soc. B*, 279 (1971).

(5) A. Streitwieser, Jr., G. R. Ziegler, P. C. Mowery, A. Lewis, and R. G. Lawler, *J. Amer. Chem. Soc.*, **90**, 1357 (1968).

(6) G. Fraenkel, Y. Asahi, M. J. Mitchell, and M. P. Cava, *Tetrahedron*, **20**, 1179 (1964).

(7) J. H. Markgraf, R. J. Katt, W. L. Scott, and R. N. Shefrin, *J. Org. Chem.*, **34**, 4131 (1969).

(8) (a) R. D. Rieke, C. F. Meares, and L. I. Rieke, *Tetrahedron Lett.*,, 5275 (1968); (b) R. D. Rieke, S. E. Bales, P. M. Hudnall, and C. F. Meares, *J. Amer. Chem. Soc.*, **92**, 1418 (1970); (c) R. D. Rieke and W. E. Rich, *ibid.*, **92**, 7349 (1970); (d) R. D. Rieke, S. E. Bales, P. M. Hudnall, and C. F. Meares, *ibid.*, **93**, 697 (1971).

(9) N. L. Bauld, F. Farr, and G. R. Stevenson, *Tetrahedron Lett.*, 625 (1970).

(10) A. R. Bassindale, C. Earborn, and D. R. M. Walton, *J. Chem. Soc., B*, 12 (1969).

(11) R. D. Rieke, W. E. Rich, and T. H. Ridgway, *Tetrahedron Lett.*, 4381 (1969).

(12) R. D. Rieke, *J. Org. Chem.*, **36**, 227 (1971).

(13) R. Taylor, *J. Chem. Soc. B*, 536 (1971).

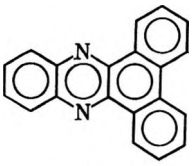
(14) (a) M. P. Cava and D. R. Napier, *J. Amer. Chem. Soc.*, **79**, 3606 (1957); (b) M. P. Cava, D. R. Napier, and R. J. Pohl, *ibid.*, **85**, 2076 (1963).

(15) C. A. Streuli, *Anal. Chem.*, **30**, 997 (1958).

(16) (a) P. Vetešník, J. Kaválek, V. Beránek, and O. Exner, *Collect. Czech. Chem. Commun.*, **33**, 566 (1968); (b) A. Albert, R. Goldacre, and J. Phillips, *J. Chem. Soc.*, 2240 (1948).

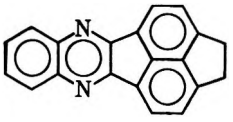
quinoline (pK_a 4.94) and quinoxaline (pK_a 1.03) is quite striking.[16b] Compared to the heteroatom effect, the influence of a strained ring is clearly secondary.

The basicities of two other compounds require comment. It was not anticipated that dibenzo[*a*,*c*]phenazine (**10**) would be the least basic of the present

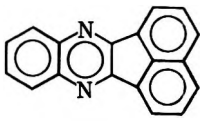


10

series. The difficulty in protonating **10**, however, can be ascribed to steric inhibition of solvation of the conjugate acid. Comparable effects have been observed with benzo[*a*]phenazine, in which the reactivity of N-12 is rendered much less than that of N-7,[17] and with benzo[*f*]- and benzo[*h*]quinoline, in which the latter is unreactive toward methyl iodide.[18] The enhanced basicity of **6** relative to **9** also was not expected. In



6



9

fact, it was assumed initially that **6** would be less basic than **9**. The molecular geometry of acenaphthene is known,[19] and the strain is accommodated mainly by changes in bond angles. These adjustments result in a C_5–C_{5a}–C_6 bond angle of 128°. Although the geometry of pyracene has not been determined, it seemed reasonable that whatever strain is present in acenaphthene would be increased by the incorporation of an ethylene bridge across C_5–C_6. This was confirmed by nmr measurements on the ^{13}C–H coupling constants for the benzylic protons of acenaphthene (129 Hz) and pyracene (132.5 Hz). A threefold enhancement in the basicity of **6** compared to **9** was, therefore, quite remarkable. This change undoubtedly reflects the electron-releasing character of the ethylene bridge in **6**. A similar effect has been observed for product distribution and partial rate factors in the nitration of acenaphthene.[20]

Experimental Section[21]

Materials.—The following compounds were obtained from Aldrich Chemical Co.: phenazine (**5**), recrystallized from acetic acid, mp 175.3–175.9° (lit.[22] mp 174.9–175.6°); quinoxaline (**7**); 2,3-diphenylquinoxaline (**8**), recrystallized from 95% ethanol, mp 125.8–126.7° (lit.[23] mp 124.0–124.5°); and dibenzo[*a*,*c*]-phenazine (**10**), recrystallized from benzene, mp 224.8–225.7° (lit.[24] mp 220–222°). Benzo[3,4]cyclobuta[1,2-*b*]quinoxaline (**3**) was prepared from benzocyclobutenedione[25] by the method of Cava,[28] mp 229.3–229.9. (lit.[28] mp 238–239°). 2,3-Dimethylquinoxaline (**4**) was prepared from biacetyl and recrystallized from water, mp 105.9–106.3° (lit.[29] mp 106°). 1,2-Dihydrocyclopent[5,6]acenaphtho[1,2-*b*]quinoxaline (**6**) was prepared from 5,6-dihydrocyclopenta[*f*,*g*]acenaphthylene-1,2-dione (diketopyracene)[30] by the method Richter and Stocker[31] and recrystallized from benzene–ligroin, mp 275.5–276.5° (lit.[31] mp 275–276°). Acenaphtho[1,2-*b*]quinoxaline (**9**) was prepared from acenaphthenequinone and recrystallized from benzene, mp 239.5–240.3° (lit.[32] mp 241°). Acetic anhydride (J. T. Baker, assay 99.2%) and 0.10 *N* perchloric acid in acetic acid (Fisher Certified Reagent) were used without further purification.

Basicity Determinations.—Basicities were determined by potentiometric titration with a Beckman Model 76 expanded scale pH meter fitted with a glass indicator electrode and a saturated calomel reference electrode, previously equilibrated with acetic anhydride for 48 hr. Titrations were carried out at 25.00 ± 0.02° under a nitrogen atmosphere in a water-jacketed cell connected to a constant temperature bath and fitted with a Teflon cover drilled to accommodate two electrodes, buret, thermometer (certified by the Natioanl Bureau of Standards), and nitrogen inlet tube. In a typical run an accurately weighed amount of the compound (*ca.* 10^{-3} mol) was dissolved in acetic anhydride in a nitrogen-swept 50-ml volumetric flask; a 20-ml aliquot was transferred under nitrogen to the titration cell, diluted with 80 ml of acetic anhydride, and with magnetic stirring titrated with 0.10 *N* $HClO_4$ in acetic acid (*ca.* 7 ml). The end point and half-neutralization potential were determined graphically; all runs were carried out in duplicate, with a precision of ±2 mV. Compounds **3** and **6** were not completely soluble at 25°; these measurements were conducted at 30.00 ± 0.05°, along with redeterminations of **5**, **7**, and **10** for calibration purposes.

Nmr Data.—The ^{13}C–H coupling constants for the benzylic protons of acenaphthene and 1,2,5,6-tetrahydrocyclopent[*f*,*g*]-acenaphthylene (pyracene) were determined as saturated solutions in CCl_4 and $DCCl_3$, respectively, with tetramethylsilane as an internal standard. The acenaphthene spectrum was obtained with the aid of a Varian time-averaging computer attached to a Varian HA-100 instrument; 100 scans were required to delineate the sidebands. The low solubility of pyracene precluded the above procedures. Its spectrum was obtained by the Fourier transform pulse mode and required 13,500 scans. The *J* (^{13}C–H) values thus obtained for acenaphthene and pyracene were 129 ± 1 Hz and 132.5 ± 1 Hz, respectively, which correspond to 25.8 and 26.5% *s* character for the benzylic C–H bonds.

Registry No.—**3**, 259-57-4; **4**, 2379-55-7; **5**, 92-82-0; **6**, 33068-15-4; **7**, 91-19-0; **8**, 1684-14-6; **9**, 207-11-4; **10**, 215-64-5.

Acknowledgment.—The authors are indebted to Messrs. John Vinson and Paul Gendler (University of California, Berkeley) for the nmr measurements and to Professor Arthur G. Anderson, Jr. (University of Washington, Seattle), for a sample of pyracene. We thank Messrs. William Homan and Peter Wege for technical assistance. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. In addition, support by Merck & Co. and funds from a grant to Williams College from the Alfred P. Sloan Foundation are gratefully acknowledged.

(17) I. J. Pachter and M. C. Kloetzel, *J. Amer. Chem. Soc.*, **73**, 4958 (1951).

(18) G. Coppens and J. Nasielski, *Bull. Soc. Chim. Belg.*, **68**, 187 (1959).

(19) H. W. W. Ehrlich, *Acta Crystallogr.*, **10**, 699 (1957).

(20) A. Davies and K. D. Warren, *J. Chem. Soc. B*, 873 (1969).

(21) Melting points are uncorrected.

(22) D. N. Bailey, D. K. Roe, and D. M. Hercules, *J. Amer. Chem. Soc.*, **90**, 6291 (1968).

(23) G. A. Russell, R. Konaka, E. T. Strom, W. C. Danen, K.-Y. Chang, and G. Kaupp, *ibid.*, **90**, 4646 (1968).

(24) F. Sparatore, *Gazz. Chim. Ital.*, **87**, 1014 (1957).

(25) Benzocyclobutenol[26] (**11**) was oxidized by the Jones reagent to benzocyclobutenone (76%), which was converted to 2,2-dibromobenzocyclobutenone (96%) and then to benzocyclobutenedione (62%).[27] In our hands, this route was superior to the direct oxidative bromination of **11**.[27]

(26) H. H. Wasserman and J. Solodar, *J. Amer. Chem. Soc.*, **87**, 4002 (1965).

(27) M. P. Cava, D. Mangold, and K. Muth, *J. Org. Chem.*, **29**, 2947 (1964).

(28) (a) M. P. Cava and D. R. Napier, *J. Amer. Chem. Soc.*, **79**, 3606 (1957); (b) M. P. Cava, D. R. Napier, and R. J. Pohl, *ibid.*, **85**, 2076 (1963).

(29) S. Gabriel and A. Sonn, *Ber.*, **40**, 4850 (1907).

(30) B. M. Trost, *J. Amer. Chem. Soc.*, **91**, 918 (1969).

(31) H. J. Richter and F. B. Stocker, *J. Org. Chem.*, **24**, 366 (1959).

(32) W. Bradley and F. W. Pexton, *J. Chem. Soc.*, 4436 (1954).

The o-Styrylnitrene Route to 2-Substituted Indoles. Pyrolysis of o-Azidostyrenes[1]

RICHARD J. SUNDBERG,* HENRY F. RUSSELL, WOODFIN V. LIGON, JR., AND LONG-SU LIN

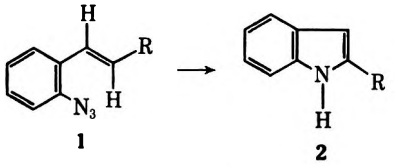
Department of Chemistry, University of Virginia, Charlottesville, Virgina 22903

Received August 12, 1971

The utility of o-azidostyrene derivatives as indole precursors *via* o-styrylnitrenes has been examined. The cyclization proceeds efficiently for β-alkyl- and β-aryl-o-azidostyrenes and is also satisfactory for β-acyl-o-azidostyrenes. A synthesis of 2-acylindoles involving two steps, base-catalyzed condensation of a methyl ketone with o-azidobenzaldehyde and pyrolysis to the indole, was carried out successfully in five cases with yields from 21 to 73%. These yields are generally superior to yields of 2-acylindoles prepared by the deoxygenation method.

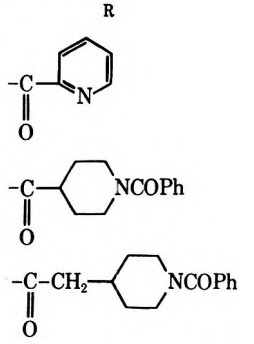
An o-styrylnitrene would be expected to cyclize to an indole on the basis of analogy with other cyclizations of aryl azides having adjacent unsaturated substituents.[2] The deoxygenation of o-nitrostyrenes to indoles may, indeed, be an example of such a cyclization.[3] In view of the efficiency with which azides serve as precursors of nitrenes on thermal or photolytic decomposition,[4] a study of the synthesis and decomposition of the requisite o-azidostyrenes was undertaken.[5] Particular attention was focused on β-acyl-o-azidostyrenes because of the desirability of developing improved methods of synthesis of 2-acylindoles. Some additional studies of the deoxygenation method are also reported for purposes of comparison.

The azides **1a** and **1b** were prepared from the corresponding o-nitrostyrenes in two steps. The nitro group was reduced with iron and acetic acid to the aniline. The azido group was introduced *via* diazotization. A mixture of azides **1c** and **1d** was obtained by condensation of o-azidobenzaldehyde with pyruvic acid followed by acid-catalyzed esterification. The azides **1e–h** were prepared by condensation of the appropriate methyl ketone with o-azidobenzaldehyde. The noncrystalline azides **1g** and **1h** were partially purified and pyrolyzed but not characterized by elemental analysis. Several attempts to condense o-azidobenzaldehyde with 4-acetylpyridine failed. Attempted condensations of o-azidobenzaldehyde with 4-acetonyl-1-benzoyl-1,2,3,6-tetrahydropyridine and 4-acetonyl-1-benzoyl-3-hydroxypiperidine also gave ill-defined products apparently containing azido groups, but no indoles could be isolated after pyrolysis of these materials. The stereochemistry about the carbon–carbon double bond is assumed to be trans in compounds **1c–h** on the basis of the known preference for formation of trans product in base-catalyzed Claissen condensations.[6]



1 **2**

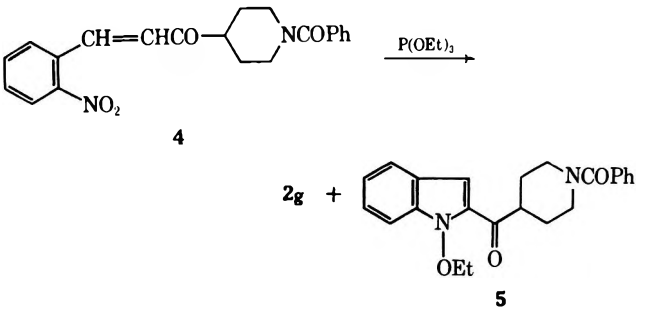
Compd	R
a	$-CH_2CH_2CH_3$
b	$-C_6H_5$
c	$-COCO_2Me$
d	$-C(OMe)_2CO_2Me$
e	$-COPh$



Pyrolysis of the azides was effected either in refluxing decalin or ethylene glycol. In the case of decalin, the solvent was removed by vacuum distillation and the indole isolated from the residue. When ethylene glycol was used, the indole could be obtained by dilution of the solution with water followed by solvent extraction.

The yields obtained in the various pyrolyses are reported in the Experimental Section. Although deoxygenation gives yields comparable to those from azidostyrene pyrolysis for alkyl- and arylindoles,[3a] the pyrolysis is usually markedly more efficient for the synthesis of 2-acylindoles.[3a,7]

The preparation of 4-acetyl-1-benzoylpiperidine (**3**) and its condensation with nitrobenzaldehyde to give **4** followed by deoxygenation to give **2g** was carried out in the course of this work. As noted previously in similar deoxygenations,[3a,7] the corresponding 1-ethoxyindole is a by-product.



4

2g + **5**

Deoxygenation provided an efficient synthesis of 2-indolyl 4-pyridyl ketone[8] **2i**, although, as mentioned above, we were unable to prepare the intermediate required for synthesis of this ketone by the o-azidostyrene route. 4-Acetylpyridine was condensed with

(1) Supported by NSF Grants GP-7951 and 19374. A preliminary account of some of these results has appeared: R. J. Sundberg, L.-S. Lin, and D. E. Blackburn, *J. Heterocycl. Chem.*, **6**, 441 (1969).

(2) P. A. S. Smith and B. B. Brown, *J. Amer. Chem. Soc.*, **73**, 2435 (1951); L. Krbechek and H. Takimoto, *J. Org. Chem.*, **29**, 1150, 3630 (1964).

(3) (a) R. J. Sundberg, *J. Org. Chem.*, **30**, 3604 (1965); (b) J. I. G. Cadogan, M. Cameron-Wood, R. K. Mackie, and R. J. G. Searle, *J. Chem. Soc.*, 4831 (1965).

(4) G. L'abbe, *Chem. Rev.*, **69**, 345 (1969).

(5) Smith and coworkers have independently studied synthesis and thermal decomposition of several o-azidostyrene derivatives: unpublished work referred to in "Nitrenes," W. Lwowski, Ed., Interscience Publishers, New York, N. Y., 1970, pp 135–139.

(6) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, pp 216–224.

(7) R. J. Sundberg, *J. Org. Chem.*, **33**, 487 (1968).

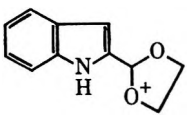
(8) Previously prepared from methyl isonicotinate by Claissen condensation with methyl propionate followed by Japp–Klingemann conversion to the phenylhydrazone and Fischer cyclization: A. Jackson, N. D. V. Wilson, A. J. Gaskell, and J. A. Joule, *J. Chem. Soc., C*, 2738 (1969).

o-nitrobenzaldehyde. The ketol was dehydrated and the resulting unsaturated ketone **6** was converted to the ethylene glycol ketal **7**. Deoxygenation of this compound proceeded efficiently to give the indole **2i**, after hydrolysis.

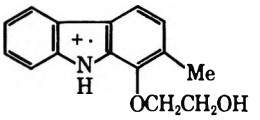
Ir, nmr, and mass spectral data were in accord with expectation for each of the new indoles **2c**,[9] **2d**, **2f**, and **2g**. Spectral data and physical constants for the known indoles **2a**,[15] **2b**,[16] **2h**,[7] and **2i**[8] were in agreement with literature values. The structure of indole **2i** was further corroborated by N-methylation to the ketone **9** which was independently prepared from 2-lithio-1-methylindole and 4-cyanopyridine.

Interrelation of **2i** and the piperidine derivative **2g** was also carried out. The ketal **8** was quaternized with ethyl bromoacetate and reduced over palladium on charcoal. The piperidine **10** was the major product along with a by-product **11** which is discussed below. These interrelations, which are summarized in Scheme I serve to establish that no substituent migration occurred in either the pyrolysis of **1g** or the deoxygenation of **7**. It was of interest to establish this, particularly in the latter case, since substituent migration is observed in deoxygenation of the phenyl analog of **7**.[7]

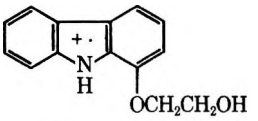
The tetracyclic skeleton assigned to the by-product **11** is that found in the uleine[17] and dasycarpidone[18] type of alkaloid. The formation of **11** under the conditions of the reduction can be rationalized by alkylation of the indole 3 position by an iminium intermediate[19] present at the dihydro or tetrahydro reduction stage. Such a cyclization might be expected to be favored by acidic hydrogenation conditions but **10** was also found to be the major product in 5% acetic acid in ethanol as well as in ethanol. Ring closures of this type have been noted using isolated tetrahydropyridine intermediates,[8] but this is the first example of the cyclization proceeding directly from the pyridine oxidation level. In addition to the molecular formula established by elemental analysis and mass spectrometry, the evidence for the structure includes a typical indole uv spectrum. The nmr shows no indole 3 H and the methylene group of the nitrogen substituent appears as an AB quartet, J_{gem} = 16 Hz, because the protons are anisochronous as a result of the introduction of the indolyl substituent at C-2 of the piperidine ring. Mass spectral comparison of **10** and **11** reveal the absence in **11** of a peak at 188 attributable to the monosubstituted indole fragment **a**. In addition peaks at 227, 210, 196, 181, and 167 can be assigned to the carbazole ring fragments of type **b**, **c**, **d**, and **e**. The mass spectrum of uleine is also dominated by fragments containing the carbazole ring system.[17]



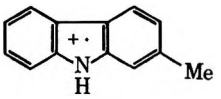
a, 188



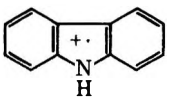
b, 241
b′, -OH (224)
b″, -CH_2OH (210)
b‴, -CH_2CH_2OH (196)



c, 227
c′, -OH (210)
c″, -CH_2OH (196)
c‴, -CH_2CH_2OH (182)



d, 181



e, 167

Experimental Section

trans-1-(*o*-Azidophenyl)-1-pentene (1a).—*trans*-*o*-(1-Pentenyl)aniline[20] (0.81 g, 5 mmol) was dissolved in a solution of glacial acetic acid (40 ml), sulfuric acid (8 ml), and water (25 ml) and cooled with an ice–salt bath. A solution of sodium nitrite (0.38 g, 5.5 mmol) in water (5 ml) was added slowly. The solution was stirred for 1 hr. The reaction mixture was diluted with ice water (50 ml) and treated with urea to destroy excess nitrous acid. A solution of sodium azide (0.67 g, 10.3 mmol) in water was added slowly. After standing 45 min at 0° and 5 hr at room temperature, the reaction mixture was extracted with petroleum ether. The extract was washed with aqueous sodium carbonate and water, dried, and concentrated on a rotary evaporator. Chromatography of the residue on alumina using petroleum ether as the eluent gave 1a as a light yellow liquid, ν_{N_3} 2125 cm^{-1}.

Anal. Calcd for $C_{11}H_{13}N_3$: C, 70.56; H, 7.00. Found: C, 70.79; H, 7.23.

2-Propylindole (2a). A. In Decalin.—A solution of 1a (1.1 g, 5.8 mmol) in decalin (100 ml) was reluxed for 4 hr. The decalin was distilled at reduced pressure and the residue chromatographed on silicic acid. Hexane–benzene (2:1) eluted 2a (0.75 g, 81%), mp 32–34° after recrystallization from benzene–hexane (lit.[15] 34°), having an infrared spectrum identical with that of an authentic sample.

B. In Ethylene Glycol.—A solution of 1a (1.0 g, 5.3 mmol) was refluxed in ethylene glycol (100 ml) for 4 hr. The cooled solution was poured into water. Ether extraction followed by purification as in A gave 2a (0.65 g, 76%).

trans-2-Azidostilbene (1b).—*trans*-2-Aminostilbene[21] (1.3 g, 5.5 mmol) was converted to 1b essentially as for 1a. Extraction of the reaction mixture with benzene and evaporation gave 1b (1.05 g, 4.8 mmol, 87%), mp 94–95.5° after recrystallization from benzene–hexane, ν_{N_3} 2150 cm^{-1}.

Anal. Calcd for $C_{14}H_{11}N_3$: C, 75.99; H, 5.01; N, 18.99. Found: C, 75.78; H, 4.90; N, 18.78.

2-Phenylindole (2b).—The pyrolysis of 2a (1 g, 4.5 mmol) was carried out in ethylene glycol as described for 2-propylindole.

(9) A report[10] that esters of indole-2-glyoxylic acid can be prepared from indolylmagnesium bromide and dialkyl glyoxalates can be discounted on the basis of (1) the known[11] selectivity of this reaction for formation of 3-substituted indoles; (2) the agreement of the reported[10] melting points of the esters with literature value is for 3 derivatives [methyl ester mp 220° (lit.[12,13] mp 224°, 231°), ethyl ester mp 184° (lit.[13,14] mp 186°, 187°)]; (3) the agreement of the melting point reported[10] for the acid, 224–225°, with that of indole-3-glyoxylic acid, lit.[13] mp 218° dec.

(10) I. I. Lapkin and Yu. P. Dormidontov, *Chem. Heterocycl. Compounds*, **3**, 678 (1967); *Chem. Abstr.*, **68**, 87092 (1968).

(11) R. J. Sundberg, "The Chemistry of Indoles," Academic Press, New York, N. Y., 1970, pp 33–35, 412–414; R. A. Heacock and S. Kašpárek, *Advan. Heterocycl. Chem.*, **10**, 43 (1969).

(12) J. W. Baker, *J. Chem. Soc.*, 458 (1940).

(13) K. N. F. Shaw, A. McMillan, A. G. Gudmundson, and M. D. Armstrong, *J. Org. Chem.*, **23**, 1171 (1958).

(14) F. Millich and E. I. Becker, *ibid.*, **23**, 1096 (1958).

(15) A. Verley and J. Beduwe, *Bull. Soc. Chim. Fr.*, **37** 189 (1925).

(16) E. Fischer and T. Schmitt, *Chem. Ber.*, **21**, 1071 (1888).

(17) J. A. Joule and C. Djerassi, *J. Chem. Soc.*, 2777 (1964).

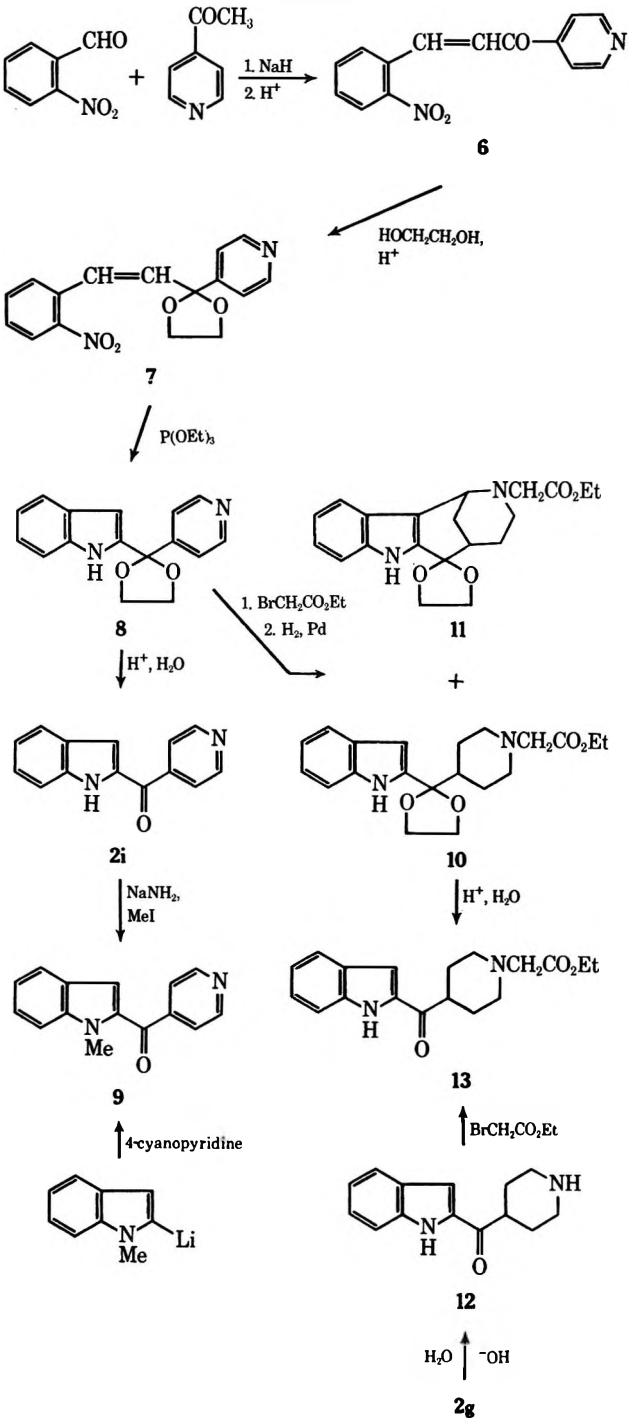
(18) J. A. Joule, M. Ohashi, B. Gilbert, and C. Djerassi, *Tetrahedron*, **21**, 1717 (1965).

(19) For a summary of electrophilic substitution of indoles by iminium intermediates, see R. J. Sundberg, "The Chemistry of Indoles," Academic Press, New York, N. Y., 1970, pp 56–67, 236–251.

(20) R. J. Sundberg, *J. Amer. Chem. Soc.*, **88**, 3781 (1966).

(21) Prepared by iron–acetic acid reduction of *trans*-2-nitrostilbene.

SCHEME I



After extraction and evaporation, there was obtained **2b** (0.75 g, 85%), mp 187–188° after recrystallization from ethanol.

Methyl Indole-2-glyoxalate (2c) and Methyl 2′,2′-Dimethoxyindole-2-acetate (2d).—*o*-Azidobenzaldehyde[22] (3.7 g, 25 mmol) and pyruvic acid (3.52 g, 25 mmol) were dissolved in 20 ml of anhydrous methanol cooled in an ice bath. To the vigorously stirred solution, there was added dropwise a solution of potassium hydroxide (2.1 g, 37.5 mmol) in methanol (20 ml). After about two-thirds of the potassium hydroxide solution had been added, the remainder was run in rapidly to minimize precipitation of potassium pyruvate prior to condensation. A voluminous yellow precipitate formed. The solution was stirred at room temperature and then refrigerated overnight. The precipitated sodium salt (~80% yield) was dissolved in warm (40°) water and added to vigorously stirred 1.6 *N* hydrochloric acid cooled in an ice bath. After 1 hr, the solution was extracted with ether giving the acid hydrate as a yellow-orange semisolid after concentration. The crude acid was dissolved in anhydrous methanol and a small amount of sulfuric acid was added. The solution was refluxed for 12 hr. The methanol solution was concentrated to 50 ml using a rotary evaporator and poured into a large excess of anhydrous ether. The ether solution was washed with $NaHCO_3$ solution, dried, and evaporated to give 3.8 g of a mixture of the ester **1c** and the corresponding ketal **1d**. Pyrolysis of this mixture in refluxing decalin (4 hr) gave a mixture of **2c** (1.2 g, 21%) and **2d** (0.5 g, 8%) after separation by chromatography on silicic acid. The keto ester **2c** was eluted by benzene and the ketal **2d** by 1:20 ether–benzene. After decolorization with charcoal and recrystallization from chloroform–hexane **2c** was obtained as a yellow solid: mp 138–139°; ν_{NH} 3370, ν_{CO} 1730, 1650 cm^{-1}; nmr peaks ($CDCl_3$) at δ 3.88 (3 H, s), 7.0–7.9 (6 H, m); uv $\lambda_{max}^{95\%\ EtOH}$ 240 (3.8), 331 nm (4.2).

Anal. Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.08; H, 4.44; N, 6.81.

Recrystallization of **2d** from chloroform–hexane gave white crystals: mp 161–162.5°; ν_{NH} 3350, ν_{OC} 1750 cm^{-1}; nmr peaks ($CDCl_3$) at δ 3.28 (6 H, s), 3.70 (3 H, s), 6.58 (1 H, d, J = 3 Hz), 7.0–7.25 (3 H, m), 7.4–7.7 (2 H, m); uv $\lambda_{max}^{95\%\ EtOH}$ 215.5 (4.53), 277.5 (4.01), 284 (4.02), 292 nm (3.89).

Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.24; H, 6.29; N, 5.74.

***trans*-1-(*o*-Azidophenyl)-3-phenylpropen-3-one (1e).**—Acetophenone (0.83 g, 6.8 mmol) was added dropwise to a solution of sodium hydroxide (0.3 g) in water (10 ml) and ethanol (5 ml) cooled in an ice bath. A solution of *o*-azidobenzaldehyde (1.0 g, 6.8 mmol) in ethanol (1 ml) was added. After 10 min the reaction solution was removed from the ice bath and stirred at room temperature for 16 hr. Filtration gave the crude product. Recrystallization from ethanol gave **1e** (1.1 g, 65%). The analytical sample was prepared by repeated recrystallization: mp 70.5–71.5°; ν_{N_3} 2145, ν_{CO} 1670 cm^{-1}; nmr peaks ($CDCl_3$) at δ 8.2–7.8 (m, 3 H), and 7.8–6.9 (m, 8 H).

Anal. Calcd for $C_{15}H_{11}N_3O$: C, 72.27; H, 4.45; N, 16.86. Found: C, 72.13; H, 4.56; N, 16.82.

2-Benzoylindole (2e).—A mixture of **1e** (0.53 g, 2.1 mmol) and decalin (80 ml) was refluxed under nitrogen for 4 hr. After removal of decalin, the residue was recrystallized from chloroform–benzene giving **2e** (0.36 g, 72%), mp 147–148.5° (lit.[23] mp 146–148°), having an ir spectrum identical with that of an authentic sample.

1-(*o*-Azidophenyl)-3-(2-pyridyl)propen-3-one (1f).—Condensation of 2-acetylpyridine (0.85 g, 7.0 mmol) and *o*-azidobenzaldehyde (1.0 g, 6.8 mmol) was carried out as for **1e**. Recrystallization of the crude product from ethanol gave **1f** (1.0 g, 59%). The analytical sample was prepared by repeated recrystallization: mp 111–112°; ν_{N_3} 2150, ν_{CO} 1680 cm^{-1}; nmr peaks ($CDCl_3$) at δ 8.7 (m, 1 H), and 8.3–7.0 (m, 9 H).

Anal. Calcd for $C_{14}H_{10}N_3O$: C, 67.19; H, 4.03; N, 22.39. Found: C, 67.37; H, 3.93; N, 22.55.

2-Indolyl 2-Pyridyl Ketone (2f).—A solution of **1f** (0.55 g, 2.2 mmol) in decalin (80 ml) was reluxed for 4 hr. The cooled reaction mixture was extracted with dilute hydrochloric acid. The aqueous extract was made alkaline and extracted with chloroform. Evaporation of the dried extract gave a residue which soon crystallized. Recrystallization from benzene gave **2f** (0.25 g, 51%). An additional recrystallization gave the analytical sample: mp 134.5–136°; ν_{NH} 3350, ν_{CO} 1630 cm^{-1}; nmr peaks ($CDCl_3$) at δ 8.7 (m, 1 H), 8.4–6.9 (m, 9 H).

Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.65; H, 4.54; N, 12.61. Found: C, 75.42; H, 4.63; N, 12.41.

4-Acetyl-1-benzoylpiperidine (3).—2-Methyl-2-(4-pyridyl)-1,3-dioxolane[24] (8.3 g, 50 mmol) in water (40 ml) was hydrogenated (50 psi) over 5% rhodium–carbon catalyst until hydrogen uptake ceased. The catalyst was removed by filtration and the filtrate was stirred vigorously for 24 hr with a mixture of potassium carbonate (32 g), water (65 ml), chloroform (70 ml), ethanol (5 ml), and benzoyl chloride (11.2 g, 80 mmol). The chloroform layer was separated and the aqueous layer was extracted again with chloroform. The crude ketal obtained by evaporation was stirred at room temperature for 1 hr with 50% aqueous ethanol containing 1% hydrochloric acid. The product was extracted with chloroform and then chromatographed on silicic acid. The major component was eluted with 1:1

(22) T. J. Schwan and C. S. Davis, *J. Pharm. Sci.*, **57**, 877 (1968).

(23) R. V. Jardine and R. K. Brown, *Can. J. Chem.*, **41**, 2067 (1963).

(24) A. T. Nielsen, D. W. Moore, J. H. Mazur, and K. H. Berry, *J. Org. Chem.*, **29**, 2898 (1964).

ether–benzene and distilled giving **3** (6.5 g, 28 mmol, 56%), bp 175–177° (0.4 mm), which readily crystallized. The analytical sample, mp 68–70°, was prepared by recrystallization from hexane: ν_{CO} 1710, 1630; nmr peaks ($CDCl_3$) at δ 1.0–3.3 (10 H, m with prominent s at 2.17), 3.5–4.7 (2 H, very broad), 7.38 (5 H, s).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.45; H, 7.32; N, 5.87.

Smaller amounts of material having ir, nmr, and mass spectral data in accord with expectation for 1-benzoyl-4-(1-benzoyloxyethyl)piperidine and 2-(1-benzoyl-4-piperidyl)-2-methyl-1,3-dioxolane were eluted prior to **3**.

2-Indolyl 4-(1-Benzoylpiperidyl) Ketone (2g). A. *Via* **1-(1-Benzoyl-4-piperidyl)-3-(2-azidophenyl)-2-propen-1-one (1g).**—The methyl ketone **3** (2.31 g, 10.0 mmol) was added to a solution of sodium hydroxide (0.8 g) in 50% aqueous ethanol (100 ml). When the ketone had completely dissolved, *o*-azidobenzaldehyde (1.5 g, 10 mmol) in ethanol (10 ml) was added slowly. After 2 hr the reaction mixture was extracted with chloroform and the chloroform was washed with brine, dried, and concentrated to an orange foam. Half of the crude product chromatographed on silicic acid with 1:4 ether–benzene gave **1g** as a tan oil (0.80 g, 2.2 mmol, 44%). The compound was not obtained in crystalline form.

A sample of chromatographed **1g** (0.60 g, 1.7 mmol) was suspended in decalin and refluxed (195°) for 4 hr. After the decalin was removed, the residual solid was chromatographed on silicic acid. Elution with 1:2 ether–benzene gave an oil which crystallized from carbon tetrachloride giving **2g** (0.20 g, 0.6 mmol, 35%): mp 166–167.5 after recrystallization from carbon tetrachloride; ν_{NH} 3350, ν_{CO} 1645 cm^{-1}; $\lambda_{max}^{95\%\ EtOH}$ 226 (log ϵ 4.30), 310 (4.37); nmr peaks ($CDCl_3$) at δ 1.6–2.2 (4 H, m), 2.8–3.7 (3 H, m), 3.8–4.2 (2 H, very broad), 7.0–7.8 (10 H, m), 9.8 (1 H, s).

Anal. Calcd for $C_{21}H_{20}N_2O_2$: C, 75.88; H, 6.07; N, 8.43. Found: C, 75.83; H, 6.19; N, 8.34.

The unchromatographed portion of **1g** gave a comparable yield of **2g** (0.24 g, 43%) when subjected to an identical pyrolysis.

B. By Deoxygenation. 1-(1-Benzoyl-4-piperidyl)-3-(o-nitrophenyl)-2-propen-1-one (4).—A solution of the ketone **3** (2.31 g, 1.00 mmol) and *o*-nitrobenzaldehyde (3.8 g, 2.5 mmol) in ether (50 ml) was treated with 3 ml of a solution prepared by dissolving 3 ml of 10% NaOH in ethanol (25 ml). The solution was stirred at 0° for 2 hr and then refrigerated overnight. The crude product was extracted into benzene and washed with sodium bicarbonate solution and dilute hydrochloric acid. The dried solution was concentrated and redissolved in benzene (100 ml) containing *p*-toluenesulfonic acid (0.5 g). This solution was refluxed for 2 hr to complete dehydration of any intermediate ketol. The cooled solution was washed with dilute sodium bicarbonate, dried, and evaporated. Chromatography of the residue on silicic acid gave **4** (1.0 g, 2.8 mmol, 28%): mp 116–117° after recrystallization from carbon tetrachloride; ν_{CO} 1695, 1640, ν_{NO_2} 1540, 1350 cm^{-1}; nmr peaks ($CDCl_3$) at δ 0.8–2.2 (4 H, m), 2.8–3.4 (3 H, m), 3.6–4.7 (2 H, very broad), 6.7 (1 H, d, J = 16 Hz), 7.45 (5 H, s), 7.68 (3 H, broad s), 8.1 (2 H, m with prominent d, J = 16 Hz).

Anal. Calcd for $C_{21}H_{20}N_2O_4$: C, 69.21; H, 5.53; N, 7.69. Found: C, 69.02; H, 5.65; N, 7.49.

2-Indolyl 4-(1-Benzoylpiperidyl) Ketone (2g) and 2-(1-Ethoxyindolyl) 4-(1-Benzoylpiperidyl) Ketone (5).—A suspension of **4** (1.05 g, 2.9 mmol) in triethyl phosphite (100 ml) was slowly heated to 145° over a 1.5-hr period using an oil bath. The nitrostyrene dissolved during this period. The solution was kept at 145° for an additional 0.5 hr. After the mixture was cooled, the triethyl phosphite was removed by distillation at 0.1 mm. The residue was dissolved in benzene and washed with sodium bicarbonate, dilute hydrochloric acid, and water. Evaporation of the dried benzene extract gave a brown oil which was chromatographed on silicic acid. Elution with 1:4 ether–benzene gave first **5** and then **2g**. The latter product (0.20 g, 0.6 mmol 21%), was identified as **2g** by mixture melting point and ir comparison with **2g** prepared by azide pyrolysis.

The by-product **5** was crystallized from benzene–hexane (0.12 g, 0.3 mmol, 11%): mp 131–132.5°; ν_{NH} none, ν_{CO} 1660, 1625 cm^{-1}; nmr peaks ($CDCl_3$) at δ 1.43 (3 H, t), 1.6–2.2 (4 H, m), 2.75–3.6 (3 H, m), 3.8–4.8 (4 H, m superimposed on q), 7.0–7.9 (10 H); $\lambda_{max}^{85\%\ EtOH}$ 232 (log ϵ 4.35), 306 (4.37).

Anal. Calcd for $C_{23}H_{24}N_2O_3$: C, 73.38; H, 6.43; N, 7.44. Found: C, 73.16; H, 6.59; N, 7.48.

1-Benzoyl-4-acetonyl-1,2,3,6-tetrahydropyridine (14) and 1-Benzoyl-$\Delta^{4,\alpha}$-piperidine-4-acetone (15).—Sodium hydride (4.2 g of 50% mineral oil dispersion) was rinsed with hexane and covered with anhydrous ether (250 ml). A solution of diethyl acetonylphosphonate[25] (21.4 g, 0.11 mol) in ether (50 ml) was added slowly. When hydrogen evolution had ceased, a solution of 1-benzoyl-4-piperidone (20.3 g, 0.10 mol) in dry benzene (100 ml) and ether (200 ml) was added in one portion. The resulting reaction mixture was refluxed under nitrogen for 20 hr. The organic solution was decanted and the gummy precipitate was washed with additional ether. The combined organic layers were filtered, washed with water, dried ($MgSO_4$), and evaporated. The residue was chromatographed on silicic acid using 30% ether in benzene to elute a mixture of the products (12.9 g of **14**, 53%; 4.3 g of **15**, 18%). Separation of the isomers could be effected by chromatography on silicic acid using 5% ether in benzene as eluant. The exocyclic ketone **15** was eluted most rapidly and was obtained as crystals: mp 70.5–72° on recrystallization from ether–hexane; ν_{CO} 1690, 1640 cm^{-1}; nmr peaks ($CDCl_3$) at δ 7.4 (s, 5 H), 6.15 (broad s, 1 H), 3.9–3.4 (broad, 4 H), 3.1–2.8 (broad t, 2 H), 2.5–2.1 (broad t, 2 H), and 2.1 (s, 3 H).

Anal. Calcd for $C_{15}H_{17}O_2N$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.84; H, 7.12; N, 5.54.

The endocyclic isomer **14** was an oil: ν_{CO} 1720, 1640 cm^{-1}; nmr peaks ($CDCl_3$) at δ 7.4 (s, 5 H), 5.5 (broad, 1 H), 4.3–3.3 (broad, 4 H), 3.1 (s, 2 H), 2.3–1.9 (broad, 2 H), and 2.1 (s, 3 H).

Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.89; H, 7.06; N, 5.62.

1-Benzoyl-4-piperidylmethyl Methyl Ketone (16).—A mixture of **14** and **15** (2.3 g, 9.4 mmol) was hydrogenated (40 psi) over platinum oxide (0.3 g) in ethanol for 30 min. The reaction solution was filtered and evaporated. The residue gave crystalline **16** (1.8 g, 78%) on trituration with ether, mp 62–64° (lit.[7] mp 63–65°). The ir spectrum was identical with that of an authentic sample.

1-Benzoyl-4-piperidylmethyl 2-Indolyl Ketone (2h).—Condensation of **16** (0.25 g, 10.0 mmol) and *o*-azidobenzaldehyde (0.15 g, 1.0 mmol) was carried out in basic aqueous ethanol as described for **2g**. After the reaction mixture was stirred overnight, it was diluted with water and extracted with chloroform. The residue was purified by chromatography on silicic acid giving **1h** (0.2 g, 0.5 mmol, 50%) as a gum: ν_N 2150, ν_{CO} 1680, 1650; nmr peaks ($CDCl_3$) at δ 8.0–6.9 (m, 10 H), 6.65 (d, 1 H) and 3.2–0.3 (braod, 11 H).

The azide (0.18 g, 0.48 mmol) was pyrolyzed in decalin in the usual way and the residue obtained after evaporation of the decalin was chromatographed on silicic acid (12 g). Elution with 1:10 ether–benzene gave **2h** (0.10 g, 60%), mp 154–155° after recrystallization from carbon tetrachloride (lit.[7] mp 154–156°). The ir and nmr spectra were identical with those of an authentic sample.

3-(o-Nitrophenyl)-1-(4-pyridyl)prop-2-en-1-one (6).—4-Acetylpyridine (10.0 g, 83 mmol), *o*-nitrobenzaldehyde (11.1 g, 83 mmol), and sodium hydride (1.00 g, 59% dispersion in mineral oil, 25 mmol) were added in that order to dry ether (150 ml). Within 2 min dark yellow crystals separated and additional ether (50 ml) was added. The solution was stirred for an additional 30 sec and then poured as rapidly as possible into a stirred 4% hydrochloric acid solution. The two-phase system was neutralized with aqueous sodium bicarbonate. During this process most of the ether evaporated as carbon dioxide was evolved. The product was obtained by filtration, washed several times with water, and dried to give **6** (18.9 g, 90%). Recrystallization from ethanol–water gave the analytical sample, mp 147°, ν_{CO} 1680 cm^{-1}.

Anal. Calcd for $C_{14}H_{10}N_2O_3$: C, 66.14; H, 3.96; N, 11.02. Found: C, 66.14; H, 4.06; N, 10.96.

2-[2-(o-Nitrophenyl)vinyl]-2-(4-pyridyl)-1,3-dioxolane (7.)—The ketone **6** (18.9 g, 75 mmol), ethylene glycol (13.5 ml), and *p*-toluenesulfonic acid (12.9 g, 83 mmol) were refluxed together in benzene (340 ml) in a flask equipped with a Dean-Stark trap. After 2 hr, more ethylene glycol (20 ml) and *p*-toluenesulfonic acid (0.36 g) were added and reflux was continued for 22 hr. The reaction solution was cooled and washed with 10% potassium carbonate solution (450 ml). The aqueous wash was reextracted with chloroform and the benzene and chloroform solutions were combined, dried over potassium carbonate, and concentrated. The residue was passed through a short Florisil

(25) N. Kreutzkamp and H. Kayser, *Chem. Ber.*, **89**, 1614 (1956).

column to give pure **7** (11.7 g, 54%) after removal of the solvent. Recrystallization from chloroform–hexane gave pale yellow needles: mp 93–94°; nmr peaks ($CDCl_3$) at δ 8.9–8.6 (broad d, 2 H), 8.2–7.8 (m, 1 H), 7.7–7.2 (m, 6 H), 6.3 (d, 1 H, J = 18 Hz) and 4.2 (m, 4 H).

Anal. Calcd for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.21; H, 4.71; N, 9.31.

2-(2-Indolyl)-2-(4-pyridyl)-1,3-dioxolane (8).—The dioxolane **7** (5.40 g, 2.03 mmol) was dissolved in triethyl phoshite (170 ml) and this solution was added dropwise during 2 hr to refluxing triethyl phosphite (130 ml) under a nitrogen atmosphere. Reflux was continued for 4 hr after the addition was complete. The reaction mixture was then cooled and unreacted triethyl phosphite was removed by distillation at reduced pressure. The residue was dissolved in ether (300 ml). The hydrochloride of the product was precipitated as a glass by passing hydrogen chloride gas through the solution. The ether was decanted when precipitation was complete. The residue was washed with ether and stirred with a mixture of chloroform and dilute sodium hydroxide until it was completely dissolved. The chloroform layer was dried and concentrated. After elution through a Florisil column, **8** was obtained as colorless plates (2.43 g, 45%): mp 166–168° from chloroform–hexane; nmr peaks ($CDCl_3$) at δ 9.30 (1 H, broad s), 8.64 (2 H, d), 7.8–7.0 (6 H, m), 6.4 (1 H, d, J = 3 Hz) and 4.0 (4 H, m).

Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.32; H, 5.11; N, 10.53.

2-Indolyl 4-Pyridyl Ketone (2i).—The ketal (1.00 g, 3.8 mmol) was heated with 10% hydrochloric acid (100 ml) on a steam bath for 5 min. The crude product precipitated when the solution was made basic with sodium hydorxide solution. Recrystallization from aqueous ethanol gave **2i** (0.80 g, 95%), mp 172–174° (lit.[8] mp 172–174°).

Imine of 2-(1-Methylindolyl) 4-Pyridyl Ketone (17).—*N*-Methylindole (1.31 g, 10.0 mmol) in anhydrous ether (20 ml) was added at 0° to 5 ml of a 2 *M* hexane solution of butyllithium.[26] The mixture was refluxed for 7 hr, cooled to 0°, and treated with a solution of 4-cyanopyridine (1.04 g, 10.0 mmol) in ether (50 ml). The mixture was stirred overnight during which time a reddish brown solid appeared. The reaction mixture was then cooled and hydrolyzed with a mixture of crushed ice and ammonium chloride resulting in the precipitation of the imine **17**. Additional amounts of **17** were obtained by ether extraction giving a total yield of 1.85 g (7.9 mmol, 79%): mp 165–166.5° after recrystallization from benzene–hexane; ν_{NH} 3245, ν_{CN} 1605 cm^{-1}; nmr peaks ($CDCl_3$) at δ 4.03 (3 H, broad s), 6.58 (1 H, s), 7.0–7.7 (7 H, m), 8.75 (2 H, d); λ_{max}^{EtOH} 222 (log ε 4.42), 277 (3.84), 3.13 (4.03).

Anal. Calcd for $C_{15}H_{13}N_3$: C, 76.57; H, 5.57; N, 17.87. Found: C, 76.55; H, 5.62; N, 17.78.

2-(1-Methylindolyl) 4-Pyridyl Ketone (9). A. By Hydrolysis of 17.—The imine **17** (1.2 g, 5 mmol) was suspended in 60 ml of 50% ether–water and 1 *N* hydrochloric acid was added at 0° until the mixture was acidic. The mixture was then refluxed for 2 hr, cooled, made alkaline, and extracted with ether. The solvent was dried, and concentrated and the residue was triturated with hexane to give **9** as a yellow solid. Recrystallization from hexane afforded **9** (0.95 g, 4.0 mmol, 80%): mp 91–92.5°; ν_{CO} 1640 cm^{-1}; nmr peaks ($CDCl_3$) at δ 4.14 (3 H, s), 7.0–7.8 (7 H, m including a d, J = 6 Hz, at 7.7), 8.83 (2 H, d, J = 6 Hz); λ_{max}^{EtOH} 224 (log ε 4.37), 268 (3.64), 325 (4.23).

Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.11; H, 5.18; N, 11.72.

B. By Methylation of 2i. A solution of sodium amide in ammonia was prepared by addition of ferric nitrate nonahydrate (1 mg) and then sodium (0.20 g) in small pieces to liquid ammonia. The solution was stirred for 1 hr and then **2i** (1.11 g, 5.0 mmol) in anhydrous tetrahydrofuran (30 ml) was added dropwise. After the mixture was stirred for 15 min, a solution of methyl iodide (1.5 g, 10 mmol) in anhydous ether (10 ml) was added. Stirring was continued for 0.5 hr and then the ammonia was allowed to evaporate. Water (10 ml) was added cautiously and the resulting mixture was extracted with ether. Drying and evaporation gave a residue which was crystallized from chloroform–hexane to give recovered **2i** (0.55 g, 50% recovery). The mother liquors contained **9** (0.45 g, 1.9 mmol, 38%), mp 89–92° after recrystallization from hexane. The ir spectrum of this material was identical with that of the product prepared as described in part A.

1-Carbethoxymethyl-4-[1-(2-indolyl)-1-dioxolanyl]pyridinium Bromide (18).—A solution of **8** (0.45 g, 1.7 mmol) in anhydrous tetrahydrofuran (40 ml) was treated with ethyl bromoacetate (5 ml) and refluxed for 2 hr. The product **18** precipitated as a bright yellow solid (0.72 g, 98%). Recrystallization from ethanol–ether gave the analytical sample: mp 150–152° dec; ν_{CO} 1750 cm^{-1}; nmr peaks (DMSO-d_6) at δ 9.3 (d, 2 H), 8.4 (d, 2 H), 6.8–7.7 (m, 4 H), 6.3 (s, 1 H), 5.38 (s, 2 H), 3.9–4.5 (6 H, m), 3.38 (s, 1 H) and 1.25 (t, 3 H).

Anal. Calcd for $C_{20}H_{21}BrN_2O_4$: C, 55.43; H, 4.85; N, 6.47. Found: C, 55.20; H, 4.95; N, 6.47.

Reduction of 18. 1-(2-Indolyl)-1-(*N*-carbethoxymethyl-4-piperidyl)dioxolane (10) and By-Product 11.—A solution of **18** (4.1 g, 95 mmol) in absolute ethanol (150 ml) was hydrogenated at 30 psi over 10% Pd/C for 12 hr. The solution was filtered and evaporated. The residue was dissolved in chloroform and washed with 10% sodium carbonate solution. Evaporation yielded an oil which was chromatographed on silicic acid using 1:1 ether–benzene for elution. The major product **10** was eluted first and crystallized from benzene–hexane (3.4 g, 79%): mp 152–153°; ν_{NH} 3200, ν_{CO} 1750 cm^{-1}; nmr peaks ($CDCl_3$) at δ 8.4 (broad s, 1 H), 6.9–7.7 (m, 4 H), 6.45 (broad s, 1 H), 3.6–4.4 (m, 6 H including q at 4.15), 2.7–3.3 (m, 4 H including s at 3.15), 1.45–2.40 (broad, 7 H), 1.21 (t, 3 H).

Anal. Calcd for $C_{20}H_{26}N_2O_4$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.13; H, 7.38; N, 7.72.

Compound **11** was eluted immediately after **10** and was crystallized from ether–hexane (0.25 g, 7%): mp 149–150.5°; ν_{NH} 3310 cm^{-1}, ν_{CO} 1730 cm^{-1}; nmr peaks at 8.55 (broad s, 1 H), 7.0–7.75 (m, 4 H), 3.95–4.50 (m, 7 H), 3.40 (d, 1 H, J = 16 Hz), 2.83 (d, 1 H, 16 Hz), 1.7–2.8 (broad, 7 H), 1.25 (t, 3 H).

Anal. Calcd for $C_{20}H_{24}N_2O_4$: C, 67.39; H, 6.79; N, 7.86. Found: C, 67.44; H, 6.89; N, 7.93.

The yields of **10** and **11** were 66 and 12%, respectively, when the reduction was carried out in ethanol containing 5% acetic acid.

2-Indolyl 4-(1-Carbethoxymethyl)piperidyl Ketone (13).—A solution of **10** (0.20 g, 0.56 mmol) in 85% ethanol containing 3 drops of concentrated HCl was refluxed for 0.5 hr and then made alkaline with 10% sodium hydroxide solution. Most of the ethanol was removed using a rotary evaporator and the resulting suspension was extracted with chloroform. The chloroform was dried and evaporated to give an oil. Trituration with ether gave **13** (0.14 g, 80%): mp 129.5–131° after two recrystallizations from benzene–hexane; ν_{NH} 3360, ν_{CO} 1740, 1645 cm^{-1} in KBr; $\lambda_{max}^{95\% EtOH}$ 227 (log ε 4.1), 234 (sh, 4.08), 311.5 (4.34); nmr peaks ($CDCl_3$) at δ 1.25 (3 H, t, J = 7 Hz), 1.75–2.7 (7 H, m), 2.85–3.35 (m with prominent s at 2.25, 4 H), 4.15 (q, 2 H), 7.0–7.8 (m, 6 H).

Anal. Calcd for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.58; H, 7.08; N, 9.11.

2-Indolyl 4-(1-Carbethoxymethyl)piperidyl Ketone (13) from 2g *via* 12.—A solution of **2g** (200 mg, 0.6 mmol) and KOH (3.5 g) in 50 ml of methanol and 15 ml of water was heated under reflux for 48 hr. The solution was cooled, diluted with water, and thoroughly extracted with $CHCl_3$. The solvent was evaporated from the combined, dried extracts to give 0.16 g of yellowish oil. Trituration with anhydrous ether gave 0.13 g (95%) of cream colored solid which thin layer chromatograph and melting point showed to be slightly impure. Four recrystallizations from benzene eventually gave 2-indolyl 4-piperidyl ketone (**12**) as a pale tan solid of constant melting point (163–164°): ν_{NH} 3345, ν_{CO} 1640 cm^{-1} in KBr; nmr peaks ($CDCl_3$) at δ 7.0–7.8 (m, 6 H), 2.5–3.6 (broad m, 6 H).

A solution of **12** (20 mg, 0.88 mmol) in anhydrous benzene (5 ml) was treated with ethyl bromoacetate (10 μl) and stirred at room temperature for 4 hr. Aqueous sodium carbonate was added and the mixture was extracted with chloroform. The extract was dried and evaporated. The residual oil (22 mg, 80%) was identified as **13** by tlc. Isolation by preparative layer chromatography (250 μ, silica gel) and crystallization from benzene–hexane gave **13** (20 mg) identified by melting point and ir spectrum.

***N*-Carbethoxymethyl-4-(indol-2-ylcarbonyl)pyridinium Bromide (19).**—A solution of **2i** (3.0 g, 0.0135 mol) and ethyl bromoacetate (20 ml) in tetrahydrofuran (50 ml) was refluxed for 1 hr. The product partially separated as a heavy oil. The mother liquor was diluted with ether to precipitate the re-

(26) D. A. Shirley and P. A. Roussel, *J. Amer. Chem. Soc.*, **75**, 375 (1953).

mainder of the product. Crystallization from ethanol–ether gave **19** (4.0 g, 76%): mp 195° dec; ν_{CO} 1750, 1640 cm^{-1}; nmr peaks (DMSO-d_6) at δ 12.3 (s, 1 H), 9.5 (d, 2 H), 8.6 (d, 2 H), 7.9–7.0 (m, 4 H), 6.0 (s, 1 H), 4.31 (q, 2 H), 3.4 (s, 2 H), and 1.32 (t, 3 H).

Anal. Calcd for $C_{18}H_{17}BrN_2O_3$: C, 55.52; H, 4.37; N, 7.19. Found: C, 55.68; H, 4.31; N, 7.10.

N-**Carbethoxymethyl-4-(1-methylindol-2-ylcarbonyl)pyridinium Bromide (20).**—A solution of **9** (2.4 g, 0.010 mmol) in anhydrous tetrahydrofuran (50 ml) was treated with 10 ml of ethyl bromoacetate with stirring. The solution was refluxed for 2 hr, cooled, and diluted with ether. The orange precipitate was recrystallized several times from ethanol–ether giving **20** (3.6 g, 89%): mp 166.5–167.5° dec; ν_{CO} 1750, 1640 cm^{-1}; nmr peaks (DMSO-d_6) at δ 9.48 (d, 2 H), 8.6 (d, 2 H), 7.0–7.9 (m, 5 H), 6.0 (s, 2 H), 4.0–4.5 (overlapping q and s, 5 H), 1.30 (t, 3 H).

Anal. Calcd for $C_{19}H_{19}BrN_2O_3$: C, 56.58; H, 4.71; N, 6.95. Found: C, 56.33; H, 4.77; N, 6.92.

Mass Spectral Data.—The principal ions in the mass spectra of compounds **2c**, **2d**, **2g**, **2i**, **9**, **10**, **11**, **12**, **13**, and **17** have been submitted in tabular form as supplementary data in the microfilm edition of this jouranl.[27]

Registry No.—**1a**, 33037-72-8; **1b**, 33037-73-9; **1e**, 33037-74-0; **1f**, 33037-75-1; **1h**, 33037-76-2; **2b**, 948-65-2; **2e**, 18132-19-9; **2d**, 33037-79-5; **2f**, 24512-42-3; **2g**, 33037-81-9; **3**, 33037-82-0; **4**, 33037-83-1; **5**, 33037-84-2; **6**, 33037-85-3; **7**, 33037-86-4; **8**, 33037-87-5; **9**, 25387-27-3; **10**, 33037-89-7; **11**, 33080-10-3; **12**, 33037-90-0; **13**, 33037-91-1; **14**, 33037-92-2; **15**, 33037-93-3; **17**, 33037-94-4; **18**, 33037-95-5; **19**, 33037-96-6; **20**, 33037-97-7.

(27) Mass spectral data 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 St., N.W., Washington, D. C. 20036, by referring to author, title of article, volume, and page number. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

Isocarbostyrils from Monomeric and Dimeric β-Styryl Isocyanates[1,2]

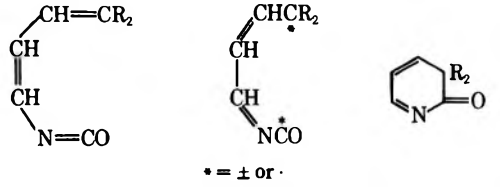
G. J. MIKOL AND J. H. BOYER*

Chemistry Department, University of Illinois, Chicago Circle Campus, Chicago, Illinois 60680

Received August 27, 1971

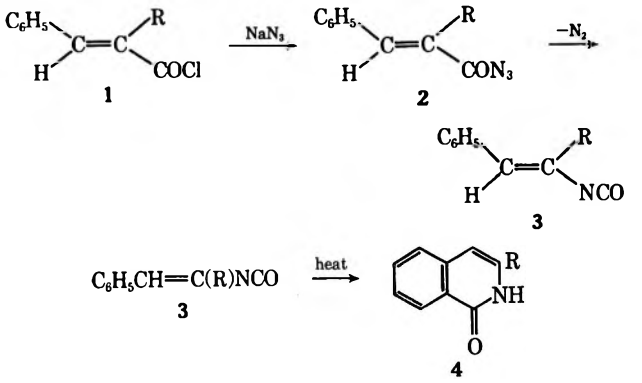
In an inert solvent at 250°, *trans*-β-styryl isocyanate (**3a**) and its β-methyl (**3b**) and β-phenyl (**3c**) derivatives were efficiently isomerized into the corresponding isocarbostyril **4a**, **4b**, and **4c**. In the presence of iodine the reaction proceeded conveniently at the reduced temperature of 140°. Two dimers of β-styryl isocyanate were obtained; one was converted into **4a** on heating in refluxing pyridine.

A formal, but unestablished, interconversion by valence isomerization may be recognized for an *s-cis*-isocyanatobutadiene-1,3 and a 2-oxo-2,3-dihydropyridine. Should ring closure proceed instead from either a zwitterionic or diradical structure, then the geometrical restriction on the isocyanate disappears. Styryl



isocyanates were selected for investigation since ring closure from closely related systems was known[3] and they are more readily available than structurally simpler isocyanatodienes.

By the thermal Curtius reaction each *trans*-cinnamoyl azide (**2**), obtained by treating *trans*-cinnamoyl chloride (**1**) with sodium azide, gave the corresponding *trans*-β-styryl isocyanate (**3**) in overall yield ranging from moderate to good. The azide could, however, be converted into the isocarbostyril without isolation of **3**.



a, R = H; **b**, R = CH_3; **c**, R = C_6H_5

Each isocyanate was efficiently isomerized in mineral oil or diphenyl ether at 250°. The isomerization **3a** → **4a** in the presence of iodine occurred in dichlorobenzene at 180° or in *m*-xylene at 140°, but there was no reaction in carbon tetrachloride at 77° and *trans*-isocyanate was quantitatively recovered.[4] Reaction progress in *o*-dichlorobenzene was monitored not only by disappearance of ir absorption at 2260 cm^{-1} (NCO), but also by development, followed by disappearance, of ir absorption (*o*-dichlorobenzene solution) at 1740 cm^{-1} and by development of permanent bands at 1665 and 1650 cm^{-1}. This indicated that the forma-

(1) Financial assistance was received from NASA Grant No. NGR-012-114.

(2) G. J. Mikol and J. H. Boyer, Abstracts, 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970, ORGN 51.

(3) The present investigations were completed when F. Eloy and A. Deryckere [*J. Heterocycl. Chem.*, 1191 (1970); *Chim. Ther.*, 48 (1971)] reported the preparation pf pyridine, isoquinoline, and other heterocyclic derivatives by the thermal cyclization of vinyl isocyanates substituted in the β position by a vinyl radical. H. M. Blatter and H. Lukaszewski [*Tetrahedron Lett.*, 855 (1964)] report a similar thermal cyclization for C_6H_5N=C(C_6H_5)NCS and discuss similar cyclizations for C_6H_5N=C(C_6H_5)NCO and for $C_6H_5C(C_6H_5)$=C(C_6H_5)CH=C=O.

(4) L. Crombie, *Quart. Rev., Chem. Soc.*, **6**, 101 (1952), reviews methods for geometrical isomerization.

TABLE I
PREPARATION AND PROPERTIES OF AZIDES 2 AND ISOCYANATES 3
$C_6H_5CH=C(X)Z$

Form, X	1, Z = COCl, Mp, °C	2, Z = CON$_3$[a] Mp, °C	Yield, %	Nmr, δ	Ir, cm^{-1}	3, Z = NCO[b] Bp, °C (mm)	Yield, %	Nmr, δ	Ir, cm^{-1}
a, H	33.5–34.5[c]	84–86[d]	72	7.68[e] 6.46[e]	2143[f]	44–45[g] (0.10)	81	6.58[h] 6.31[h]	2260[i]
b, CH_3	49–50[j]	*k*		7.61[l] 2.05[m]	2140[f]	57–59[n] (0.17)	78	6.20[o] 2.05[p]	2255[i]
c, C_6H_5	Oil[q]	70–72[r]	49	7.90[e]	2150[f]	*t*	37[u]	6.50[s]	2250[i]

[a] Each azide was prepared from the corresponding acyl chloride, assumed to be trans, and sodium azide according to a general procedure described by P. A. S. Smith, in "Organic Reactions," Vol. III, R. Adams, Ed., Wiley, New York, N. Y., 1946, p 373, but with acetonitrile as solvent. [b] Each isocyanate was prepared by heating the corresponding acyl azide in refluxing benzene according to a general procedure described by M. O. Forster, *J. Chem. Soc.*, 433 (1909), with the added precaution of purging with nitrogen before and during pyrolysis. [c] As obtained from Distillation Products, Rochester, N. Y. [d] L. W. Jones and J. P. Mason, *J. Amer. Chem. Soc.*, 49, 2528 (1927), reported mp 86°. [e] Trans vinyl protons with J_{ab} = 16 Hz. [f] Azido group. [g] M. O. Forster (ref *b*) reported bp 107° (12 mm). [h] Trans vinyl protons with J_{ab} = 15 Hz. [i] Isocyanate group. [j] J. A. Moore, *J. Org. Chem.*, 20, 1607 (1955), reported mp 49–50°. In the present work the preparation followed a general procedure reported by H. E. Zimmerman, L. Singer, and B .S. Thyagarajan, *J. Amer. Chem. Soc.*, 81, 108 (1959). [k] The preparation was carried out below 10°. A quantitative yield of impure product which solidified at 0° and melted with decomposition at room temperature could not be purified for analysis. On a silica gel column there was appreciable decomposition, but about 50% of the azide was eluted with hexane–benzene (4:1). [l] Vinyl proton quartet, J_{ac} = 1.5 Hz. [m] Methyl protons as a doublet, J_{ac} = 1.5 Hz. [n] Mp 27–28°. *Anal.* Calcd for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.36; H, 5.82; N, 8.76. [o] Vinyl proton quartet, J_{ac} = 1.2 Hz. [p] Methyl protons as a doublet, J_{ac} = 1.2 Hz. [q] R. Riemschneider and H. Kampfer, *Monatsh. Chem.*, 90, 518 (1959), reported mp 47–48°. The preparation here followed a general procedure (see ref *j*). [r] The preparation was carried out below 10°. The product was obtained initially as an oil which solidified on cooling. Apparently heat of crystallization was sufficient to cause nitrogen evolution. It melted with decomposition. It was not purified for analysis. Trituration with hexane removed isocyanate and other impurities. [s] Vinyl proton singlet. [t] The isocyanate undergoes ring closure on heating. [u] Eluted with benzene–hexane (3:2) from a silica gel column containing crude product.

tion of **4a** might be proceeding from either an isocyanate monomer **3a** or one of its dimers **5a**.

A solid dimer **5a**, mp 167–168°, ir 1725 and 1650 cm^{-1} (chloroform solution), was isolated from a reaction carried out in a mixture of *m*-xylene and carbon tetrachloride (15:1) containing a trace of iodine. Absence of absorption near 2260 cm^{-1} (NCO) required the dimerization to consume isocyanato groups. It was converted into **4a** by heating in diphenyl ether or in pyridine. Refluxing **3a** in a mixture of benzene and pyridine did not convert the isocyanate to **4a**; another dimer **5a′**, mp 229–230°, was the only product isolated.

Whether or not the separate conversions of an isocyanate and its dimer into an isocarbostyril are unrelated or proceed from a common intermediate has not been determined. In either event the ring closure required for isocarbostyril formation could be available either from a zwitterionic or diradical intermediate or from a cis olefin by valence isomerization. The present data tends to disallow a concerted valence isomerization, since cyclization is subject to catalysis.

Experimental Section

Instrumental data were obtained from a Beckman IR-10 and/or a Perkin-Elmer Model 521 infrared spectrometer, a Varian A-60A nmr spectrometer, and a Perkin-Elmer Model 270 mass spectrometer except where noted. Melting points were determined with a Thomas-Hoover capillary apparatus. Both melting points and boiling points are uncorrected. Elemental analyses were obtained from Microtech Laboratories, Skokie, Ill. The preparation of styryl isocyanates is described in Table I.

Thermal Reactions of β-Styryl Isocyanates 3.—A solution of 725 mg (5 mmol) of *trans*-β-styryl isocyanate (**3a**) in 4 ml of mineral oil (Fisher Scientific Company No. 13639) was heated at 240–250° for 4 hr. Isocarbostyril (**4a**) was isolated by precipitation on cooling and by dilution with hexane. The solid product, 688 mg, 95%, after trituration with hexane, recrystallized from ethanol as tan needles, mp 205–207°, ir ($CHCl_3$) 3440 (NH), 1660 (C=O), and 1640 cm^{-1} (C=C). A mixture melting point with an authentic sample showed no depression and the ir spectrum was superimposable on the spectrum obtained from authentic material. Isocarbostyril (**4a**) was obtained in 70% yield from a similar treatment of **3a** in refluxing diphenyl ether, bp 250°, for 2.5 hr.

In a similar way in mineral oil at 240–250°, 3-methylisocarbostyril (**4b**), 80% yield, mp 208–210°, ir ($CHCl_3$) 3420 (NH),1660 (C=O), and 1650–1670 cm^{-1} (C=C), was obtained from *trans*-β-(β-methyl)styryl isocyanate (**3b**), and 3-phenylisocarbostyril (**4c**), 75% yield, mp 197–198°, ir ($CHCl_3$) 3420 (NH), 1660 (C=O), and 1645 cm^{-1} (C=C), was obtained from *trans*-β-(β-phenyl)styryl isocyanate (**3c**), prepared *in situ* by heating α-phenylcinnamoyl azide (**2c**) in mineral oil at 80°.

β-Styryl isocyanate (**3a**) was prepared *in situ* by heating cinnamoyl azide (**2a**), 1.2 g (6.94 mmol) in refluxing carbon tetrachloride for 4 hr (or until ir monitoring showed disappearance of absorption for the azido group). Continued heating for 24 hr at the reflux temperature after adding a few flakes of iodine produced no change in the trans isocyanate. After replacing the solvent with *m*-xylene to which a flake of iodine was added, heating at the reflux temperature, 139°, for 166 hr brought about slow development of an absorption peak at 1740 cm^{-1} (C=O). Removal of solvent left a solid residue from which a small amount of colorless needles, mp 167–168° after recrystallization from acetonitrile, was obtained: ir ($CHCl_3$) 3300–2800, 1725 (C=O), 1650, 1640, 1628 (C=C), and 1410 cm^{-1}; nmr ($CDCl_3$) δ 6.0–7.0 (C_6H_5), 5.77 and 7.30 (doublets, J_{ab} = 8 Hz), and 5.52 and 6.78 (doublets, J_{ab} = 15 Hz). It appears to be a dimer (**5a**) of β-styryl isocyanate. *Anal.* Calcd for $(C_9H_7NO)_2$: C, 74.46; H, 4.86; N, 9.64; mol wt, 290.4. Found: C, 74.51; H, 4.91; N, 9.47; mol wt (osmometric), 262.

A similar treatment of *trans*-β-styryl isocyanate (**3a**) in refluxing *o*-dichlorobenzene, bp 179°, to which a flake of iodine was added brought about disappearance of absorption at 2260 cm^{-1} while a new carbonyl band initially developed at 1740 cm^{-1} (solvent was *o*-dichlorobenzene), but after 4 hr began to disappear as a band at 1665 cm^{-1} developed. Isocarbostyril (**4a**), mp 204–207°, was isolated in 90% yield. The solid dimer **5a**, mp 167–168°, ir 1725 cm^{-1} ($CHCl_3$), was also transformed into isocarbostyril in 34% yield on heating in refluxing diphenyl ether for 15 min, the time required for disappearance of the 1725-cm^{-1} absorption band and development of absorption at 1660 cm^{-1}.

A different dimer (**5a′**) of β-styryl isocyanate was obtained. After generating the isocyanate *in situ* by heating 2.4 g (13.9 mmol) of cinnamoyl azide in 25 ml of refluxing benzene for 4 hr, 0.7 ml of pyridine was added and the solution was heated at reflux for 190 hr. On standing at room temperature for 7 days

a granular solid, 0.62 g, 38.7%, separated. Recrystallization from a mixture of ethyl acetate and acetonitrile gave colorless needles: mp 229–230°; ir ($CHCl_3$) 3030, 1705 (C=O), 1430 and 960 cm^{-1}; nmr (CH_3COCH_3) δ 7.2–7.8. *Anal.* Calcd for $(C_9H_7NO)_2$: C, 74.46; H, 4.86; mol wt, 290.4. Found: C, 74.25; H, 4.91; mol wt, 325 (osmometric).

In contrast the dimer **5a**, mp 167–168°, on heating in pyridine for 1 hr was transformed into isocarbostyril; its ir (pyridine) absorption was identical with a spectrum for authentic material in pyridine.

Registry No.—**2a**, 33066-17-0; **2b**, 33066-18-1; **2c**, 32528-95-3; **3a**, 33066-20-5; **3b**, 33066-21-6; **3c**, 33066-22-7; **4a**, 491-30-5; **4b**, 7114-80-9; **4c**, 7115-13-1; **5a**, 33041-36-0.

The Reaction of Acyl Cyanides with Grignard Reagents

RICHARD F. BORCH,*[1a] STEPHEN R. LEVITAN,[1b] AND FREDERIC A. VAN-CATLEDGE

Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

Received July 22, 1971

The reaction of benzoyl cyanide (**1**) with Grignard reagents occurs *via* addition to the carbonyl group to give the corresponding phenyl ketones **2** in good yield. Acetyl cyanide (**3**), however, reacts with aliphatic Grignard reagents predominantly by reduction of the carbonyl group and subsequent acylation by **3** to give cyano ester **5**. Carbonyl cyanide (**6**) is attacked by isopropylmagnesium bromide at carbonyl to give isobutyryl cyanide, which is further reduced and acylated to give isobutyraldehyde cyanohydrin and its isobutyl ester. Finally, **6** reacts with phenylmagnesium bromide by attack at both the carbonyl and cyano groups to give benzil, benzophenone, and minor amounts of benzonitrile and benzoyl cyanide. These variations in reaction selectivity are discussed in light of the mechanisms postulated, and INDO calculations of electron density and infrared stretching frequencies are brought to bear on the reactivity of these compounds.

Part A

The reaction of Grignard reagents with carboxylic acid derivatives has been extensively investigated;[2] one apparent exception to this is the acyl cyanide derivative. Some time ago we began an investigation of acyl cyanide and carbonyl cyanide reactions with Grignard reagents in order to answer the following questions. (1) Would these compounds react as "deactivated" acid chlorides; *i.e.*, would the cyano group act exclusively as a carbonyl activating group, or would it compete with the organometallic reagent? (2) Would the intermediate cyanohydrin magnesium salt (I or IV in eq 1 or 2) have sufficient stability to block further addition to the carbonyl group, thus permitting the synthesis of ketones, or would it compete with the carbonyl group in reaction with the organometallic reagent? (3) Could sequential addition to carbonyl cyanide be controlled to permit synthesis of unsymmetrical ketones?[3] The answers to these questions constitute the subject of this two-part paper.

We began by investigating the reactions of benzoyl cyanide (**1**) and acetyl cyanide (**3**) to determine the selectivity of carbonyl addition. Reaction of **1** with a variety of Grignard reagents proceeded as expected; the corresponding phenyl ketones **2a–c** were obtained in 65–84% yield when **1** was treated with 1 equiv of the organomagnesium compound in ether at −40°. Gas chromatographic analyses of the crude products showed <5% of the tertiary alcohol and no trace of product derived from addition to the cyano group of **1**. Similarly, reaction of **3** with phenylmagnesium bromide at −70° resulted in a 70% yield of **2a**. When **3** was allowed to react with isopropyl-, *n*-amyl-, or cyclohexylmagnesium bromide, however, a new product **5** was isolated in 58–77% yield in addition to minor amounts of the expected ketone. The structure of **5** was confirmed by nmr and by synthesis of an authentic sample; its mode of formation is postulated in eq 1 (R = R′ = CH_3). It is apparent that, in the case of **3**, reduction of the carbonyl group *via* hydride transfer predominates over addition. There was no evidence of addition or reduction at the cyano group of **3**.

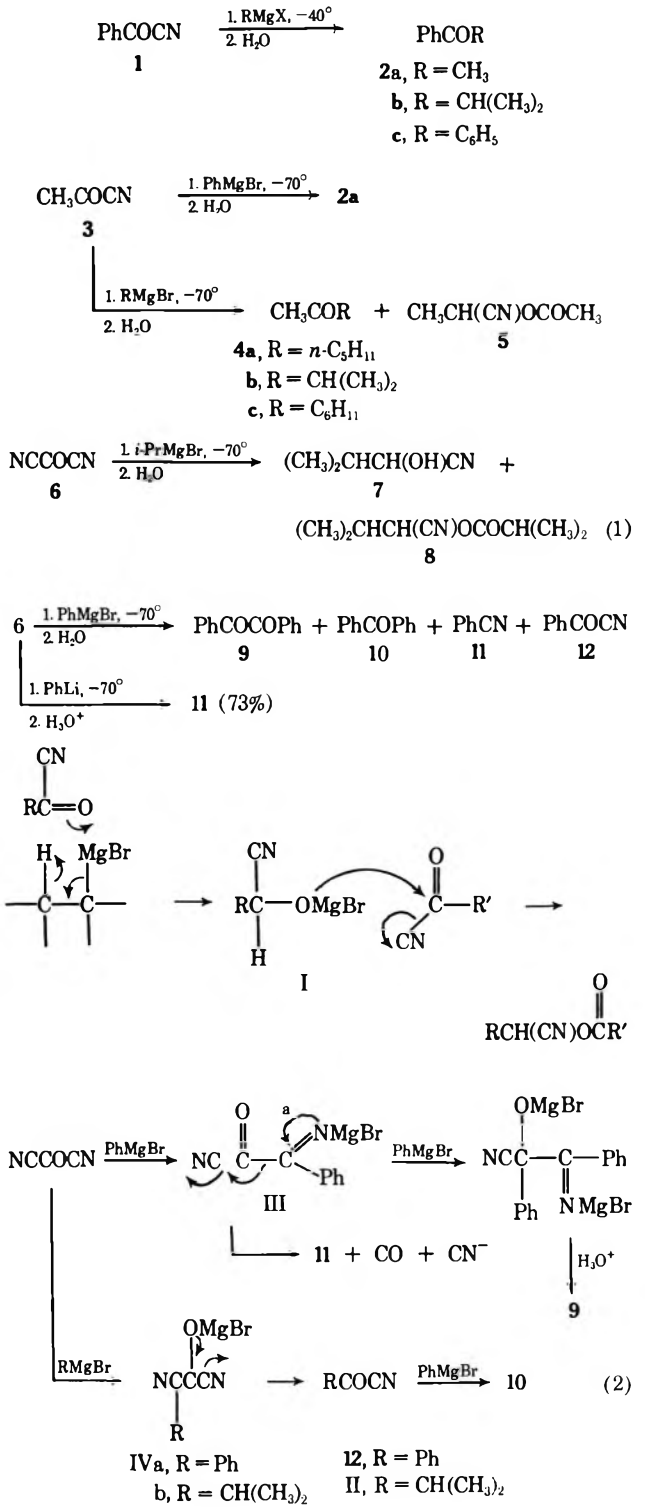
Reaction of carbonyl cyanide **6** with Grignard reagents also occurred by distinct pathways depending on the nature of the organomagnesium reagent. It should of course be noted that products resulting from reduction of **6** would be sufficiently volatile to escape detection under the reaction conditions. When **6** was treated with 1 equiv of isopropylmagnesium bromide in ether at −70°, **7** and **8** were isolated in 51 and 21% yield, respectively. The initial step in both cases involves addition at carbonyl and subsequent elimination of cyanide to give isobutyryl cyanide II as an intermediate. Reduction of II as in the case of **3** followed by trapping of the cyanohydrin magnesium salt I by **6** or II leads to the cyanohydrin esters (for R′ = CN, eq 2, the cyanoformate hydrolyses in water to give the cyanohydrin **7**).

When **6** was treated with phenylmagnesium bromide in ether at −70°, however, four identifiable products were obtained as a result of addition at *both* the carbonyl and cyano groups: benzil (**9**), 49%; benzophenone (**10**), 19%; benzonitrile (**11**), 8%; and benzoyl cyanide (**12**), 5%. The formation of these products is postulated in eq 2; addition to the cyano group predominates over addition to carbonyl in **6** by 2.4 to 1. We have postulated the formation of **11** as occurring *via* intermediate III rather than IVa on the basis of the fact that IVb rapidly eliminates cyanide to give II (and ultimately **7** and **8**) under the reaction conditions. Thus, IVa would be expected to collapse to **12** before addition of a second phenyl group could occur. When phenyllithium was used as the organometallic reagent, **11** was the only detectable product,

(1) (a) Alfred P. Sloan Foundation Fellow; (b) taken in part from the Ph.D. thesis of S. R. L., University of Minnesota, 1971.

(2) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Non-Metallic Substances," Prentice-Hall, New York, N. Y., 1954, pp 709–724.

(3) During the course of this work an excellent general method for unsymmetrical ketone synthesis was reported; for a review see D. Seebach, *Synthesis*, 1, 17 (1969).



isolated in 73% yield. Presumably the more ionic nitrogen–lithium bond in III promotes more rapid collapse to **11**.

Part B

Experimental Section

Infrared (ir) spectra were measured on a Unicam SP-200 or a Perkin-Elmer 257 spectrophotometer. Nuclear magnetic resonance (nmr) spectra were obtained on Varian T-60 and A-60D instruments and are given in parts per million (δ) downfield from tetramethylsilane as an internal standard. Mass spectra were determined at 70 eV on a Hitachi RMU-6 instrument. Gas chromatographic (glpc) analyses were carried out on a Varian A90-P gas chromatograph using 0.25 in. × 10 ft columns with Chromosorb W as support. Microanalyses were determined by the Microanalytical Laboratory, University of Minnesota.

Benzoyl cyanide (1) was prepared by the method of Oakwood and Weisgerber[4] in 76% yield, mp 28–30°.

Reaction of Acyl Cyanides with Grignard Reagents. General Procedure.—A 50-ml three-neck flask was fitted with an air-tight mechanical stirrer and pressure-equalizing funnel and placed under an atmosphere of nitrogen. A solution of the acyl cyanide in 25 ml of anhydrous ether was added to the flask, and the resulting solution was cooled to the specified temperature. An equimolar quantity of the Grignard solution in ether was added dropwise over 1 hr; stirring was continued for the specified time. The mixture was removed from the cooling bath and poured into 200 ml of saturated aqueous ammonium chloride. The ether layer was separated, and the aqueous solution was extracted with three 25-ml portions of ether. The combined extracts were washed with water and dried ($MgSO_4$), and the solvent was removed by fractionation.

Grignard Reaction of 1. A. Methylmagnesium Iodide.—Benzoyl cyanide (0.66 g, 5.0 mmol) was treated with 3.7 ml (5.0 mmol) of 1.36 *M* methylmagnesium iodide at −40° for 8 hr. Work-up afforded 0.53 g of an oil which was 82% acetophenone (**2a**) (73% yield) and 18% unreacted **1** by glpc analysis.

B. Isopropylmagnesium Bromide.—A solution of 5.0 ml (5.0 mmol) of 1.0 *M* isopropylmagnesium bromide was added to 0.66 g (5.0 mmol) of benzoyl cyanide at −40° and stirred for 8 hr. Work-up afforded 0.64 g of an oil which was 98% isobutrophenone (**2b**) by glpc analysis (84% yield). A collected sample was identified by comparison of ir and nmr spectra with those of an authentic sample.

C. Phenylmagnesium Bromide.—Benzoyl cyanide (1.00 g, 7.6 mmol) was treated with 9.7 ml (7.6 mmol) of 0.79 *M* phenylmagnesium bromide for 2 hr at −40°. Work-up afforded 1.31 g of crude product. A 1.23-g sample of this product was chromatographed on silica gel (30 g). Elution with 2:3 benzene–petroleum ether (bp 30–60°) gave 0.85 g (66%) of benzophenone (**2c**), 2,4-DNP mp 236–238°. Elution with 1:19 chloroform–benzene gave 0.06 g (3%) of triphenylcarbinol, identified by ir and tlc comparison with an authentic sample.

Grignard Reaction of 3. A. Phenylmagnesium Bromide.—Acetyl cyanide[5] (**3**) (0.98 g, 14.1 mmol) was treated with 13.0 ml (14.1 mmol) of 1.08 *M* phenylmagnesium bromide for 1.5 hr at −70°. Work-up afforded 1.43 g of yellow oil which was shown by glpc analysis to contain 83% acetophenone (**2a**) (70% yield), 2,4-DNP mp 246–248°.

B. *n*-Amylmagnesium bromide is representative of the "reducing" Grignard reagents. Acetyl cyanide (0.49 g, 7.1 mmol) was allowed to react with 8.3 ml (7.1 mmol) of 0.85 *M* *n*-amylmagnesium bromide for 5 hr at −70°. Work-up afforded 0.63 g of an oil which was shown to be 22% 2-heptanone (**4a**) and 49% α-cyanoethyl acetate (**5**) by glpc analysis. A collected sample of **5** was identified by ir and nmr comparison with an authentic sample prepared as described below: ir (CCl_4) 1760 cm^{-1}; nmr (CCl_4) δ 1.59 (d, 3, J = 7 Hz), 2.10 (s, 3), 5.32 (q, 1, J = 7 Hz). Yields of 2-heptanone and **5** based on acetyl cyanide were 22 and 77%, respectively.

α-Cyanoethyl Acetate (**5**).—To a mixture of 5.6 ml (0.10 mol) of a 20% aqueous solution of acetaldehyde and 10.2 g (0.10 mol) of acetic anhydride at 5° was added over 10 min with stirring a solution of sodium cyanide (4.90 g, 0.10 mol) in 25 ml of water. Stirring was continued for 30 min at 10–20°, and the reaction mixture was then extracted with three 25-ml portions of ether. The combined extracts were washed with aqueous sodium bicarbonate, dried ($MgSO_4$), and evaporated *in vacuo* to give 5.77 g of crude product. Distillation afforded one major fraction (3.8 g): bp 166–170°; ir (CCl_4) 1760 cm^{-1}; nmr (CCl_4) 1.61 (d, 3, J = 7 Hz), 2.10 (s, 3), 5.33 (q, 1, J = 7 Hz). An analytical sample was prepared by preparative glpc. *Anal.* Calcd for $C_5H_7NO_2$: C, 53.05; H, 6.23; N, 12.39. Found: C, 52.78; H, 6.15; N, 12.41.

Carbonyl cyanide (**6**) was prepared in 80% yield from tetracyanoethylene oxide according to the procedure of Linn, Webster, and Benson,[6] bp 64–66° (lit. bp 65–66°).

(4) T. S. Oakwood and C. A. Weisgerber, "Organic Syntheses," Collect Vol. III, Wiley, New York, N. Y., p 112.

(5) Available as pyruvonitrile from Aldrich Chemical Co., Milwaukee, Wis.

(6) W. Linn, O. W. Webster, and R. Benson, *J. Amer. Chem. Soc.*, **87**, 3651 (1965).

Reactions of Carbonyl Cyanide. A. Isopropylmagnesium Bromide.—Carbonyl cyanide (1.74 g, 21.8 mmol) was treated with 25.6 ml (21.8 mmol) of 0.85 *M* isopropylmagnesium bromide for 4 hr at −70°. Work-up afforded 1.23 g of dark oil, which was shown by glpc analysis to contain 45% α-hydroxyisovaleronitrile (**7**) [ir (CCl_4) 3620 cm^{-1}; nmr (CCl_4) δ 1.09 (d, 6), 1.96 (m, 1), 3.61 (s, 1), and 4.20 (d, 1); mass spectrum *m/e* (rel intensity) 72 (11), 43 (32), 27 (37)] and 32% α-cyanoisobutyl isobutyrate (**8**) [ir (CCl_4) 1760 cm^{-1}; nmr (CCl_4) δ 1.06 (m, 12), 2.16 (m, 2), 5.14 (d, 1)].

Anal. Calcd for $C_9H_{15}NO_2$: C, 63.98; H, 8.95. Found: C, 63.95; H, 9.20.

Yields of **7** and **8** based on isopropylmagnesium bromide were 51 and 21% respectively.

B. Phenylmagnesium Bromide.—Carbonyl cyanide (0.54 g, 6.8 mmol) was treated with 6.3 ml (6.8 mmol) of 1.08 *M* phenylmagnesium bromide for 4 hr at −70°. Following work-up with 1 *N* hydrochloric acid, removal of ether gave 0.66 g of yellow oil which contained (glpc) benzil (**9**), 49%; benzophenone (**10**), 19%; benzonitrile (**11**), 8%; and benzoyl cyanide (**12**), 5%. Collected samples were identified by comparison of their ir spectra and glpc retention times with those of authentic samples.

C. Phenyllithium.—Carbonyl cyanide (0.75 g, 9.3 mmol) was allowed to react with 9.0 ml (9.3 mmol) of 1.04 *M* phenyllithium in ether for 3 hr at −70°. Work-up afforded 0.99 g of oil which contained 69% benzonitrile by glpc analysis. Benzil and benzophenone were completely absent from the reaction mixture (glpc). The yield of benzonitrile was 73% based on carbonyl cyanide.

Discussion

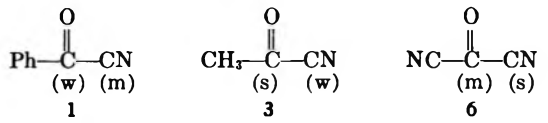
Infrared Spectra and Electron Density Calculations.—In order to gain insight into the detailed structure of the acyl cyanides and thus explain the apparent inconsistencies in the results, we calculated electron densities on **1**, **3**, and **6** *via* SCF calculations in INDO approximation.[7] These results together with the corresponding infrared stretching frequencies are reported in Table I. The most surprising result was the

TABLE I
INFRARED ABSORPTION FREQUENCIES AND INDO II ELECTRON DENSITY CALCULATIONS FOR THE C=O AND C≡N GROUPS IN ACYL CYANIDES

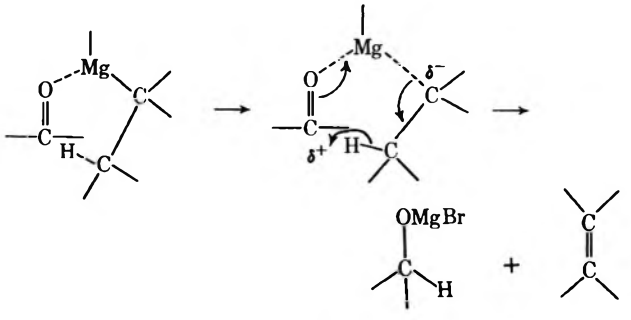
Compd	$\nu_{max}^{C=O}$, cm^{-1}	$\nu_{max}^{C\equiv N}$, cm^{-1}	$q_c^{C=O}$	$q_o^{C=O}$	$\lvert q_o q_c \rvert$	$q_c^{C\equiv N}$
PhCOCN	1680	2225	+0.297	−0.307	0.091	+0.059
CH_3COCN	1730	2220	+0.366	−0.331	0.121	+0.049
NCCOCN	1710	2240	+0.326	−0.243	0.079	+0.070

sequence observed for the carbonyl stretching frequencies. For the series benzoyl chloride–acetyl chloride–phosgene ($\nu_{max}^{C=O}$ 1773, 1790, and 1810 cm^{-1}, respectively), the carbonyl stretching frequency increases as a result of the progressively greater electron-withdrawing effect in going from methyl to phenyl to chlorine in increasing the force constant for the C=O bond. Based on both the σ_m values for –Cl and –CN[8a] and on the p*K* values for chloro- and cyanoacetic acids,[8b] one would expect the same order for the acyl cyanide C=O frequencies. However, carbonyl cyanide is intermediate between acetyl cyanide and benzoyl cyanide. The INDO results are in agreement with this result, the partial charge on the carbonyl carbon of **6** falling between that of **1** and **3**. Similarly, the nitrile stretching frequencies correlate with the partial charge on the nitrile carbon, the order being **6** > **1** > **3**. It is interesting to note that the infrared and INDO results are in excellent qualitative agreement and support the theory that electrostatic interactions make a major contribution in determining bond strength for two-electron (as apposed to one-electron) bonds.[9]

Thus the electronic character of the three acyl cyanides can be summarized as follows (s, m, w = strong, medium, and weakly electropositive). Delocalization of the carbonyl charge is clearly responsible for the electron distribution in **1**. In the case of acetyl cyanide, the inductive effect of the cyano group creates a sizable electron deficiency at the central carbon; the charge at the cyano carbon is presumably minimized as a result of charge repulsion. One might anticipate that the presence of two cyano groups bonded to carbonyl would increase this effect, as occurs for the acyl chlorides. Such an electron distribution would have a large repulsion energy, however, arising from three adjacent electropositive carbon atoms. Thus **6** achieves a more stable configuration by lengthening the C=O bond (relative to $COCl_2$) and shortening the C≡N bond (relative to **3**).



Addition *vs.* Reduction.—Having in hand a qualitative picture of the electron distribution in **1**, **3**, and **6**, we can attempt to correlate this data with the experimental results. It has been established[10] that carbonyl group reduction by Grignard reagents is enhanced by the presence of strong electron-withdrawing groups proximate to the carbonyl carbon, *i.e.*, is enhanced by increased bond polarization ($q_c q_o$ in Table I) in the carbonyl group. For example, acetaldehyde reacts with isopropylmagnesium bromide exclusively by addition, but trifluoroacetaldehyde reacts by reduction to give trifluoroethanol in 87% yield.[10] Thus our results concerning addition *vs.* reduction are consistent with the spectral and calculated data. Benzoyl and carbonyl cyanides, with their relatively stabilized carbonyl groups, undergo addition exclusively; acetyl and isobutyryl cyanides, however, react predominantly by reduction. We do not completely understand the reason for this correlation between carbonyl group polarization and reduction. A possible explanation lies in the fact that the complexing of an organomagnesium reagent will be



(7) J. A. Pople and D. L. Beveridge, (a) *J. Chem. Phys.*, **47**, 158 (1967); (b) "Approximate Molecular Orbital Theory," McGraw-Hill, New York, N. Y., 1970, Chapter 3.

(8) (a) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart, and Winston, New York, N. Y., 1959, p 221; (b) p 201.

(9) R. Ferreira, *J. Phys. Chem.*, **75**, 3012 (1971).

(10) E. T. McBee, O. R. Pierce, and J. F. Higgins, *J. Amer. Chem. Soc.*, **74**, 1736 (1952).

much stronger in the case of a highly polarized carbonyl group, and thus the magnesium–carbon bond will be substantially weakened. This in turn would assist in the hydride transfer from the β carbon due to the increase in electron density on the carbon bonded to magnesium.

Addition at C=O *vs.* C≡N.—Addition of organomagnesium reagents occurs exclusively at carbonyl in both the aroyl and acyl cyanide systems. The nitrile functions only as an activating group and does not compete in electrophilic addition. Similarly, carbonyl cyanide suffers initial attack by isopropylmagnesium bromide exclusively at the carbonyl group. In contrast, however, phenylmagnesium bromide attacks predominantly (and phenyllithium exclusively) at the cyano group. These results can be explained as follows. The carbonyl group is undoubtedly the more electrophilic site in **6**, and in the absence of other factors addition occurs at this site. The generation of intermediate IVb (see eq 2) also removes the charge repulsion interactions present in **6**. In the case of phenyl Grignard addition, however, the stabilization of intermediate III renders addition at the cyano group competitive with addition at carbonyl, and both products are formed. This type of stabilization would be expected to be more important in the case of the more ionic lithium intermediate (III where MgBr is replaced by Li), and hence addition at the cyano group occurs exclusively.

It is apparent that these explanations do not provide complete support for the results described; other factors must be operating in the transition state complexes. It is interesting to note, however, that a consistent pattern emerges with spectral, experimental, and calculated data in agreement to support what we consider *a priori* to be surprising results.

Registry No.—**1**, 613-90-1; **2a** 2,4-DNP, 1677-87-8; **2c** 2,4-DNP, 1733-62-6; **3**, 631-57-2; **5**, 15657-96-2; **6**, 1115-12-4; **7**, 15344-34-0; **8**, 32861-42-0; methylmagnesium chloride, 676-58-4; isopropylmagnesium bromide, 920-39-8.

Formation of 1,1′-Oligomeric Ferrocenes from Mixed Ullmann Reactions of Haloferrocenes

P. V. Roling and M. D. Rausch*

Department of Chemistry, University of Massachusetts, Amherst, Massachusetts 01002

Received June 11, 1971

A series of 1,1′-oligomeric ferrocenes, including biferrocene, 1,1′-terferrocene, 1,1′-quaterferrocene, 1,1′-quinqueferrocene, and 1,1′-sexiferrocene, have been formed from a mixed Ullmann reaction between a haloferrocene and 1,1′-diiodoferrocene. Conditions were varied as to the haloferrocene, the ratio of haloferrocene to 1,1′-diiodoferrocene, and the type of copper used in order to ascertain the maximum yields of each oligomer. Mass spectra of all the 1,1′-oligomeric ferrocenes have been obtained.

Considerable interest has been focused recently on the thermal and conductivity properties of oligomeric ferrocenes;[1-4] yet the chemistry of ferrocene oligomers larger than biferrocene is virtually unknown. In the last 11 years, biferrocene (**1**) has been synthesized in many ways.[4-12] The most useful of these methods has utilized the Ullmann reaction.[7,12] Iodoferrocene is an extremely reactive compound in the Ullmann reaction, since a 97% yield of biferrocene can be obtained at temperatures as low as 60°.[12]

Nesmeyanov and coworkers[13] first isolated 1,1′-terferrocene (**2**) when they conducted a mixed Ullmann reaction with bromoferrocene (**7**) and 1,1′-dibromoferrocene to give a 57% yield of biferrocene, a 14% yield of 1,1′-terferrocene (**2**), and other higher oligomeric ferrocenes which were not separated. 1,1′-Terferrocene (**2**) has also been synthesized in an unequivocal manner from cyclopentadienylferrocene by Rinehart and coworkers.[14] More recently, Watanabe, *et al.*,[15] have described the formation of the 1,1′-oligomeric ferrocenes from biferrocene (**1**) to sexiferrocene (**5**), resulting from the treatment of a mixture of mono- and 1,1′-dilithioferrocenes with cobalt chloride. The yields were low and a number of butylated products, resulting from the excess *n*-butyllithium being present, were also isolated.

Results and Discussion

Based on our earlier successful studies on the Ullmann coupling of haloferrocenes,[12] and also on current interest in oligomeric ferrocenes, we decided to investigate in some detail the formation of this series of organometallic compounds *via* the Ullmann route. The mixed Ullmann reaction (eq 1) between a haloferrocene and 1,1′-diiodoferrocene (**9**) has indeed been found to give higher yields of the 1,1′-oligomeric ferrocenes than have the previous methods.[1,13,15,16] A reaction time of

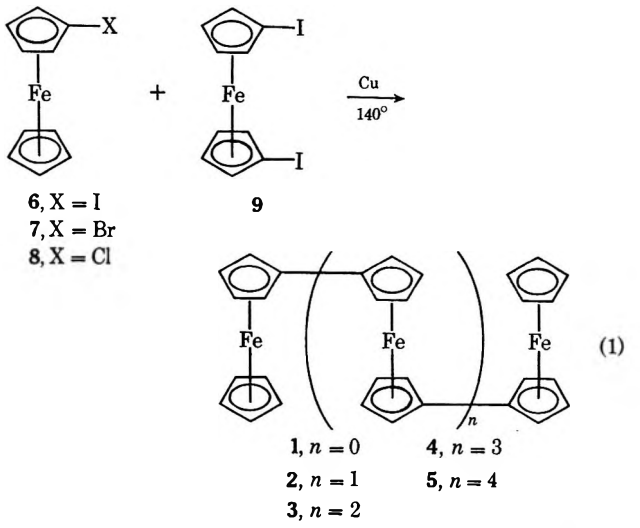
(1) M. D. Rausch, R. F. Kovar, and C. S. Kraihanzel, *J. Amer. Chem. Soc.*, **91**, 1259 (1969).
(2) D. O. Cowan and F. Kaufman, *ibid.*, **92**, 219 (1970).
(3) H. Watanabe, I. Motoyama, and K. Hata, *Bull. Chem. Soc. Jap.*, **39**, 850 (1966).
(4) N. Rosenberg and E. W. Neuse, *J. Organometal. Chem.*, **6**, 76 (1966).
(5) S. I. Goldberg and D. W. Mayo, *Chem. Ind. (London)*, 671 (1959).
(6) A. N. Nesmeyanov, V. A. Sazonova, and V. N. Drozd, *Dokl. Akad. Nauk SSSR*, **126**, 1004 (1959).
(7) E. G. Perevalova and O. A. Nesmeyanova, *ibid.*, **132**, 1093 (1960).
(8) O. A. Nesmeyanova and E. G. Perevalova, *ibid.*, **126**, 1007 (1959).
(9) M. D. Rausch, *Inorg. Chem.*, **1**, 414 (1962).
(10) H. Shechter and J. F. Helling, *J. Org. Chem.*, **26**, 1034 (1961).
(11) J. F. Helling, Ph.D. Dissertation, The Ohio State University, 1960.
(12) M. D. Rausch, *J. Org. Chem.*, **26**, 1802 (1961).
(13) A. N. Nesmeyanov, V. N. Drozd, V. A. Sazonova, V. I. Romanenko, A. K. Prokof'ev, and L. A. Nikonova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 667 (1963).
(14) K. L. Rinehart, Jr., D. G. Ries, C. N. Parks, and P. A. Kittle, 146th National Meeting of the American Chemical Society, Denver, Colo., Jan 1964, Abstracts of Papers, p 23c.
(15) N. Watanabe, I. Motoyama, and K. Hata, *Bull. Chem. Soc. Jap.*, **39**, 790 (1966).
(16) A preliminary communication of this work has already been published: M. D. Rausch, P. V. Roling, and A. Siegel, *Chem. Commun.*, 502 (1970).

TABLE I

PERCENTAGE YIELDS[a] OF 1,1′-OLIGOMERIC FERROCENES

Run	$FeC_{10}H_9X$	Copper	Ratio[b]	1	2	3	4	5	Total
1	I	U. S.	2:1	37	10	2			49
2	I	U. S.	2:2	23	8	3	1		35
3	I[c]	U. S.	2:4	18	13	7	4	1	43
4	I	German	2:1	50	21	12	4	1	88
5	I	German	2:2	48	21	9	6	1	85
6	I	German	2:4	52	24	11	6	1	94
7	Br[c]	German	2:4	35	29	9	4	2	79
8	Cl	German	2:4	71	11	10	6	2	100

[a] Yields are based on the limiting reagent in each reaction. [b] This ratio represents the molar ratio of haloferrocene to 1,1′-diiodoferrocene used. [c] A duplicate run was made in this case, and the yields of all products were reproducible.



23 hr was used to ensure that total reaction between the haloferrocene and copper had taken place. The various oligomeric ferrocenes were separated by a combination of crystallization and chromatography on alumina.

As seen in Table I (runs 6–8), different product ratios were obtained depending on the haloferrocene used. These variations are undoubtedly related to the known gradation in reactivity of haloferrocenes under Ullmann conditions[12] and may possibly be accounted for as follows. Iodoferrocene (6), being very reactive in the Ullmann reaction, undergoes self-coupling (Scheme If) faster than mixed coupling (Scheme I a,b), thus

SCHEME I[a]

$$FcX + FclI_2 \longrightarrow Fc—Fcl—I \quad (a)$$

$$FcX + I—Fcl—Fcl—I \longrightarrow Fc—Fcl—Fcl—I \quad (b)$$

$$FclI_2 + FclI_2 \longrightarrow I—Fcl—Fcl—I \quad (c)$$

$$I—Fcl—Fcl—I + FclI_2 \longrightarrow I—Fcl—Fcl—Fcl—I, \text{ etc.} \quad (d)$$

$$Fc—Fcl—I + FclI_2 \longrightarrow Fc—Fcl—Fcl—I, \text{ etc.} \quad (e)$$

$$FcX + FcX \longrightarrow Fc—Fc \quad (f)$$

[a] Fc = ferrocenyl, $FeC_{10}H_9$; Fcl = 1,1′-ferrocenylene, $Fe(C_5H_4)_2$.

giving the high yield of biferrocene (1). Bromoferrocene (7) evidently undergoes mixed coupling (Scheme Ia,b) more rapidly than does iodoferrocene (6), and thus the yields of the higher oligomers are slightly raised compared to the yield of biferrocene (1). Chloroferrocene (8), on the other hand, is known to be much less reactive than either bromoferrocene (7) or iodoferrocene (6) under Ullmann conditions. Self-coupling of 1,1′-diiodoferrocene (9) (Scheme Ic–e) evidently proceeds faster than mixed coupling (Scheme Ia,b). The remaining chloroferrocene (8) then undergoes self-coupling (Scheme If) to give a high yield of biferrocene (1).

The copper powder used in the present studies was obtained from two different sources: the Schuchardt Co. (Germany) and the U. S. Bronze Powder Co., Inc. Table I shows that the overall percentage yields of the oligomers varies, depending on the source of copper used. The German copper was found superior to the U. S. copper in all Ullmann reactions attempted (compare runs 1–3 *vs.* runs 4–6), even though both powders had been activated in exactly the same manner.[17] An Ullmann reaction carried out on *o*-iodophenylferrocene gave, under identical conditions, 100% recovery of starting material with the U. S. copper and an 11% yield of 2,2′-diferrocenylbiphenyl with German copper. The difference in the reactivity of the two copper powders is not known at the present time. A variation in the molar ratio of monohaloferrocene to 1,1′-diiodoferrocene (9) did not significantly affect the product percentages when German copper was used (Table I). With the U. S. copper, however, there was a noticeable trend: as the ratio decreased the amount of higher oligomers increased. No 1,1′-biferrocenylene [bis(fulvalene)diiron] could be detected in these studies, even though it might have been an expected product on the basis of previous work.[1,18]

1,1′-Terferrocene (2) prepared in this study agrees in its properties with the 1,1′-terferrocene obtained by Motoyama, Watanabe, and Hata,[15] and its melting point indicates that the 1,1′-terferrocene reported by Nesmeyanov, *et al.*,[13] was perhaps slightly impure. The present 1,1′-terferrocene also showed the polymorphic properties reported by the Japanese workers.[15] The material of Rosenberg and Neuse[4] that melted at 224–226° can then also be assigned as 1,1′-terferrocene (2). The properties of the higher oligomers (3–5) obtained in our studies are in general agreement with those prepared by the Japanese workers.[15]

The mass spectra of the 1,1′-oligomeric ferrocenes are summarized in Table II. Each oligomer shows the expected parent ion peak as well as a doubly charged ion peak at $m/2e$, except in the case of 1,1′-sexiferrocene (5), where only the parent peak is observed. For 1,1′-quaterferrocene (3), a triply charged ion peak at $m/3e$ is observed. The mass spectrum of 1,1′-terferro-

(17) A. I. Vogel, "A Textbook of Practical Organic Chemistry," 3rd ed, Wiley, New York, N. Y., 1962, p 193.

(18) F. L. Hedberg and H. Rosenberg, *J. Amer. Chem. Soc.*, **91**, 1258 (1969).

Table II

Relative Abundance of Mass Spectral Peaks of 1,1′-Oligomeric Ferrocenes

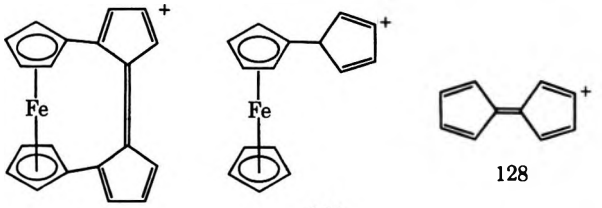
Peak, m/e	1	2	3	4	5
1106					2
922				6	7
738			61	12	4
554		100	5	1	5
489		10	29	5	2
461				2	
423		14	22	3	4
370	100	7	19	6	12
369	4	14	88	33	28
368	15	48	100	100	100
310		5	5	7	5
305	42	20	22	2	29
277		30	4		
249	6	8	4		8
246			6		
185	23				
184	6	5	6	90	15
128	4	5	4	7	19
121	27	17	9	4	28
56	20	7	6	15	30

cene (2) shows a metastable peak at m/e 431.6, which corresponds to a parent ion of m_1 554 and a daughter ion of m_2 489. This result indicates that a neutral fragment, cyclopentadienyl radical, is lost in the probe in a one-step process from the parent ion to form the daughter ion. No other metastable peaks were observed in the other spectra.

The fragmentation patterns of the 1,1′-oligomeric ferrocenes are very similar throughout the series and involve the loss of ferrocenyl units, cyclopentadienyl units, as well as iron and hydrogen atoms. Some plausible structures are given in Chart I for the fragments

Chart I

Proposed Structures for Some Ions Produced in the Mass Spectra of 1,1′-Oligomeric Ferrocenes



310 249 128

with their respective mass units. Of special interest is the fulvalene structure assigned to m/e 310. Such a structure is plausible for this ion and is in analogy with the formation of fulvalene in the fragmentation of ferrocene itself.[19] The 310 peak has almost the same relative abundance in the spectra of 1,1′-terferrocene to 1,1′-sexiferrocene, indicating that this substituted fulvalene is possibly a function of the 1,1′-oligomeric arrangement. Table III shows that the calculated values[20] and found values for the isotopic abundances of iron are in excellent agreement, and that the various 1,1′-oligomeric ferrocenes analyze well for the natural abundance distribution of iron and carbon.

(19) A. Mandelbaum and M. Cais, *Tetrahedron Lett.*, 3847 (1964).

(20) H. C. Hill, "Introduction to Mass Spectrometry," Heyden & Sons Ltd., London, 1966, p 20.

Experimental Section

General.—Nmr spectra were recorded on a Varian A-60 spectrometer in 5–10% $CDCl_3$ solutions. Mass spectra were recorded either on an AEI MS-9 or a Hitachi RMU-6E mass spectrometer at 70 eV. The German copper used is Kupfer, KU300, Pulver mind. 99.75%; it was obtained from the Schuchardt Co., Munich, Germany. The U. S. copper used is Copper 4000, Lot 3767; it was obtained from the U. S. Bronze Powder Co., Inc., Flemington, N. J. Chloroferrocene,[21] bromoferrocene,[22] iodoferrocene,[10,23] and 1,1′-diiodoferrocene[24] were prepared by standard literature methods. The alumina of activity grade III used in this work was prepared by shaking 1 kg of neutral, activated CAMAG alumina (Alfa Inorganics) with 60 ml of water. All chromatographic columns were packed dry. The dimensions of the column were not considered important as long as the stated amount of alumina was used and the column was packed evenly. Melting points were taken on a Mel-Temp apparatus and are corrected. All microanalyses were carried out by Mr. Charles Meade of the Microanalytical Laboratory, Office of Research Services, University of Massachusetts.

1,1′-Oligomeric Ferrocenes.—A typical example (run 5) is given. In a 50-ml round-bottomed flask were melted 1.00 g (3.2 mmol) of iodoferrocene (6) and 1.41 g (3.2 mmol) of 1,1′-diiodoferrocene (9). Next was added 6.2 g (98 mmol) of activated German copper,[17] a glass stopper was inserted, and the mixture was shaken. The flask, flushed with nitrogen, was submerged in an oil bath to the depth of the bottom of the stopper, and the oil bath temperature was raised from 30 to 145° over 1.5 hr. The temperature was then maintained at 145° for an additional 21.5 hr. At the end of the heating period, the contents of the flask were extracted with benzene until the benzene extracts were colorless. The benzene was evaporated to yield substance A. The copper residue was further extracted with boiling toluene until the toluene extracts were colorless, and the toluene was evaporated to yield substance B. Finally, the copper residue was extracted with boiling bromobenzene, the extracts were allowed to cool, and the resulting precipitate was collected to give substance C.

Substance A was dissolved in 25 ml of benzene and 25 ml of hexane was added. A precipitate formed and was collected to yield 0.05 g of a yellow product. This product was crystallized from benzene and was identified as 1,1′-quinqueferrocene (4), mp (sealed under N_2) 262–264° dec (lit.[15] mp 240–245°).

Anal. Calcd for $C_{50}H_{42}Fe_5$: C, 65.13; H, 4.59; Fe, 30.28; mol wt, 922. Found: C, 64.90; H, 4.89; Fe, 30.2; mol wt, 922 (mass spectrometry).

The filtrate was placed on a column of 300 g of alumina (activity grade III) and the column was eluted with hexane to yield 0.01 g of ferrocene, mp 170–172°. Elution with hexane–benzene (8:2 by volume) gave 0.26 g of biferrocene (1), mp (sealed under N_2) 238–240° dec (lit.[12] mp 238–239°). *Anal.* Calcd: mol wt, 370. Found: mol wt, 370 (mass spectrometry).

The third band was eluted with hexane–benzene (6:4) to yield 0.18 g of a yellow material, which was crystallized from a mixture of hexane–benzene. This material was 1,1′-terferrocene (2): mp (sealed under N_2) 224–226° dec (lit.[15] 226.5–227.2° dec); nmr ($CDCl_3$) singlet at τ 6.04 [10 H, unsubstituted cyclopentadienyl ring protons), multiplet at 5.70–5.95 (16 H, α and β protons on the substituted rings).

Anal. Calcd for $C_{30}H_{26}Fe_3$: C, 65.03; H, 4.73; Fe, 30.24; mol wt, 554. Found: C, 65.10; H, 4.88; Fe, 30.2; mol wt, 554 (mass spectrometry).

The last band was eluted with benzene to give 0.09 g of a red-orange compound, which was crystallized from benzene to yield 1,1′-quaterferrocene (3), mp (sealed under N_2) 279–281° dec (lit.[15] mp 280°).

Anal. Calcd for $C_{40}H_{34}Fe_4$: C, 65.09; H, 4.64; Fe, 30.27; mol wt, 738. Found: C, 65.20; H, 4.92; Fe, 30.0; mol wt, 738 (mass spectrometry).

Substance B was purified in a manner similar to substance A to yield 0.02 g of biferrocene, 0.01 g of 1,1′-terferrocene, 0.01 g of 1,1′-quaterferrocene, and 0.01 g of 1,1′-quinqueferrocene.

(21) V. A. Nefedov and M. N. Nefedova, *Zh. Obshch. Khim.*, **36**, 122 (1966).

(22) R. W. Fish and M. Rosenblum, *J. Org. Chem.*, **30**, 1253 (1965).

(23) A. N. Nesmeyanov, T. G. Perevalova, and O. A. Nesmeyanova, *Dokl. Akad. Nauk SSSR*, **100**, 1099 (1955).

(24) R. F. Kovar, M. D. Rausch, and H. Rosenberg, *Organometal. Chem. Syn.*, **1**, 173 (1971).

TABLE III

ISOTOPIC ABUNDANCES[a,b] FOR THE 1,1′-OLIGOMERIC FERROCENES

	1		2		3		4		5	
Peak	Calcd	Found	Calcd	Found	Calcd	Found	Calcd	Found	Calcd	Found
M + 4	0.0	0	0.2	0	0.5	1	1.1		1.4	2
M + 3	0.5	0	1.4	1	3.1	3	5.8	5	9.3	9
M + 2	4.2	4	9.0	9	15.4	16	23.2	24	31.5	32
M + 1	27.2	27	40.4	40	53.2	53	65.1	64	75.7	75
M	100.0	100	100.0	100	100.0	100	100.0	100	100.0	100
M − 1	3.1	4	7.2	8	12.8	14	19.6	20	27.3	28
M − 2	12.7	15	18.8	19	24.8	25	30.4	30	35.5	42
M − 3	0.1	0	0.4	0	1.2	1	2.4		4.2	5
M − 4	0.4	0	1.2	1	2.3	3	3.8		5.5	8

[a] All found isotopic abundances are the average of two or more spectra. [b] The isotopic abundances were calculated on a computer by an appropriate expansion of the expression, $(a + b + c + d)^m (e + f)^n$, where a = 5.82% natural abundance of ^{54}Fe, b = 91.66% ^{56}Fe, c = 2.19% ^{57}Fe, d = 0.33% ^{58}Fe, e = 98.89% ^{12}C, f = 1.11% ^{13}C, m = number of iron atoms, and n = number of carbon atoms. Hydrogen was disregarded since the natural abundance of deuterium is low (0.015%).

Substance C was extracted with boiling benzene until the extracts were colorless. The benzene was allowed to cool to yield 0.01 g of a yellow-brown material, 1,1′-sexiferrocene (5), mp (sealed under N_2) 270–272° dec (lit.[15] mp 252–256°).

Anal. Calcd for $C_{60}H_{60}Fe_6$: C, 65.15; H, 4.56; Fe, 30.29; mol wt, 1106. Found: C, 65.15; H, 4.63; Fe, 30.3; mol wt, 1106 (msss spectrometry).

The residue remaining after the benzene extraction of substance C was in turn extracted with toluene to give 0.01 g of a substance with the following analysis.

Anal. Found: C, 63.80, 63.20; H, 4.67, 5.05.

The total amounts and percentage yields of oligomeric ferrocenes from this reaction follow: biferrocene (1), 0.28 g (48%); 1,1′-terferrocene (2), 0.19 g (21%); 1,1′-quaterferrocene (3), 0.10 g (9%); 1,1′-quinqueferrocene (4), 0.06 g (6%); 1,1′-sexiferrocene (5), 0.01 g (1%). Yields of products from other runs are summarized in Table I.

Thin layer chromatography (tlc), using 6:4 hexane–benzene as eluent and silica gel as adsorbant, was very useful in identifying the oligomers. The approximate R_f values under these conditions are as follows: ferrocene 0.7, biferrocene (1) 0.5, 1,1′-terferrocene (2) 0.4, 1,1′-quaterferrocene (3) 0.3, and 1,1′-quinqueferrocene (4) 0.2. 1,1′-Sexiferrocene (5) was too insoluble for tlc studies. All oligomers after separation and purification were found to be pure by tlc.

2,2′-Diferrocenylbiphenyl.—In a Schlenk tube under nitrogen were placed 1.20 g (3.1 mmol) of *o*-iodophenylferrocene[25] and 5.5 g (86.5 mmol) of activated German copper.[16] This mixture was heated at 147° in an oil bath for 22 hr. The reaction mixture was then extracted with ethyl ether and the ether evaporated. The residue was dissolved in hexane and placed on a column of 75 g of alumina. The first band was eluted with an 8:2 mixture of hexane–benzene. An nmr spectrum of the material indicated it to be a mixture of starting material and phenylferrocene. The second band was eluted with 1:1 hexane–benzene. Crystallization from hexane yielded 0.09 g (11%) of 2,2′-diferrocenylbiphenyl: mp 172.5–174°; nmr ($CDCl_3$) apparent singlet at τ 5.99 (18 H, ferrocenyl protons), multiplet at 2.6–3.2 (6 H, protons meta and para to the ferrocenyl group), multiplet at 2.1–2.4 (2 H, protons ortho to the ferrocenyl group).[26]

Anal. Calcd for $C_{32}H_{26}Fe_2$: C, 73.59; H, 5.02. Found: C, 73.40; H, 5.18.

In a similar run with the U. S. copper, no 2,2′-diferrocenylbiphenyl was obtained.

Registry No.—**1**, 1287-38-3; **2**, 1273-59-2; **3**, 1299-15-6; **4**, 1299-19-0; **5**, 1299-20-3; 2,2′-diferrocenylbiphenyl, 12597-74-9.

Acknowledgments.—The authors are grateful to the donors to the Petroleum Research Fund, administered by the American Chemical Society, for a grant in support of this research program. They also wish to thank Drs. A. Siegel and D. Hunt for assistance in obtaining the mass spectra, Dr. D. Garrett for writing the computer program, and the U. S. Bronze Powder Co. for a gift of the copper powder.

(25) W. F. Little, C. N. Reilley, J. D. Johnson, K. N. Lynn, and A. P. Sanders, *J. Amer. Chem. Soc.*, **86**, 1376 (1964).

(26) For a discussion of shielding effects in *o*-biphenylylferrocenes of this type, see M. Rosenblum, "Chemistry of the Iron-Group Metallocenes, Part I," Wiley, New York, N. Y., 1965, p 217.

Hydroboration and Thermal Isomerization of Unsaturated Alcohols

KEIITI SISIDO, MIKIO NARUSE, AKIHISA SAITO, AND KIITIRO UTIMOTO*

Department of Industrial Chemistry, Kyoto University, Kyoto, Japan

Received April 30, 1971

Hydroboration and thermal isomerization of undecenols (**1**, **2**, and **3**), pentenol (**11**), and 2,2-dimethyl-3-nonenol-1 (**21**) were studied. Undecane-1,3- and -1,4-diols were obtained from undecenols *via* oxaborolane and oxaborinane. π-Complex mechanism for thermal isomerization (mechanism 1) was supposed and was confirmed by the studies using diborane-d_6 and 5-ethyl-4-heptenol-1 (**39**).

Hydroboration and successive thermal isomerization of simple olefins have been studied and have become useful synthetic methods.[1] On the other hand, few examples have been reported in the case of olefins bearing functional groups.[2] From the viewpoint of mechanistic studies and of synthetic applications, the hydroboration and thermal isomerization of unsaturated alcohols were reinvestigated.

Hydroboration and Thermal Isomerization.—Three undecenols, 10-undecenol-1 (**1**), 6-undecenol-1 (**2**), and 3-undecenol-1 (**3**), were chosen and were hydroborated at room temperature and thermally isomerized at 160° followed by the usual oxidation. Products were converted into trimethylsilyl ethers and analyzed by

$CH_2{=}CH(CH_2)_9OH$ **1**

$CH_3(CH_2)_mCH{=}CH(CH_2)_nOH$ **2**, $m = 3$; $n = 5$ **3**, $m = 6$; $n = 2$

$HO(CH_2)_{11}OH$ **4**

$CH_3(CH_2)_mCH(OH)(CH_2)_nOH$ **5**, $m = 0$; $n = 9$ **6**, $m = 6$, $n = 3$ **7**, $m = 7$, $n = 2$

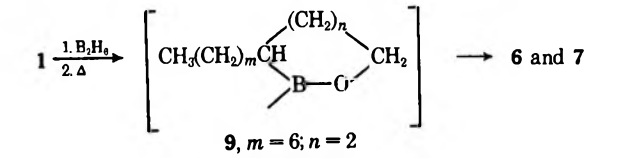
$CH_3(CH_2)_{10}OH$ **8**

glc and mass spectrometry.[3] The results of such analyses are shown in Table I.

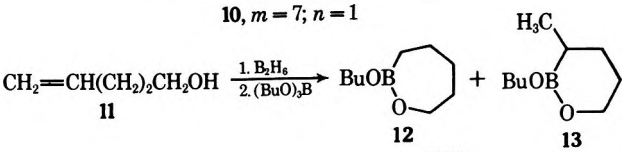
TABLE I
HYDROBORATION AND THERMAL ISOMERIZATION OF UNDECENOLS AT 160°

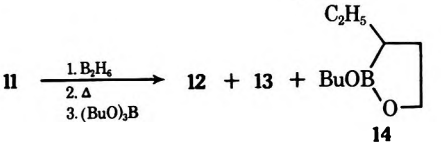
Undecenol	Reaction time, hr	Yield of undecanediol, % 1,3- (7)	1,4- (6)	1,6-	1,7-	1,10- (5)	1,11- (4)	Yield of undecanol (8), %
10-Undecenol-1 (1)	0	0	0	0	0	8	92	0
	3	1	56	0	0	1	40	1
	7	11	66	0	0	1	19	1
	10	12	67	0	0	1	18	1
	22	12	70	0	0	1	15	1
	34	13	70	0	0	<1	15	2
6-Undecenol-1 (2)	0	0	0	51	49	0	0	0
	2	27	57	<1	<1	<1	1	9
	5	27	58	<1	<1	<1	1	9
	10	26	55	<1	<1	<1	1	11
3-Undecenol-1 (3)	0	61	33	0	0	0	0	6
	0.5	60	34	0	0	0	0	6
	2	60	32	0	0	0	0	7
	5	58	32	0	0	0	0	10
	10	53	31	0	0	0	0	16

Inspection of Table I indicates that undecane-1,3- and 1,4-diol (**7** and **6**) are the main products in each case. The formation of the diols, **6** and **7**, suggests that the boron atom was trapped on C_3 or C_4. This might be explained by the formation of oxaborolane (**10**)[4] and oxaborinane (**9**) derivatives. For experimental convenience,[5] 4-pentenol-1 (**11**) was chosen to confirm the intermediary oxaborolane and oxaborinane formation. Hydroboration of **11** at room temperature



9, $m = 6$; $n = 2$
10, $m = 7$; $n = 1$

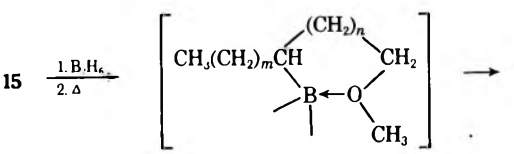




and successive treatment with tributyl borate gave a mixture of **12** and **13**. Similarly, **11** gave a mixture of **12**, **13**, and **14** by hydroboration, thermal isomerization, and successive treatment with tributyl borate. The structure of **12**, **13**, and **14** were determined by ir, mass spectral, and elemental analyses and by the analyses of their oxidation products. These results indicated the formation of oxaborinane during thermal isomerization.

The assumption of coordinate bond formation between boron and oxygen[2b] also might explain the trapping of boron on C_3 or C_4. Provided that such a coordinate bond does exist, the oxygen atom of the

$CH_2{=}CH(CH_2)_8CH_2OCH_3$ **15** $CH_3(CH_2)_6CH{=}CHCH_2CH_2OCH_3$ **16**



17, $m = 6$; $n = 2$
18, $m = 7$; $n = 1$

$[CH_3(CH_2)_mCH(OH)(CH_2)_nCH_2OCH_3]$
19, $m = 6$; $n = 2$
20, $m = 7$; $n = 1$

(1) H. C. Brown, "Hydroboration," W. A. Benjamin, New York, N. Y., 1962; G. Zweifel and H. C. Brown, *Org. React.*, **13**, 1 (1963); H. C. Brown and M. V. Bhatt, *J. Amer. Chem. Soc.*, **88**, 1440 (1966).

(2) (a) S. P. Fore and W. G. Bickford, *J. Org. Chem.*, **24**, 920 (1959); (b) T. J. Logan, *ibid.*, **26**, 3657 (1961).

(3) (a) J. Diekman, J. B. Thomson, and C. Djerassi, *ibid.*, **32**, 3904 (1967); **33**, 2271 (1968); (b) G. H. Draffan, R. N. Stillwell, and J. A. McCloskey, *Org. Mass Spectrom.*, **1**, 669 (1968).

(4) Isolation of oxaborolane: B. M. Mikhailov and V. A. Dorohov, *Izv. Akad. Nauk SSSR*, 1661 (1964).

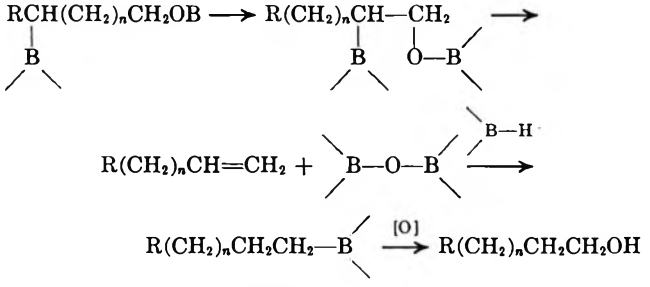
(5) The method used in this experiment is conveniently applicable when the boiling point of the organoboron compound is lower than that of tributyl borate.

methoxy group, instead of the hydroxy group, may similarly trap the boron atom at the C_3 or C_4 position. From the results of hydroboration and thermal isomerization of methyl 10- and 3-undecenyl ether (**15** and **16**), no evidence of intramolecular coordinate bond formation was obtained (Table II).

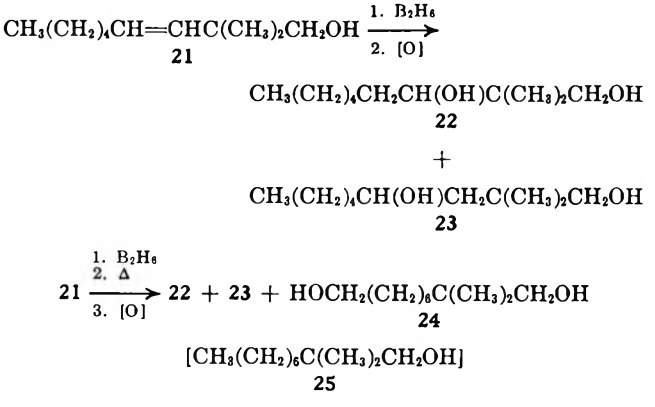
TABLE II
HYDROBORATION AND THERMAL ISOMERIZATION OF METHYL UNDECENYL ETHER AT 160° (CH_3OR)

R	Reaction time, hr	Solvent	Yield of hydroxyundecyl methyl ether, % 3- (20)	4- (19)	10-	11-	Yield of undecanol (8), %
10-Undecenyl	0	Diglyme	0	0	16	84	0
(15)	20	Diglyme	0	0	3	29	59
	20	Decalin	0	0	5	74	17
3-Undecenyl	0	Diglyme	51	43	0	0	6
(16)	8	Diglyme	<1	<1	<1	7	93

The formation of the monofunctional alcohol, undecanol-1, may be explained by rehydroboration of 1-undecene, produced by 1,2 elimination of a hydroxyl group and the vicinally situated boron, by a mechanism similar to that of Brown and Cope.[6] This considera-

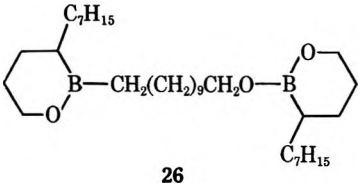


tion was supported by the reaction of 2,2-dimethyl-3-nonenol-1 (**21**) with diborane. Hydroboration and thermal isomerization of **21** gave a mixture of **22** (8%),

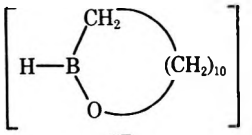


23 (90%), and **24** (2%), but 2,2-dimethylnonanol-1 (**25**) could not be detected. Considering these facts, as well as Brown's thermal isomerization mechanism,[7] the above-mentioned explanation for the formation of undecanol seems plausible.

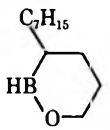
A comparison between entries 3 (10-undecenol-1, 7-hr thermal isomerization) and 12 (3-undecenol-1, 0.5-hr thermal isomerization) of Table I shows that the yield of 1,3-diol was only 11% in the former case and 60% in the latter case. This difference may be explained by the following considerations. In the case of 10-undecenol-1, 19% of 1,11-diol was obtained. The organoboron compound which gave rise to undecane-1,11-diol might be compound **26** rather than



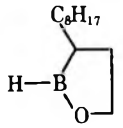
26



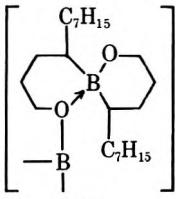
27



28



29



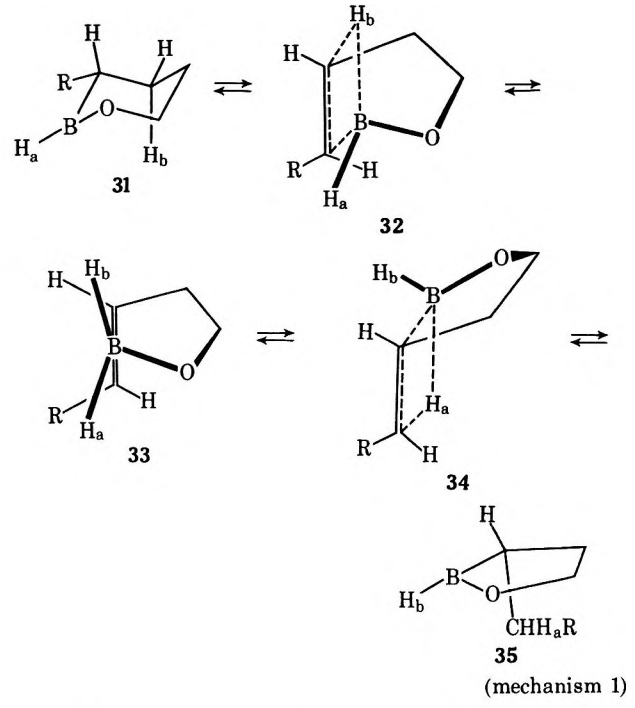
30

27. The reaction mixture from 10-undecenol-1 was considered to be a mixture of compounds **26**, **28**, and **29**. On the other hand, the reaction mixture from 3-undecenol-1 was considered to be a mixture of **28** and **29**. Formation of **29** from **1** also indicated that **28** was the precursor of **29**.

From these considerations, migration of the boron atom from the C_4 position to the C_3 position was considered to be explained by the following mechanism (using as an analogy a previously proposed mechanism).[8,9] The thermal isomerization of organoboron compounds seems to proceed *via* dehydroboration to form a π complex (**32** → **33**) followed by rehydroboration (**33** → **34** → **35**). The boron atom eliminated from the C_4 position of the six-membered cyclic organoboron compound forms a π complex with the newly produced olefinic linkage, and the rotation around the π complex results in the original hydrogen atom (H_a) being situated close to the C_4 position (**34**). Then rehydroboration gives the five-membered cyclic organoboron compound (**35**). Thus, the isomerization from oxaborinane to oxaborolane proceeds without difficulty, and is also considered to be reversible. This thermal isomerization is considered to be rather difficult when the boron atom of complex **37** has only one hydrogen on boron, as in the case of **36** (R′ = alkyl or alkoxy). In this case, the transformation of **36** into **41** is considered to be rather difficult without first destroying the intramolecular π complex (**37**). Upon destroying the π complex followed by rotation around the C_2–C_3 bond or the B–O bond, the complex **39** would be reconstructed and oxaborolane (**41**) would be formed *via* **40**. This rotation around the C–C or B–O bond is, however, hindered by the bulkiness of the alkyl or alkoxy group attached to the boron atom and/or of the remaining alkyl residue of the olefinic group. Using this reasoning, rehydroboration from the complex **37** is considered to give oxaborinane **36** rather than oxaborolane **41**.

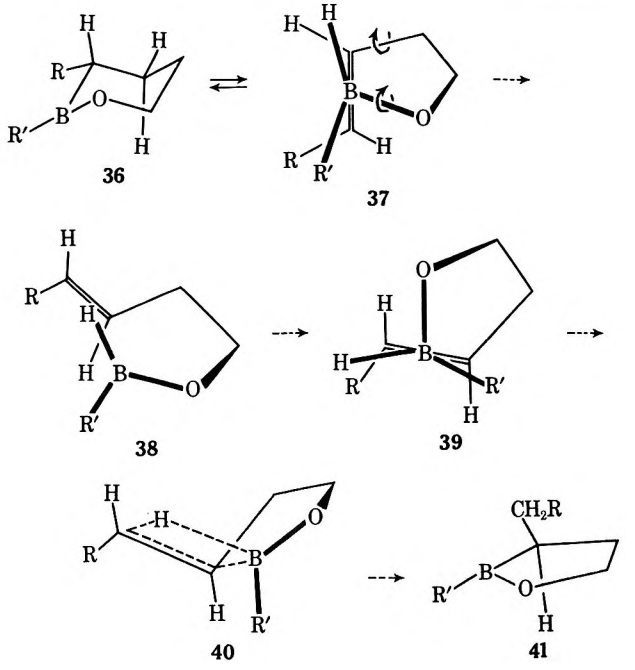
Mechanistic Studies.—In order to obtain further evidence for the thermal isomerization mechanism (mechanism 1), deuterium-labeling experiments were undertaken. Taking account of the conceivable facility of oxaborinane formation, 5-ethyl-4-heptenol-1 (**42**)

(6) H. C. Brown and O. J. Cope, *J. Amer. Chem. Soc.*, **86**, 1801 (1964).
(7) H. C. Brown and G. Zweifel, *ibid.*, **82**, 1504 (1960).
(8) A. Streitwieser, Jr., L. Verbit, and R. Bittman, *J. Org. Chem.*, **32**, 1530 (1967).
(9) F. M. Rossi, P. A. McCusker, and G. F. Hennion, *ibid.*, **32**, 450 (1967).



31 32 33 34 35

(mechanism 1)



36 37 38 39 40 41

was chosen and was treated with diborane-d_6 (deuterium content 86%[10]).

Reaction of **42** and diborane-d_6 in the molar ratio of 2:1 at room temperature afforded a mixture of 1,4-diol **43** (99%) and 1,5-diol **44** (1%). Deuterium analysis showed that the total deuterium content in **43** was 87% and the deuterium was exclusively located at C_5. Thermal isomerization of the reaction mixture at 160° for 2 hr gave 1,4-diol **43** (64%), 1,3-diol **45** (26%), 1,7-diol **46** (4%), and 5-ethylheptanol-1 (**47**) (6%). From this mixture, 1,3-diol **45** was isolated *via* the six-membered cyclic butaneborinic ester **49**.[11]

(10) Diborane-d_6 was generated from sodium borodeuteride and boron trifluoride etherate in Diglyme and used in THF solution. Deuterium content of the diborane-d_6 was calculated from that of the cyclohexanol produced by the reaction of diborane-d_6 with excess cyclohexene followed by oxidation.

(11) G. M. Anthony, C. J. W. Brooks, I. Maclean and I. Sangster, *J. Chromatogr. Sci.*, **7**, 623 (1969).

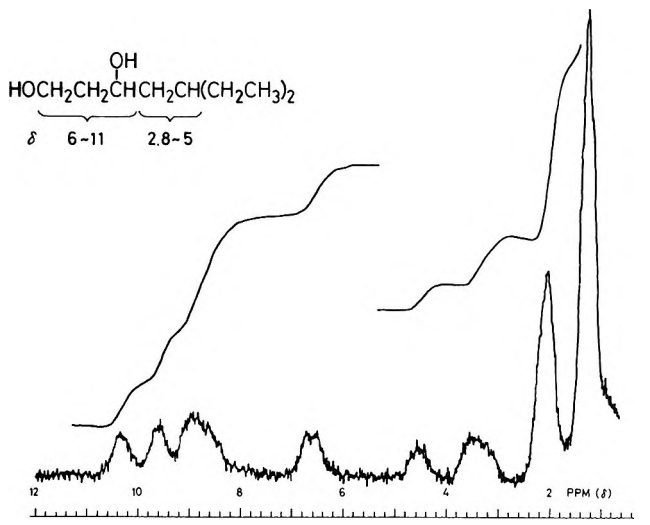
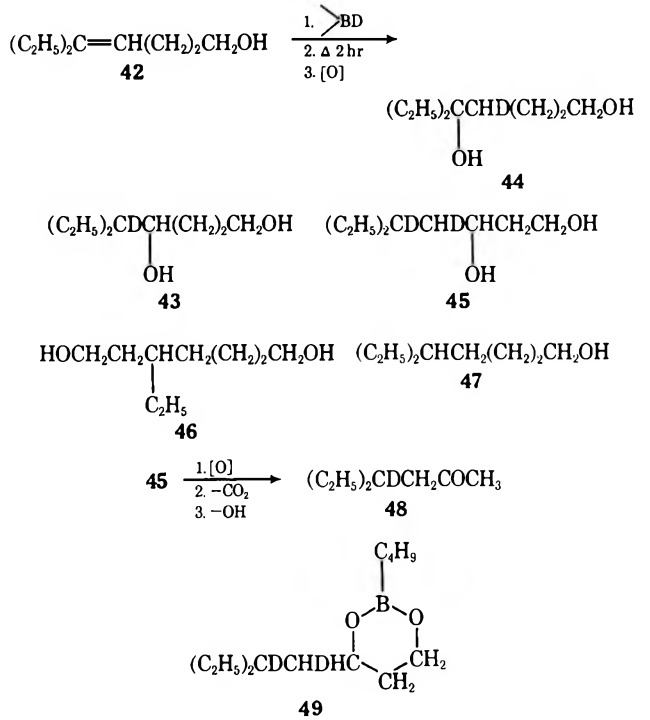


Figure 1.—60-MHz nmr spectrum of deuterated **45** (12 mg) in CCl_4 (150 μl) after addition of Eu(dpm)$_3$ (30 mg).

Since mass spectrometric determination of the deuterium distribution in **45** was considered to be unreliable,[12] it was performed by nmr and mass spectrometry.



42 43 44 45 46 47

48

49

Total deuterium content at C_4 and C_5 was determined by the nmr spectrum (Figure 1) of a carbon tetrachloride solution of **45** and tris(dipivaloylmethanato)europium.[13] The protons situated on C_1–C_3, C_4–C_5, C_6, and C_7 were assigned[14] as shown in Figure

(12) Because the mass spectra of the TMS derivative of **45** showed a very small parent peak (0.07%) and large M − 1 peak (0.15%), the total deuterium content in **45** was difficult to determine using the molecular ion peak. The M − 15 ion was prominent and considered to be possible to use for the determination of deuterium content, but was less accurate, for this fragment is said to be the one due to methyl group loss from the trimethylsilyl group, but there is no evidence that there is no intramolecular hydrogen–hydrogen exchange before fragmentation.

(13) (a) A. F. Cockerill and D. M. Rackham, *Tetrahedron Lett.*, 5153 (1970); (b) J. K. M. Sanders and D. H. Williams, *J. Amer. Chem. Soc.*, **93**, 641 (1971), and references cited therein.

(14) The assignment of the signals shown in Figure 1 was sufficient for the calculation of the deuterium content on C_4 and C_5.

1, analogously to the case of 2-hydroxy-1-(2-hydroxyethyl)adamantane.[13a] The integration of the hydrogen atoms at C_1, C_2, and C_3 was used for deuterium analyses, because the deuterium content at these positions was considered to be negligible. The total deuterium content on C_4 and C_5 was observed to be 1.56 from the integral of Figure 1. The 1,3-diol **45** was converted into 4-ethyl-2-hexanone (**48**) by oxidation and decarboxylation. After complete deuterium–hydrogen exchange of the hydrogens α to the carbonyl group by aqueous base treatment, the deuterium content on C_4 and C_5–C_6 (C_5 and C_6–C_7 positions, respectively, in the precursor **45**) was determined to be 0.72 and 0.06, respectively, by mass spectrometry. The deuterium distribution in **45** was calculated from the above described data, and is summarized in Table III.

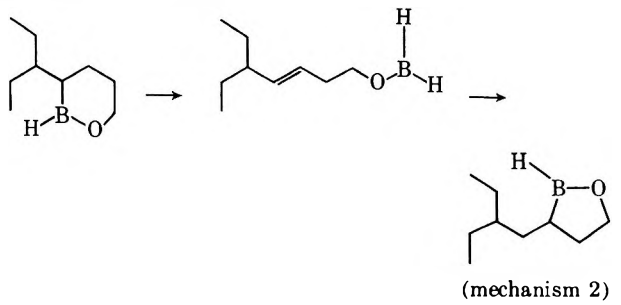
TABLE III
DEUTERIUM CONTENT IN 45

	Amount of deuterium atom at position		
	4	5	6
Observed	0.84	0.72	0.06
Mechanism 1	0.86	0.86	*a*
Mechanism 2	0.43	0.86	*a*

[a] Deuterium content on C_6 could not be obtained by mechanism 1 and 2.

As described in the above section, hydroboration and thermal isomerization of 5-ethyl-4-heptenol-1 (**42**) was considered to proceed mainly from oxaborinane **31** to oxaborolane **35**, since 99% of **43** was obtained by hydroboration and successive oxidation. The expected deuterium distribution for each of the mechanisms, mechanism 1 and 2, is shown in Table III.

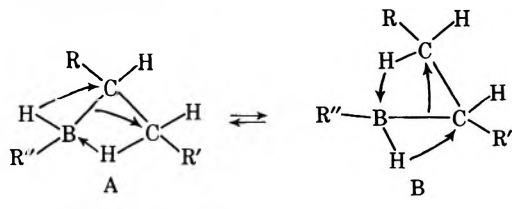
Inspection of the data shown in Table III indicates that mechanism 1 is considered to be the probable one because of the good agreement between the observed values and the expected ones. Mechanism 2 is not considered to be suitable for this case since the deuterium content on C_4 is too small.



(mechanism 2)

The above-mentioned inspection for each mechanism indicated that thermal isomerization of oxaborinane **31** to oxaborolane **35** proceeds *via* an intramolecular π complex (mechanism 1).[15]

(15) Williams' mechanism[16] (A ⇄ B) was omitted. Inspection of Dreiding models indicated that the application of this mechanism to oxaborinane was considered to be difficult.



(16) R. E. Williams, *Inorg. Chem.*, **1**, 971 (1962).

Experimental Section

Gas chromatography was performed on a Shimazu GC-4APT and a Hitachi K-23 with a 3 m × 3 mm column packed with 15% polyethylene glycol and 10% HVSG on Chromosorb W (80–100 mesh), and with a 45 m × 0.5 mm BDS Golay column. Mass spectra were obtained with an Hitachi RMS-4 spectrometer with 70 eV ionization potential. Nuclear magnetic resonance spectra were recorded with a Jeolco CL-60 spectrometer, with tetramethylsilane as internal standard and carbon tetrachloride as solvent.

6-Undecenol-1 (**2**).—6-Undeconic acid was prepared by the Wittig reaction between valeraldehyde and the phosphonium salt made from triphenylphosphine and 6-bromohexenoic acid. Methyl esterification of 6-undecenoic acid followed by lithium aluminum hydride reduction gave **2**: bp 130° (16 mm); mass spectrum *m/e* (rel intensity) 170 (M^+, 1); ir 3330 and 1655 cm^{-1}.

Anal. Calcd for $C_{11}H_{22}O$: C, 77.58; H, 13.02. Found: C, 77.31; H, 12.90.

3-Undecenol-1 (**3**).—3-Undecenoic acid was prepared *via* the Knoevenagel reaction of malonic acid, nonyl aldehyde, and triethanolamine. Methyl esterification of 3-undecenoic acid followed by lithium aluminum hydride reduction gave **3**: bp 121° (12 mm); ir 3320 cm^{-1}; mass spectrum *m/e* (rel intensity) 170 (M^+, 0.9).

Methyl 10-Undecenyl Ether (**15**).—Excess sodium hydride treatment of a THF solution of **1** followed by excess methyl iodide treatment gave **15**: bp 116–119° (18 mm); ir 3100, 1640, 1110 cm^{-1}.

Anal. Calcd for $C_{12}H_{24}O$: C, 78.19; H, 13.13. Found: C, 78.28; H, 13.35.

Methyl 3-Undecenyl Ether (**16**).—This ether was prepared as described above: bp 124° (35 mm); ir 1110 cm^{-1}; mass spectrum *m/e* (rel intensity) 184 (M^+, 1), 55 (100).

Anal. Calcd for $C_{12}H_{24}O$: C, 78.19; H, 13.13. Found: C, 78.26; H, 13.36.

2,2-Dimethyl-3-nonenol-1 (**21**).—Wittig reaction between *n*-hexylidenetriphenylphosphorane and 2,2-dimethyl-3-tetrahydropyranyloxypropanal gave 1-tetrahydropyranyloxy-2,2-dimethyl-3-nonene. Acid-catalyzed hydrolysis of this tetrahydropyranyl ether gave **21**: bp 114° (19 mm); ir 3350, 1640 cm^{-1}; mass spectrum *m/e* (rel intensity) 170 (M^+, 1), 69 (100).

Anal. Calcd for $C_{11}H_{22}O$: C, 77.58; H, 13.02. Found: C, 77.43; H, 13.03.

General Procedure for Hydroboration–Isomerization. A.—To the ice-cooled solution of unsaturated alcohol in diglyme a THF solution of diborane (molar ratio alcohol/diborane = 2) was added during 5 min under nitrogen. The mixture was stirred at room temperature for over 4 hr. THF was distilled off *in vacuo* and the mixture was refluxed. A 5-ml portion of the reaction mixture was periodically taken out and treated with excess alkaline hydrogen peroxide. The resulting mixture was extracted with ether and dried (Na_2SO_4), and ether and diglyme were distilled off. The crude product was converted to the trimethylsilyl ether derivative[3] and analyzed by glc.

B.—For the purpose of confirming the yield of reaction product, heat treatment was continued for 20 hr. After alkaline hydrogen peroxide oxidation the reaction mixture was extracted with ether and dried (Na_2SO_4), ether and diglyme were distilled off, and then distillation gave the product mixture. The product mixture was converted to the trimethylsilyl derivatives and analyzed by glc.

Hydroboration–Isomerization of 10-Undecenol-1 (**1**). **A.**—Besides the general procedure, **1** (4.25 g, 25 mmol) was hydroborated internally with sodium borohydride (0.71 g, 18.8 mmol) and boron trifluoride etherate (3.55 g, 25 mmol) in diglyme (120 ml). After completion of hydroboration at room temperature (overnight), the reaction mixture was refluxed and a 20-ml portion of the mixture was taken out after 3, 7, 10, 22, 34, and 48 hr, and was treated as described above. The results are shown in Table I.

B.—Hydroboration–isomerization of **1** (1.7 g, 10 mmol) in diglyme (20 ml) was performed by general procedure B, yield 1.76 g, bp 140–145° (4 mm). Glc analysis of the trimethylsilyl ether of the product showed that the product was a mixture of **4** (23%), **6** (55%), **7** (15%), **8** (2%), and other diols (5%).

Hydroboration–Isomerization of 6-Undecenol-1 (**2**). **A.**—Hydroboration–isomerization and work-up of **2** (500 mg, 2.93

mmol) in diglyme (25 ml) was performed by general procedure A. The results are shown in Table I.

B.—Hydroboration–isomerization of **2** (340 mg, 2 mmol) in diglyme (15 ml) was performed by general procedure B, yield 301 mg, bp 146° (4 mm). Glc analysis of the trimethylsilyl ether of the product showed that the product was a mixture of **4** (2%), **6** (77%), **8** (3%), **7** (17%), and other diols (1%).

Hydroboration–Isomerization of 3-Undecenol-1 (3). A.—3-Undecenol-1 (**3**) was hydroborated and isomerized by general procedure A. The results are shown in Table I.

B.—Hydroboration–isomerization of **3** (340 mg, 2 mmol) in diglyme (15 ml) was performed by general procedure B, yield 306 mg, bp 142° (4 mm). Glc analysis of trimethylsilyl ethers of the products showed that the products were **6** (42%), **7** (52%), and **8** (6%).

Hydroboration–Isomerization of Methyl 10-Undecenyl Ether (15). A. In Diglyme.—Methyl 10-undecenyl ether (**15**) (0.43 g, 11.3 mmol) was hydroborated internally with sodium borohydride (0.43 g, 11.3 mmol) and boron trifluoride etherate (2.17 g, 15 mmol) in diglyme (50 ml) at 0°. After completion of the hydroboration at room temperature, a half of the mixture was taken out. Usual work-up and distillation gave 0.90 g of a mixture, bp 136–143° (8 mm). The residue was refluxed for 20 hr. Usual work-up and distillation of this isomerization product gave 0.89 g of a product mixture, bp 110–134° (10 mm). The results are shown in Table II.

B. In Decalin.—To the solution of **15** (0.81 g, 4.4 mmol) in decalin (50 ml), a THF solution of diborane (4.2 mmol in 4.0 ml) was added at 0°. The reaction mixture was stirred overnight, THF was distilled off, and the mixture was heated at 160° for 20 hr. General work-up and distillation of this resulting mixture gave 0.71 g of product mixture, bp 136–140° (6 mm). The results are shown in Table II.

Hydroboration of Methyl 3-Undecenyl Ether (16).—To the solution of **16** (461 mg, 2.5 mmol) in diglyme (10 ml), a THF solution of diborane (0.62 mmol in 0.5 ml) was added at 0°. The reaction mixture was stirred at room temperature for 3 hr and allowed to stand overnight. After the general work-up, the crude product was analyzed. The results are shown in Table II.

Hydroboration–Isomerization of Methyl 3-Undecenyl Ether (16).—To the solution of **16** (461 mg, 2.5 mmol) in diglyme (10 ml), a THF solution of diborane (1.25 mmol in 1.1 ml) was added at 0°. The reaction mixture was stirred for 6 hr at room temperature, and the mixture was refluxed for 8 hr. General work-up and distillation gave 393 mg of product mixture, bp 110–125° (10 mm). The results are shown in Table II.

1-*n*-Butoxy-2-oxaborepane (12), 1-*n*-Butoxy-2-oxa-6-methylborinane (13), and 1-*n*-Butoxy-2-oxa-5-ethylborolane (14). A.—To a solution of **11** (2.15 g, 25 mmol) in THF (15 ml), a THF solution of diborane (12.5 mmol in 10 ml) was added at 0°. The reaction mixture was stirred overnight at room temperature, and the solvent and excess of diborane were removed *in vacuo*. To the residue, tributyl borate (3.3 g, 14.3 mmol) was added. About 4 g of liquid was distilled out during heating at 210–225° for 10 hr. Redistillation gave a mixture of boron compounds: yield 3.12 g (73%) from 4-pentenol-1; bp 80–96° (16.5 mm); ir 1330 cm^{-1}, absence of –OH absorption; mass spectrum *m/e* (rel intensity) 170 (M^+, 1), 56 (100).

Anal. Calcd for $C_9H_{19}O_2B$: C, 63.57; H, 11.26. Found: C, 63.68; H, 11.37.

The components of this organoboron mixture were determined by alkaline hydrogen peroxide oxidation of these organoboron compounds. Glc analysis of the oxidation products, with *n*-octyl alcohol as internal standard, showed that these oxidation products were *n*-butyl alcohol (51%) and some pentanediols (total 49%). Yield of the oxidation reaction was 89% (by glc), and diols were pentane-1,5-diol (75%) and pentane-1,4-diol (25%). These results showed that the initial organoboron compounds were **12** (75%) and **13** (25%).

B.—To a solution of **11** (2.15 g, 25 mmol) in diglyme (20 ml), a THF solution of diborane (12.5 mmol in 10 ml) was added at 0°, the mixture was stirred at room temperature, and THF was removed and then refluxed for 6 hr. Then the solvent was removed *in vacuo*. To the residue, tributyl borate (3.3 g, 14.3 mmol) was added and the mixture was heated to 220–225° for 7 hr. The distilled liquid was redistilled, bp 90–96° (15 mm), yield 1.5 g (35%) from **11**. Product analysis as described above showed that the products were **12** (76%), **13** (23%), and **14** (1%).

Hydroboration–Isomerization of 2,2-Dimethyl-3-nonenol-1 (21). A.—Hydroboration–isomerization and work-up was performed by general procedure A. The products are (i) before heating, **22** (44%) and **23** (56%); and (ii) after heating, **22** (8%), **23** (90%), and **24** (2%).

B.—Hydroboration–isomerization of **21** (340 mg, 2 mmol) in diglyme (15 ml) was performed by general procedure B, yield 293 mg, bp 122° (3.5 mm). The products were **22**, **23** (total 99%), and **24** (1%).

Anal. Calcd for $C_{11}H_{24}O_2$: C, 70.16; H, 12.85. Found: C, 70.02; H, 12.95.

5-Ethyl-4-heptenol-1 (42).—5-Ethyl-4-heptenal was prepared by the reported method[17] from 15 g of 3-vinyl-3-pentanol and 19.7 g of ethyl vinyl ether, yield 5.4 g (24%). Lithium aluminum hydride reduction of this aldehyde gave **42** in quantitative yield: bp 106° (21 mm); ir 3370, 2950, 2890, 1660 cm^{-1}; mass spectrum *m/e* (rel intensity) 55 (100), 142 (M^+, 24).

Anal. Calcd for $C_9H_{18}O$: C, 75.99; H, 12.76. Found: C, 75.87; H, 13.00.

Hydroboration–Isomerization of 5-Ethyl-4-heptenol-1 (42).—Hydroboration–isomerization of **42** (0.71 g, 5 mmol) in diglyme (20 ml) was performed by general procedure A. The products were (a) before heating, **43** (99%), **44** (1%); (b) 20 min, **43** (85%), **45** (15%); (c) 60 min, **43** (83%), **45** (17%); (d) 120 min, **43** (82%), **45** (18%).

Deuterioboration of 5-Ethyl-4-heptenol-1 (42).—To the stirred solution of **42** (710 mg, 5 mmol) in diglyme (20 ml), THF solution of diborane-d_6 (2.5 mmol in 2.7 ml) was added at 0° under nitrogen. The mixture was stirred for 3 hr at room temperature. Then a quarter portion of this mixture was taken out. Usual work-up followed by distillation of this portion gave 187 mg of a mixture of **43** (99%) and **44** (1%). The mass spectrum of the trimethylsilyl derivative of **43** follows: *m/e* (rel intensity) 305 (M^+, 0.01), 304 (0.04), 290 (0.07), 233 (17.8), 143 (100), 73 (57); relative abundance of M − 15 fragments,[18] 289 (15.5), 290 (100), 291 (28.8), 292 (12.0).

Deuterioboration–Isomerization of 5-Ethyl-4-heptenol-1 (42).—To the stirred solution of **42** (1.14 g, 8 mmol) in diglyme (23 ml), a THF solution of diborane-d_6 (4 mmol in 6.4 ml) was added at 0° under nitrogen. The mixture was stirred for 4 hr at room temperature. Then the mixture was heated and THF was distilled off after 30 min refluxing, and the mixture was refluxed for a further 1.5 hr. After general work-up, the crude yield was 1.10 g. The products were **43** (64%), **45** (26%), **46** (4%), and **47** (6%).

Isolation of 5-Ethylheptane-1,3-diol (45).—To the crude product (1.10 g) obtained above, 0.95 g of *n*-butaneboronic acid and 5 ml of pyridine were added. After standing for 30 min, pyridine was distilled off under nitrogen. The residue was chromatographed on silica gel by elution with ethyl acetate–carbon tetrachloride (1:1). The cyclic boronate **49** was isolated. The boronate **49** was oxidized by alkaline hydrogen peroxide, extracted with ether, and dried (Na_2SO_4). Distillation and preparative glc gave 40 mg of pure **45**.

Deuterioboration of Cyclohexene.—To a solution of diborane-d_6 in THF, a large excess of cyclohexene was added at 0° under nitrogen. The reaction mixture was stirred for 10 hr at room temperature, oxidized by alkaline hydrogen peroxide, extracted with ether, and dried (Na_2SO_4); ether and THF were distilled off under reduced pressure and the residue was separated by glc. The deuterium content of cyclohexanol was determined by mass spectrography at 70 eV using molecular ion: mass spectrum *m/e* (rel intensity) 57 (100), 83 (55), 101 (M^+, 4); relative abundance of molecular ions,[19] 99 (7.0), 100 (58.2), 101 (100), 102 (8.9).

4-Ethyl-2-hexanone (48).—To the stirred solution of diols obtained by deuterioboration and thermal isomerization of **42**, Jones reagent (8 *N*) was added dropwise until the reddish-brown color remained. The stirring was continued for a further 15 min, the organic layer was decanted, diluted with ether, and washed with water, and the solvents were removed under reduced pressure. The remainder was stirred with about 20% aqueous

(17) R. Marbet and G. Saucy, *Helv. Chim. Acta*, **50**, 2095 (1967).

(18) Relative abundances of M − 15 fragments of trimethylsilyl derivatives of undeuterated **43** were as follows: *m/e* (rel intensity) 289 (100), 290 (23.8), 291 (15.9). Relative abundances of M − 3-pentyl fragments of trimethylsilated **43** (*m/e* 233–235) were superimposable with those of undeuterated **43**.

(19) Relative abundances of molecular ions of undeuterated cyclohexanol were as follows: *m/e* (rel intensity) 99 (42.8), 100 (100), 101 (9.1).

sodium carbonate solution for 4 hr, extracted with ether, and dried (Na_2SO_4), and ether was separated by glc: mass spectrum *m/e* (rel intensity) 43 (85), 85 (100), 110 (25), 129 (M^+, 9); relative abundance of molecular ions,[20] 128 (45.5), 129 (100), 130 (17.1), 131 (3.0).

5-Ethylheptane-1,3-diol (45).—Methyl 5-ethyl-3-oxoheptanoate was synthesized by the method of Weiler[21] from methyl acetoacetate (3.48 g, 30 mmol) and 3-bromopentane (6.6 g, 33 mmol), bp 116–118° (18 mm), yield 1.4 g, (40%) from methyl acetoacetate. Reduction of this β-keto ester by the method of Cope and Wood[22] gave **45** in 83% yield: bp 126–130° (8 mm); ir 3320, 2925, 1460, 1380, 1050 cm^{-1}; mass spectrum of trimethylsilyl derivative *m/e* (rel intensity) 304 (M^+, 0.07), 289 (2), 261 (4), 219 (53), 187 (46), 103 (100), 73 (79).

Anal. Calcd for $C_9H_{20}O_2$: C, 67.45; H, 12.58. Found: C, 67.57; H, 12.66.

(20) Relative abundances of molecular ions of undeuterated **48** were as follows: *m/e* (rel intensity) 128 (100), 129 (9.3), 130 (0.6).

(21) L. Weiler, *J. Amer. Chem. Soc.*, **92**, 6702 (1970).

(22) A. C. Cope and G. W. Wood, *ibid.*, **79**, 3885 (1957).

5-Ethylheptane-1,4-diol (43).—Hydroboration of **42** at 0° under nitrogen and usual work-up gave **43** (purity 99% by glc): bp 120–125° (6 mm); mass spectrum of trimethylsilyl derivative *m/e* (rel intensity) 304 (M^+, 0.05), 289 (1), 247 (2), 233 (19), 143 (100), 73 (57).

Anal. Calcd for $C_9H_{20}O_2$: C, 67.45; H, 12.58. Found: C, 67.48; H, 12.84.

Registry No.—**1**, 112-43-6; **2**, 32970-48-2; **3**, 32970-49-3; **12**, 32970-50-6; **13**, 32970-51-7; **14**, 32970-52-8; **15**, 7289-47-6; **16**, 32970-54-0; **21**, 32970-55-1; **22**, 32970-56-2; **23**, 32970-57-3; **24**, 32970-58-4; **42**, 998-67-4; **43**, 32970-60-8; **45**, 33021-05-5; **48**, 6022-26-0.

Acknowledgment.—The authors are indebted to Mr. H. Kusakabe for mass spectra and Mrs. K. Huzimoto for elemental analyses.

Conformational Aspects of the Directive Effect of the Homoallylic Hydroxyl Group in the Simmons–Smith Reaction

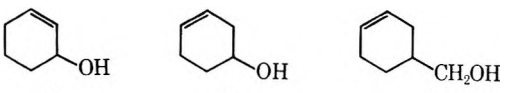
JAMES A. STAROSCIK AND BRUCE RICKBORN*[1]

Department of Chemistry, University of California, Santa Barbara, California 93106

Received August 2, 1971

A series of substituted 3-cyclohexenols was prepared and subjected to the iodomethylzinc iodide methylenation reaction. Competitive kinetics establish that, in contrast to the allylic 2-cyclohexenols, the homoallylic 3-cyclohexenols react through the axial hydroxyl conformer. The compounds examined (k_{rel}) are 3-cyclohexenol (1.0), *cis*-6-methyl-3-cyclohexenol (5.2), 1-methyl-3-cyclohexenol (4.0), *trans*-6-methyl-3-cyclohexenol (2.6), *trans*-1,4,5,6,7,8-4a(8a*H*)-hexahydronapthol (1.6), and 4-methoxycyclohexene (0.18). All of these olefins exhibited stereospecific methylenation reactions.

Since its introduction in 1958, the Simmons–Smith methylenation reaction[2] has been widely used in organic synthesis. A particularly interesting aspect is the directive effect of a neighboring hydroxyl group in the substrate olefin.[3] In cyclopentenes and cyclohexenes, an allylic or homoallylic hydroxyl group leads to stereospecific cis introduction of the methylene group. Higher cyclic olefins can give trans product with high selectivity provided the hydroxyl group–organometallic complex affords more facile access to the trans face of the olefin.[3] In our earlier work[4] it was established that both allylic and homoallylic hydroxyl groups in cyclohexene cause very large rate enhancement. In fact, both types of alcohols react immeasurably faster than the parent unsubstituted olefin, although a significant factor also separates the rates of **1** and **2**. Interestingly,



1	2	3
$k_{rel} = 11$	1.0	very slow

when the hydroxyl group is removed to the γ position, as in **3**, the rate becomes comparable to that of cyclohexene itself, and the reaction becomes effectively nonstereoselective.[4] By determining the relative rates of methyl-substituted 2-cyclohexenols, it was established that the cis directive effect of the allylic hydroxyl group is exerted by this group in the pseudoequatorial conformation. This result bears on the question of the structure of the Simmons–Smith reagent in ether solution; models indicate that a monomeric iodomethylzinc species, in which the metal is complexed to the pseudoequatorial hydroxyl oxygen, cannot attain the necessary geometry for reaction with the double bond. For this reason a dimeric structure for the reactive organometallic species was proposed.[4]

The rate difference between **1** and **2**, as well as the lack of any significant influence (stereochemical or kinetic) of the hydroxyl group in compound **3**, clearly indicates, that the directive effect of the hydroxyl group has very specific geometric requirements. It was therefore of interest to determine which conformer of the homoallylic cyclohexenol causes cis selectivity.

Ginsig and Cross,[5] in applying the Simmons–Smith reaction to estr-5(10)-ene-3,17-diol, found that both the 3α and 3β alcohols gave stereospecific methylenation (cis to the homoallylic 3-OH group in both cases), but the 3α isomer was quite sluggish in reaction and required forcing conditions. Levine and coworkers[6] have presented convincing evidence that the preferred half-chair conformation of ring A in estr-5(10)-ene is such that the 3α hydroxyl group would be equatorial, and conversely the 3β group would be axial. The methylenation results[5] therefore would support the

(1) Author to whom correspondence should be addressed.

(2) H. E. Simmons and R. D. Smith, *J. Amer. Chem. Soc.*, **80**, 5323 (1958).

(3) A recent discussion of this phenomenon and references to earlier work are found in the work of C. D. Poulter, E. C. Friedrich, and S. Winstein, *ibid.*, **91**, 6892 (1969).

(4) J. H. Chan and B. Rickborn, *ibid.*, **90**, 6406 (1968).

(5) R. Ginsig and A. D. Cross, *ibid.*, **87**, 4629 (1965).

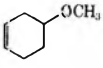
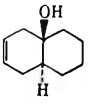
(6) S. G. Levine, N. H. Eudy, and E. C. Farthing, *Tetrahedron Lett.*, 1517 (1963); S. G. Levine, D. M. Feigl, and N. H. Eudy, *ibid.*, 4615 (1967).

premise that the directive influence of the homoallylic hydroxyl group occurs preferentially *via* the axial conformer, in contrast to the allylic cyclohexenol[4] situation. However, long-range steric interactions in the steroidol systems could confuse this interpretation; we therefore decided to examine some simpler homoallylic cyclohexenols.

Results and Discussion

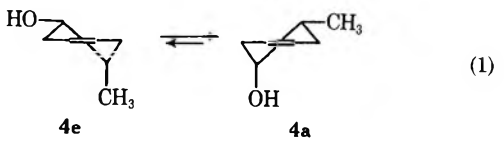
The competitive kinetic technique described earlier[4] was applied to the series of homoallylic alcohols shown in Table I. The unsubstituted 3-cyclohexenol **2** should

TABLE I
RELATIVE RATES OF METHYLENATION WITH IODOMETHYLZINC IODIDE

Olefin		k_{rel}
2		1.0
	(4)	5.2 ± 0.4
	(5)	4.0 ± 0.3
	(6)	2.6 ± 0.2
	(7)	0.18 ± 0.02
	(8)	1.6 ± 0.2

exist in two rapidly interconverting half-chair conformers. Although the conformational preference of the homoallylic hydroxyl group has not been determined, the experimental values for 4-methyl-[7] and the 4-halocyclohexenes[8] suggest that the hydroxyl group preference will be small. Compound **2** was therefore chosen as the reference material, with the expectation that alkyl-substituted analogs with stronger conformational preferences would exhibit either faster or slower rates of reaction with iodomethylzinc iodide.

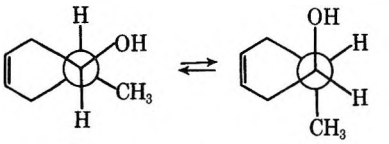
Compounds **4** and **5** both react faster than **2** (see Table I); this observation is compatible with the view that the homoallylic methyl group has a considerably stronger conformational preference than homoallylic hydroxyl, and that the directive effect of the hydroxyl group is exerted *via* its axial conformer. This is illustrated by the conformational equilibrium for **4** (eq 1).



4e **4a** (1)

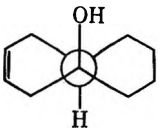
One would expect the equilibrium to favor **4a**, and, if **4a** is the conformer through which methylenation occurs, **4** should react more rapidly than **2**.

Conversely, the same reasoning indicates that compound **6** should undergo methylenation at a lower rate than **2**. This condition is not fulfilled, even though **6** is less reactive than **4** or **5**. One possible explanation for this apparent anomaly is that the gauche CH_3–OH interaction in **6e** causes **6a** to be favored (relative to the



6e **6a** (2)

axial OH conformer of **2**). Alternatively, it may be that geminal or vicinal substitution by an alkyl group causes a distortion of the cyclohexene ring;[9] even a small change in geometry could lead to the rate differences observed for compounds **2**, **4**, **5**, and **6**. Ring distortion could in fact overshadow any conformational effects on rate and negate the conclusion regarding the preferred conformation for reaction. To circumvent this difficulty, compound **8** was prepared. As the Newman projection formula **8a** illustrates, this material



8a

is constrained conformationally by the trans-fused cyclohexane ring so that the hydroxyl group must remain axial. The rapid reaction of **8** shows conclusively that the directive influence of the homoallylic hydroxyl group is exerted through the axial conformation. The still faster rates of **4**, **5**, and **6**, even though the ground-state populations of their axial hydroxyl conformers cannot exceed that of **8**, may then be ascribed to the inherently lower flexibility of the latter compound.

We have earlier concluded[4] that the similarity in rates of Simmons–Smith methylenation of 2-cyclohexenol and its methyl ether (3-methoxycyclohexene) mitigated against a mechanism involving prior zinc salt formation with the alcohol. Since 3-cyclohexenol is a factor of ten less reactive than the 2-ol, the question of prior salt formation in the homoallylic system remains open. Using the same approach, it is found that 4-methoxycyclohexene (**7**) undergoes methylenation at a fivefold slower rate than **2**. Although this factor is somewhat greater than that observed with the allylic system, it is still too small to support any proposal of fundamentally different mechanisms for the alcohols and ethers. Simple complex formation between the oxygen atom and the zinc reagent is supported; this feature is common to the reactions of both the allylic and homoallylic systems.

In contrast to the situation with 2-cyclohexenol, the axial OH reactive conformation of the homoallylic alcohol does not preclude any particular state of aggregation for the Simmons–Smith reagent. Assuming first-order (in the organometallic) reaction with both alcohols, indirect support for a dimeric structure is provided.[4] The reason for the absence of any directive

(7) B. Rickborn and S. Lwo, *J. Org. Chem.*, **30**, 2212 (1965).
(8) F. R. Jensen and C. H. Bushweller, *J. Amer. Chem. Soc.*, **91**, 5774 (1969).
(9) Distortion of this olefin by a single large group (4-*tert*-butyl) is well documented.[7,10]
(10) D. J. Pasto and F. M. Klein, *J. Org. Chem.*, **33**, 1468 (1968).

effect, kinetic or stereochemical, for the γ-hydroxy group of **3** remains unclear.

Experimental Section

Kinetics.—Relative rate constants were determined as described previously,[4] using the following olefin pairs and vpc columns as indicated in footnote 11: **2** and **5**, column a[11] at 130°; **4** and **5**, column a at 130°; **2** and **6**, column b at 130°; **4** and **8**, column c at 185°; **2** and **7**, column c at 116°. At least three runs were made for each olefin pair, and vpc peak areas were corrected as described earlier.[12]

3-Cyclohexenol (2).—Reduction of benzene with lithium and ethanol in liquid ammonia[13] gave 1,4-cyclohexadiene; treatment of 125 g (1.56 mol) of this diene with 1 mol of peracetic acid[14] afforded, after distillation through a short Vigreux column, 100 g (67%) of 1,2-epoxy-4-cyclohexene, bp 62–63° (33 Torr). Reduction by $LiAlH_4$ gave 86 g (85%) of **2**, purified by distillation through a Teflon annular band column, bp 75.0–75.5° (15 Torr).[4]

A portion (7.0 g, 0.071 mol) of **2** was treated with sodium hydride and methyl iodide to furnish the ether **7**, 5.7 g (72%), bp 135–136°,[15] which was separated from traces of starting material contaminant by chromatography on alumina.

***cis*-6-Methyl-3-cyclohexenol (4) and 1-Methyl-3-cyclohexenol (5).**—Treatment of 276 g (3.0 mol) of toluene with 6 g-atoms of lithium wire and 9 mol of absolute ethanol in 2.5 l. of liquid ammonia gave 237 g (84%) of 1-methyl-1,4-cyclohexadiene,[16] bp 115–116°.

The diene, 237 g (2.52 mol), was treated with 1 equiv of peracetic acid.[14] Purification by distillation through a Teflon annular band column gave 209 g (75%) of 1-methyl-1,2-epoxy-4-cyclohexene, bp 153°. Integration of the nmr of this material showed a ratio of one epoxide proton to two vinyl protons.

The epoxide, 207 g (1.88 mol), was added slowly to an ice-cooled, stirred solution of 50 g (1.32 mol) of lithium aluminum hydride and 176 g (1.32 mol) of aluminum chloride in 2.1 l. of ether.[17] After the addition was complete the mixture was stirred for a few minutes and then hydrolyzed by sequential treatment with 50 ml of water, 50 ml of 15% sodium hydroxide solution, and 150 ml of water. The ether was decanted and the salt residue was washed several times with fresh solvent. The combined ether solutions were dried, evaporated, and distilled, bp 58–68° (6 Torr), to give 135 g (64%) of alcohol product. Vpc analysis (column a)[11] indicated a nearly equimolar mixture of the tertiary and secondary alcohol products.

Pure samples were readily obtained by redistillation through the Teflon annular band column.

1-Methyl-3-cyclohexenol (5): bp 70–71° (33 Torr); nmr ($CDCl_3$) δ 1.24 (s, 3), 1.39–1.82 (m, 2), 1.82–2.38 (m, 4), 2.40 (s, OH), 5.40–5.90 ppm (m, 2); ir (CCl_4) 3350, 3590 cm^{-1}. *Anal.*[18] Calcd for $C_7H_{12}O$: C, 74.95; H, 10.78. Found: C, 74.68; H, 10.74.

***cis*-6-Methyl-3-cyclohexenol (4):** bp 89–90° (33 Torr); nmr (CCl_4) δ 1.03 (d, 3, J = 7 Hz), 1.68–2.90 (m, 5), 3.75 (s, OH), 4.07–4.40 (m, 1), 6.09–6.48 (m, 2); ir 3475 cm^{-1}. *Anal.* Found: C, 74.88; H, 10.51.

trans-6-Methyl-3-cyclohexenol (6).—Various methods for preparing this material by the addition of methylorganometallic reagents to 1,2-epoxy-4-cyclohexene were explored, and the results have been presented earlier.[19] The following procedure is the method of choice.

A solution of lithium dimethylcuprate[20] was prepared by the slow addition of 50 ml of 0.84 *M* methyllithium in ether to a stirred slurry of 2.60 g (0.021 mol) of cuprous thiocyanate in ether, maintained at −15°. Slow addition of 1,2-epoxy-4-cyclohexene, 2.02 g (0.021 mol), in ether was done at the reduced temperature, after which the mixture was allowed to warm to 0° (2.5 hr). The mixture was then hydrolyzed by the addition of 5 ml of 10% sodium hydroxide solution. The combined ether phases from extraction were dried, evaporated, and distilled through a short Vigreux column, bp 46–48° (2.5 Torr), to give 1.59 g (68%) of **6**. Vpc analysis of this material indicated >98% purity (column a):[11] nmr (CCl_4) δ 1.05 (d, 3, J = 5.5 Hz), 1.45–2.85 (m, 5), 3.25–3.82 (m, 1), 3.90 (s, OH), 5.75 ppm (br s, 2); ir 3330 cm^{-1}. *Anal.* Found: C, 74.87; H, 11.00.

Further structural evidence was provided by careful Jones oxidation of a sample of **4** to give 6-methyl-3-cyclohexenone; this in turn was reduced with lithium aluminum hydride to give a mixture of **4** (34%) and **6** (64%).

***trans*-Bicyclo[4.4.0]dec-3-en-1-ol (8).**—Tetralin was reduced by lithium and ethanol in liquid ammonia to give bicyclo[4.4.0]-deca-1(5),3-diene, bp 65–70° (3.5 Torr).[21] The Korach procedure[14] using 120 g (0.89 mol) of peracetic acid gave on distillation 125.4 g (94%) of the tetrasubstituted epoxide, 11-oxatricyclo[4.4.1.0]undec-3-ene, bp 45–50° (0.10 Torr).[22]

Reduction of this epoxide, 118.4 g (0.79 mol), with aluminum hydride (prepared from lithium aluminum hydride and aluminum chloride in a 3:1 molar ratio[17]) in ether afforded, after distillation through a Vigreux column, 112.7 g (94%) of alcohol product, bp 36–40° (0.05 Torr). This material was further purified by chromatography on alumina: nmr (CCl_4) δ 0.75–2.10 (m, 14) and 5.34–5.64 (m, 2); ir (thin film) 3470 cm^{-1}. *Anal.* Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.91; H, 10.50.

Cyclopropanes.—The Simmons–Smith procedure was used to prepare samples of the cyclopropane derivatives described in this work. All methylenation products appeared as single, symmetrical peaks under a variety of vpc conditions,[11] and are therefore presumed to be isomerically pure. By analogy to the reaction of 3-cyclohexenol itself, these products are believed to have the methylene bridge *cis* to the hydroxyl group.

All products exhibited the high-field multiplets characteristic of *gem*-cyclopropyl protons, and had satisfactory ir and nmr spectra.

trans-4-Methylbicyclo[4.1.0]heptan-*cis*-3-ol (from methylenation of **6**). *Anal.* Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 75.79; H, 10.93.

trans-3-Methylbicyclo[4.1.0]heptan-*cis*-3-ol (from **5**). *Anal.* Found: C, 76.32; H, 11.32.

cis-4-Methylbicyclo[4.1.0]heptan-*cis*-3-ol (from **4**). *Anal.* Found: C, 76.31; H, 11.31.

Tricyclo[5.4.0.$0^{3,5}$]undecan-1-ol (from **8**). *Anal.* Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.53; H, 11.04.

Registry No.—**2**, 822-67-3; **4**, 33066-05-6; **5**, 33061-16-4; **6**, 33066-06-7; **7**, 15766-93-5; **8**, 33066-07-8; 1,2-epoxy-4-cyclohexene, 6253-27-6; 1-methyl-1,2-epoxy-4-cyclohexene, 31152-30-4; *trans*-4-methylbicyclo[4.1.0]heptan-*cis*-3-ol, 33066-08-9; *trans*-3-methylbicyclo[4.1.0]heptan-*cis*-3-ol, 33066-09-0; *cis*-4-methylbicyclo[4.1.0]heptan-*cis*-3-ol, 33066-10-3; tricyclo[5.4.0.$0^{3,5}$]undecan-1-ol, 33061-19-7.

Acknowledgment.—This work was supported in part by the National Science Foundation, GP 6043.

(11) (a) 6 m × 3.2 mm 10% Carbowax 20M; (b) 6 m × 3.2 mm 15% diisodecylphthalate; (c) 6.5 m × 3.2 mm 18% XF-1150; (d) 6.5 m × 6.4 mm 13% Carbowax 4M; (e) 1.6 m × 6.4 mm 20% TCEP; (f) 3 m × 6.4 mm 10% Carbowax 20M, with 2% K_2CO_3 added to the solid support; (g) 2 m × 6.4 mm 20% SF-96.

(12) B. Rickborn and J. H. Chan, *J. Org. Chem.*, **32**, 3576 (1967).

(13) A. P. Krapcho and A. A. Bothner-By, *J. Amer. Chem. Soc.*, **81**, 3658 (1959).

(14) M. Korach, D. R. Nielsen, and W. H. Rideout, *ibid.*, **82**, 4328 (1960).

(15) C. J. Gogek, R. Y. Moir, and G. B. Purves, *Can. J. Chem.*, **29**, 946 (1951).

(16) R. A. Benkeser, M. L. Burrows, J. J. Hazdra, and E. M. Kaiser, *J. Org. Chem.*, **28**, 1094 (1963).

(17) These conditions were chosen to maximize the amount of tertiary cleavage; see D. K. Murphy, R. L. Alumbaugh, and B. Rickborn, *J. Amer. Chem. Soc.*, **91**, 2649 (1969).

(18) Analysis by C. F. Geiger, 312 E. Yale St., Ontario, Calif.

(19) J. Staroscik and B. Rickborn, *J. Amer. Chem. Soc.*, **93**, 3046 (1971).

(20) H. Gilman, R. G. Jones, and L. A. Woods, *J. Org. Chem.*, **17**, 1630 (1952).

(21) A. J. Birch, *J. Chem. Soc.*, 430 (1944).

(22) W. Hückel and U. Wörffel, *Chem. Ber.*, **89**, 2098 (1956).

A Rapid Amide Cleavage Assisted by a Neighboring Hydroxylamino Function[1]

THEODORE COHEN* AND WILLIAM F. GRAY

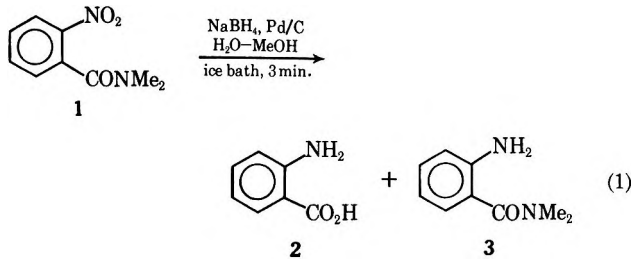
Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15213

Received August 13, 1971

An attempted reduction of *o*-nitro-*N*,*N*-dimethylbenzamide (1) to the amine **3** by subjecting it, over a 3-min period, to an ice-cooled water–methanol solution of sodium borohydride containing suspended palladium on carbon resulted in the production of anthranilic acid (**2**) in 58% crude yield. The rapid amide cleavage is believed to occur in the intermediate *o*-hydroxylamino-*N*,*N*-dimethylbenzamide (**4**) by loss of a proton from the hydroxylamino group followed by nucleophilic attack on the carbonyl group to provide 2,1-benzisoxazolone (**5**), which is then reduced to **2**. Evidence for each of these steps is presented. The cleavage of the amide group of **4** (which can be obtained from some of the reduction reactions) in 0.1 *N* aqueous alkali at room temperature is at least 3.7×10^3 times as fast as that of *N*,*N*-dimethylbenzamide under the same conditions.

In recent years, a number of instances of neighboring group assistance in the cleavage of amides have been reported.[2-4] A few of these involve benzamide cleavage which is assisted by an ortho substituent. One of the earliest examples, reported by Bender and coworkers,[5] is the participation of the *o*-carboxyl group in the hydrolysis of phthalamic acid. Morawetz and Shafer[6] attributed a rate enhancement in the hydrolysis of *o*-carboxyphthalanilic acid to bifunctional catalysis involving the neighboring carboxyl groups of both rings. Bruice and Tanner[7] provided evidence that the *o*-hydroxy groups of salicylamides in their ionized forms enhance the rate of alkaline hydrolysis by exerting a general base catalytic effect. Cohen and Lipowitz[8] showed that the rate of acid hydrolysis of *N*,*N*-dicyclohexylbenzamide was greatly enhanced by the presence of an ortho benzamido group, which appeared to provide nucleophilic assistance to the hydrolysis. We now report another example of an extremely facile cleavage of a *tert*-benzamide and suggest a mechanism which involves nucleophilic assistance by a neighboring hydroxylamino group.

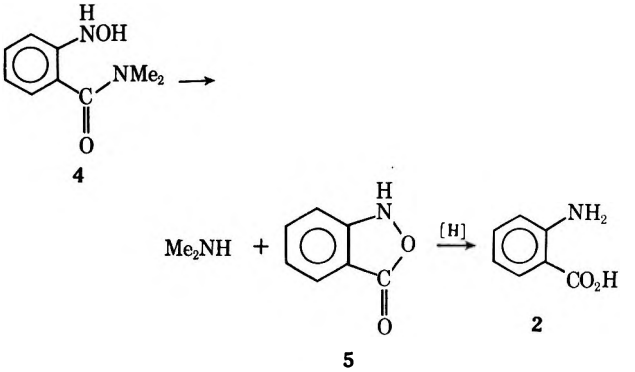
During an attempted reduction of *o*-nitro-*N*,*N*-dimethylbenzamide (**1**) to the amine by the use[9] of palladium on carbon and sodium borohydride in a water–methanol solution which was cooled in an ice bath, anthranilic acid (**2**, 58% crude yield) was produced along with the expected *o*-amino-*N*,*N*-dimethylbenzamide (**3**, 26% yield) (eq 1) after a reaction time of only 3 min. The ratio of **2** to **3** produced varied widely



1 → 2 + 3 (1)

depending on the exact experimental conditions. It was shown that **3** is not cleaved under the reaction conditions and that the nitro compound **1** is stable in the reaction mixture used provided that the sodium borohydride is not present.

It is thus likely that cleavage of the amide linkage is occurring in a reduction intermediate. A very likely intermediate in the reduction of the nitro compound and one which has the proper structure for neighboring group participation is *o*-hydroxylamino-*N*,*N*-dimethylbenzamide (**4**). The gross features of a reasonable mechanism are shown.



4 → 5 → 2

The first step would presumably be promoted by the alkalinity that develops in sodium borohydride solutions. An analogy for this step is the finding by Bamberger and Pyman[10] that methyl and ethyl *o*-hydroxylaminobenzoate (**6**) are cleaved in high yield to 2,1-benzisoxazolone (**5**) at room temperature by the use of 1 *N* sodium hydroxide. Participation of the general type suggested here, albeit in acid solution, has been claimed for the electrochemical reduction of *o*-nitrobenzoic acid and the corresponding amide and ethyl ester (**7**) in 2–5 *N* sulfuric acid at 60–80°; the product was considered to be **5**, but no evidence for its structure was presented.[11] Another analogy is the

(1) This work was supported by Grant GP 22955 from the National Science Foundation.

(2) Reviews of intramolecular participation in the cleavage of carboxylic acid derivatives: M. L. Bender, *Chem. Rev.*, **60**, 53 (1960); B. Capon, *Quart. Rev., Chem. Soc.*, **18**, 45 (1964); T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. 1, W. A. Benjamin, New York, N. Y., 1966, Chapter 1; S. L. Johnson, *Advan. Phys. Org. Chem.*, **5**, 237 (1967).

(3) For a recent review of intramolecular assistance in amide cleavage, see B. C. Challis and J. A. Challis, "The Chemistry of Amides," J. A. Zabicky, Ed., Interscience, New York, N. Y., 1970, pp 833–840. For other examples see footnote 4.

(4) H. Zahn and L. Zürn, *Justus Liebigs Ann. Chem.*, **613**, 76 (1958); T. A. Dobson, M. A. Davis, A. M. Hartung, and J. M. Manson, *Can. J. Chem.*, **46**, 2843 (1968); B. Vigneron, P. Crooy, F. Kezdy, and A. Bruylants, *Bull. Soc. Chim. Belg.*, **69**, 616 (1960); P. Crooy and A. Bruylants, *ibid.*, **73**, 44 (1964); J. A. Shafer and H. Morawetz, *J. Org. Chem.*, **28**, 1899 (1963); A. Signor and E. Bordignon, *ibid.*, **30**, 3447 (1965); W. H. Puterbaugh and C. R. Hauser, *ibid.*, **29**, 853 (1964); E. M. Levi, C. L. Mao, and C. R. Hauser, *Can. J. Chem.*, **47**, 3671 (1969); C. L. Mao, I. T. Barnish, and C. R. Hauser, *J. Heterocycl. Chem.*, **6**, 475 (1969); G. I. Glover, R. B. Smith, and H. Rapoport, *J. Amer. Chem. Soc.*, **87**, 2003 (1965).

(5) M. L. Bender, *J. Amer. Chem. Soc.*, **79**, 1258 (1957); M. L. Bender, Y. L. Chow, and F. Chloupek, *ibid.*, **80**, 5380 (1958).

(6) H. Morawetz and J. Shafer, *ibid.*, **84**, 3783 (1962).

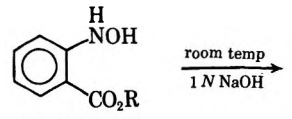
(7) T. C. Bruice and D. W. Tanner, *J. Org. Chem.*, **30**, 1668 (1965).

(8) T. Cohen and J. Lipowitz, *J. Amer. Chem. Soc.*, **86**, 5611 (1964).

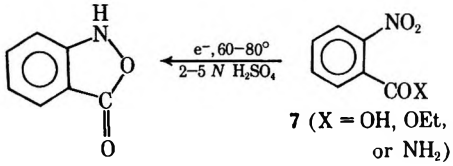
(9) T. Neilson, H. C. S. Wood, and A. G. Wylie, *J. Chem. Soc.*, 371 (1962).

(10) E. Bamberger and F. L. Pyman, *Chem. Ber.*, **42**, 2297 (1909).

(11) M. Le Guyader and D. Peltier, *C. R. Acad. Sci.*, **253**, 2544 (1961); M. Le Guyader, A. Tallec, and R. Legoff, *ibid.*, **258**, 6175 (1964); A. Tallec, *ibid.*, **263**, 722 (1966).



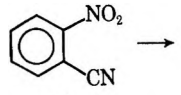
6 R = Me or Et



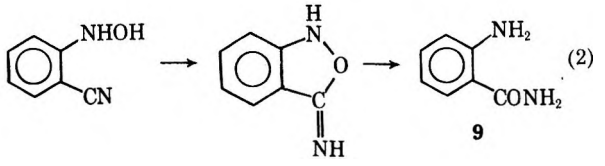
5

7 (X = OH, OEt, or NH_2)

conversion of *o*-nitrobenzonitrile (**8**) to *o*-aminobenzamide (**9**) by reduction with Raney nickel; evidence was presented for the reaction scheme shown (eq 2).[12]



8



(2)

9

In the present work, preliminary support for the intermediate formation of 2,1-benzisoxazolone (**5**) was obtained by isolation of its *N*-acetyl derivative from an acidified reaction mixture in which the reduction of **1** had been performed under conditions similar to those which produced anthranilic acid. The acetyl derivative was identified by comparison of its infrared and mass spectra with those of the acetyl derivative of an independently prepared sample of **5** (see below).

When a different batch of palladium on carbon catalyst was used for the reduction of **1**, it was possible to isolate the unstable proposed intermediate, *o*-hydroxylamino-*N*,*N*-dimethylbenzamide (**4**) in a crude yield of up to 50%. The material had similar spectral properties to those of a sample[13] prepared by the careful reduction of **1** with zinc and ammonium chloride; the procedure used is a modification of that developed by Bamberger and Pyman[10] for the preparation of methyl and ethyl *o*-hydroxylaminobenzoate.

(12) H. Musso and H. Schröder, *Chem. Ber.*, **98**, 1562 (1965).

(13) Since recrystallized samples of this material deteriorate rather rapidly, the purity of the sample obtained by zinc reduction has not been definitely established. It apparently contains some *o*-amino-*N*,*N*-dimethylbenzamide (**3**), since its glpc trace shows only one small peak at the same retention time as the amine; evidently the hydroxylamine does not survive the gas chromatographic conditions. The mass spectrum, obtained utilizing a direct probe, also closely resembles that of **3** except for the presence of a weak parent peak at *m/e* 180 and one of moderate intensity at *m/e* 135, possibly a result of the cyclization to **5** in the mass spectrometer; since it is known that loss of oxygen is a major mode of fragmentation of *N*-arylhydroxylamines, often producing the base peak in the mass spectrum,[14] this spectrum is not surprising.

Fortunately, the infrared spectrum of the crude hydroxylamine is quite different from that of the amine (see Experimental Section). For example, the peaks at 3480 and 3390 cm^{-1} in the spectrum of the amine are not present in that of the hydroxylamine; instead, the latter has a sharp peak at 3584 cm^{-1} and a broad one at 3322 cm^{-1} which are indicative of the hydroxylamino function. Further, the amide absorption of the amine occurs at 1609 cm^{-1} while that of the hydroxylamine is at 1621 cm^{-1}.

The most convincing evidence for the structure of the hydroxylamine is the cleavage to the benzisoxazolone (**5**) in 51% isolated yield (see text).

(14) R. T. Coutts and G. Mukherjee, *Org. Mass Spectrom.*, **3**, 63 (1970).

Evidence for the suggested participation of the hydroxylamino function in the cleavage of the amide group has been obtained by the isolation of 2,1-benzisoxazolone (**5**, 51% yield) from a weakly alkaline (0.1 *N*) aqueous solution of **4** which was allowed to remain at room temperature and then neutralized; the total reaction time was less than 7 min. The benzisoxazolone was identified by its melting point,[10] its mass spectrum (at 15 eV peaks at *m/e* 135, parent and base; 119, P − O; 91, P − CO_2; and 79), infrared spectrum (3311, sharp, N–H; 1773 and 1751 cm^{-1}, 5-ring carbonyl) and nmr spectrum (τ 1.17, broad singlet, one proton, NH; 2.0–2.9, multiplet, 4 aromatic protons), and its conversion to the known *N*-acetyl derivative.

An attempt to monitor the cleavage reaction of **4** in deuterium oxide by infrared spectroscopy failed because of the high rate of the reaction; the spectral scan, which was started 70 sec after mixing (scan rate 80 cm^{-1} per minute from 1300–1800 cm^{-1}), indicated that the amide **4** had been converted to the sodium salt of *o*-hydroxylaminobenzoic acid (the open form of **5** exists in alkaline solution; see Experimental Section). In contrast, a solution of the amide in neutral heavy water gave a spectrum which was clearly that of the uncleaved amide and which did not change during a 0.5-hr period. It is thus apparent that the amide cleavage is base catalyzed. This is consistent with the proposed mechanism, since the anionic form of the hydroxylamino function should be far more nucleophilic than the un-ionized form.

In an attempt to estimate the enhancement of the cleavage rate provided by the hydroxylamino function, *N*,*N*-dimethylbenzamide was subjected to the reaction conditions used to prepare the benzisoxazolone (**5**) from **4**. After 18 days in 0.1 *N* aqueous base at room temperature, 56% of the amide could be recovered unchanged. Thus, the half-life of the hydrolysis is greater than 18 days. Since the half-life of the assisted hydrolysis is less than 7 min, 3.7×10^3 is a minimum factor for the enhancement. In view of the facts that the 7-min figure may be too large by a factor of 2 or 3 and that in the absence of nucleophilic participation an electron-donating ortho substituent would be expected to decrease the rate of alkaline hydrolysis by decreasing the electrophilicity of the carbonyl group[15] and probably by steric hindrance, the actual rate enhancement may be several times this factor.

Finally, it was demonstrated that 2,1-benzisoxazolone (**5**) could be reduced to anthranilic acid (**2**, 76% yield) under the reaction conditions.

Experimental Section

Infrared spectra were determined with a Beckman IR-8 or IR-12 spectrophotometer; sodium chloride cell windows were used throughout except for work in aqueous solution, where calcium fluoride windows were employed. Nmr spectra were determined with a Varian A-60 spectrometer; chemical shifts are expressed in τ values relative to internal tetramethylsilane. Mass spectra were obtained with an LKB-9000 combined gas chromatograph–mass spectrometer at 70 eV, unless otherwise stated; the *m/e* values of major peaks are reported, followed in parentheses by intensity values as percentages of the base peak. Melting points were taken on a Thomas-Kofler micro hot stage and are corrected. Two different lots of Matheson Coleman and Bell 10% Pd/C were used. Micro silicic acid columns were prepared with Mallincrodt TLC-7GF silicic acid.

(15) K. T. Koshy, *J. Pharm. Sci.*, **58**, 560 (1969).

Catalytic Reduction of *o*-Nitro-*N*,*N*-dimethylbenzamide in the Presence of Sodium Borohydride. A. Isolation of Anthranilic Acid.—A solution of 0.97 g (5.0 mmol) of *o*-nitro-*N*,*N*-dimethylbenzamide[16] in 22 ml of water and 3 ml of methanol was rapidly added to a slurry of 0.05 g of 10% Pd/C in an ice-cooled solution of 0.7 g (18 mmol) of sodium borohydride in 15 ml of water. The mixture was stirred for 3 min and the catalyst was removed by filtration. The basic solution was made slightly acidic with 18% hydrochloric acid, extracted with ether, made basic with sodium carbonate, and reextracted with chloroform. The two extracts were separately dried ($MgSO_4$) and the solvents were removed by evaporation to produce 0.40 g (58%) of crude anthranilic acid (**2**) and 0.21 g (26%) of crude *o*-amino-*N*,*N*-dimethylbenzamide (**3**) from the ether and chloroform extracts, respectively. The infrared spectrum of the anthranilic acid strongly resembles that reported.[17] The crude *o*-amino-*N*,*N*-dimethylbenzamide was identified by comparison of its infrared spectrum with that of an authentic sample:[16] ir ($CHCl_3$) 3480 (m), 3390 (m), 3010 (s), 2940 (m), 1609 (vs), 1587 (vs), 1480 (s), 1390 (s), 1300 (m), 1255 (m), 1201 (m), 1151 (m), 1075 (s), and 1058 cm^{-1} (sh). Its mass spectrum is very similar to that of **4** and is presented below under the description of the latter.

Another reaction was performed as above, except at one-half the scale. The mixture was stirred this time for 15 min and the catalyst was then removed by filtration. The basic solution was extracted with chloroform (five 5-ml portions), neutralized with 18% hydrochloric acid, reextracted, acidified, and finally extracted a third time. The acid extract was dried ($MgSO_4$) and concentrated to leave 67 mg of residue, which was partially purified by passage through a micro silicic acid column ($CHCl_3$), and was then sublimed at 100° (0.5 Torr) in a micro sublimator. There was significant decomposition of the residue during sublimation, but the sublimed anthranilic acid consisted of 20.3 mg (5.7% yield) of white crystals, mp 147.0–147.5° (lit.[18] mp 144.9–145.4°; lit.[19] mp 144–145°), whose infrared spectrum matched that reported.[17]

When the aminoamide **3** was subjected to the reaction conditions except that ice cooling was not employed, over 90% of it was recovered. The starting nitro compound was recovered unchanged under these couditions when the sodium borohydride was not present and cooling was not employed.

In another run, using the same quantities of reactants but in a solution of 30 ml of water, 5 ml of methanol, and one drop of 1 *N* sodium hydroxide, less catalyst (0.02 g), and a longer reaction time (1 hr), the yield of crude anthranilic acid was 42% and that of crude aminoamide was 60%. In a third run, in which the solution of nitro compound was added slowly, a 5.7% yield of pure anthranilic acid could be obtained; in this run there was a large basic fraction, the infrared spectrum of which indicated that it was largely a mixture of 2,1-benzisoxazolone and *o*-hydroxylamino-*N*,*N*-dimethylbenzamide. The detection of the former by acetylation of the basic fraction of a similar run is described below.

B. Isolation of *N*-Acetyl-2,1-benzisoxazolone.—A solution of 1.00 g (5.15 mmol) of the nitroamide in 22 ml of water and 3 ml of methanol was added at a rate of 5 drops/sec to a slurry of 0.04 g of 10% Pd/C in an ice-cooled solution of sodium borohydride (1.0 g, 27 mmol) in 15 ml of water. After the addition, the solution was stirred for 5 min, the catalyst was removed by filtration, and the basic filtrate was acidified with 18% hydrochloric acid and extracted with methylene chloride. Acetic anhydride (1.00 g, 9.8 mmol) was added to the aqueous solution followed by enough sodium acetate to neutralize the solution. The mixture was stirred at room temperature for 1 hr and the white precipitate was removed by filtration and dried in a vacuum desiccator. This material (100 mg, 12% yield) gave a single peak when chromatographed from 140° at a rate of 8°/min on a 10-ft column of 3% OV-17 on Gas-Chrom Q. Its infrared and mass spectra matched those of an authentic sample of *N*-acetyl-2,1-benzisoxazolone.

C. Isolation of *o*-Hydroxylamino-*N*,*N*-dimethylbenzamide (4).—The procedure in **B** was used except that a different batch of Pd/C was employed. After removal of the catalyst, the basic yellow solution was extracted with methylene chloride (five 5-ml portions) and the extract was dried ($MgSO_4$) and concentrated to yield 372 mg (crude yield 40%) of light yellow oil, the ir spectrum of which matched that of a sample of **4** prepared by reduction of the nitro compound with zinc and ammonium chloride. Addition of hexane to a chloroform solution of the oil resulted in the precipitation of 218 mg (23%) of white solid which discolored in air. It also had the correct ir spectrum. Another similar run yielded 50% of **4** as a crude, light yellow solid.

***o*-Hydroxylamino-*N*,*N*-dimethylbenzamide (4).**—Zinc dust (795 mg, 12.1 mmol) was added in small portions over a 5-min period to a vigorously stirred mixture of 6 ml of water and 4 ml of ether containing 388 mg (2.00 mmol) of *o*-nitro-*N*,*N*-dimethylbenzamide and 300 mg (5.60 mmol) of ammonium chloride. The temperature was maintained below 23° by intermittent cooling. The mixture was stirred for an additional 10 min and the zinc oxide and unreacted zinc were removed by filtration. The residue was washed with ether, the water and ether layers were separated, and the aqueous layer was extracted with ether. The combined ether extract was dried ($MgSO_4$) and evaporated to yield 218 mg (crude yield 60%) of yellowish-white solid, the spectroscopic properties of which indicate that it is predominantly *o*-hydroxylamino-*N*,*N*-dimethylbenzamide. Upon glpc, the material exhibited one small peak at the same retention time as the amine; apparently the hydroxylamine is itself not capable of being chromatographed but is contaminated with some of the corresponding amine. The mass spectrum at 15 eV is given in the discussion. That at 70 eV (direct probe) is very similar to that of *o*-amino-*N*,*N*-dimethylbenzamide (**3**) and the two are now compared; the first number in parenthesis is the per cent of the base peak in the spectrum of **4** and the second is the corresponding figure for the spectrum of pure amine (**3**): *m/e* 181 (0.2, 0), 180 (1.3, 0), 164 (36, 36), 163 (7, 12), 137 (2.3, 0), 136 (2, 0.07), 135 (21, 0.4), 121 (8, 12), 120 (100, 100), 119 (12, 12), 92 (46, 51), 91 (9, 5) 65 (32, 33), 64 (12, 5), 52 (12, 3), 51 (5, 1), 50 (5, 1), 46 (5, 1), 44 (21, 23), 41 (5, 2), 39 (13, 7). The following ir spectrum (chloroform solution) of **4** is similar to but distinctly different from that of **3**: 3584 (w, sharp), 3322 (broad), 3003 (s), 2933 (m), 1621 (s), 1504 (m), 1481 (m), 1453 (m, sharp), 1397 (s, sharp), 1350 (w), 1190 (w), 1119 (w), 1071 (m), 1042 cm^{-1} (sh). Nmr: τ 2.6–3.8 (m, 6 H, aromatic and NHOH) and 7.0 (three sharp peaks, separated by about 1 Hz, 6 H, methyls). There is no discernible absorption at about τ 5.75 where the corresponding amine exhibits a peak for amine protons.

Conversion of *o*-Hydroxylamino-*N*-*N*-dimethylbenzamide (4) to 2,1-Benzisoxazolone (5).—A sample of **4** (148.7 mg, 0.825 mmol) was added in one portion to 8.3 ml (0.83 mmol) of *ca.* 0.1 *N* sodium hydroxide solution which was maintained at 23° in a water bath; it dissolved within 1.3 min to give a golden yellow solution. The solution was stirred for an additional 3.2 min, cooled to 10° during 2 min, and made slightly acidic with 18% hydrochloric acid. The white precipitate was immediately removed by filtration and placed under vacuum in a desiccator (dry weight 48.1 mg, mp 104–109° dec) and the filtrate was rapidly extracted with ether (two 5-ml portions). Evaporation of the dried ($MgSO_4$) ether extract yielded 21.7 mg of tan crystals, recrystallization of which from ethanol–water (with noticeable handling losses) gave 8.6 mg of white crystals, mp 106–111° dec (lit.[10] mp for 2,1-benzisoxazolone 112° dec). The combined yield of this fairly pure material is thus 51%: ir ($CHCl_3$) 3311 (w), 3040 (w), 1773 (s), 1751 (s), 1610 (w), 1513 (w), 1473 (w), 1330 (w), 1297 (w), 1149 (w), 1111 (w), 1040 cm^{-1} (m); nmr ($CDCl_3$) τ 2.0–2.9 (m, 4 H, aromatic) and 1.17 (s, broad, 1H, NH); mass spectrum, direct probe, 137 (3.8), 136 (8), 135 (100), 119 (5), 104 (5), 91 (23), 79 (15), 77 (9), 76 (14), 65 (8), 64 (25), 63 (16), 62 (6), 61 (38), 52 (13), 51 (10), 50 (13), 39 (7), 38 (10), 37 (6).

A rapidly prepared solution of the hydroxylamine **4** in D_2O was scanned from 1800 to 1300 cm^{-1} six times over a period of 30 min; the spectra were the same and quite consistent with uncleaved amide: 1616 (vs, sharp), 1540–1440 (broad envelope containing several peaks), 1412 cm^{-1} (w). An entirely different ir spectrum was exhibited by the same material dissolved in 0.1 *N* NaOD in D_2O and it did not change with time; the strongest peaks are considerably broader and less well defined than those in the nonbasic case and they are found at 1625, 1612, 1597, and 1581 cm^{-1}; in addition there is a broad envelope from 1600 to 1350 cm^{-1} which contains peaks at 1570–1550, 1484, 1460, 1412, and 1381 cm^{-1}. The spectrum of 2,1-benzisoxazolone in the

(16) T. Cohen, R. M. Moran, and G. Sowinski, *J. Org. Chem.*, **26**, 1 (1961).

(17) Sadtler Standard Spectra, No. 2703, Sadtler Research Laboratories, Inc., Philadelphia, Pa.

(18) J. M. Sugihara and S. R. Newman, *J. Org. Chem.*, **21**, 1445 (1956).

(19) A. F. Isbell and H. R. Henze, *J. Amer. Chem. Soc.*, **66**, 2096 (1944).

same solution is very similar, but cleaner (of course, the absorptions for dimethylamine would be absent from the latter solution): 1631, 1598, 1551, 1486, 1455, 1380, and 1339 cm^{-1}. It seems clear that the latter two solutions contain sodium *o*-hydroxylaminobenzoate.

Alkaline Hydrolysis of *N*,*N*-Dimethylbenzamide.—A solution of 152.5 mg (1.022 mmol) of *N*,*N*-dimethylbenzamide dissolved in 1 equiv of the same solution of NaOH used for the cleavage of **4** was left at room temperature (*ca.* 23°) for 432 hr and then extracted with CH_2Cl_2 (eight 5-ml portions). The dried extract yielded 85.5 mg (56%) of residue, the infrared spectrum of which was identical with that of the starting amide.

***N*-Acetyl-2,1-benzisoxazolone.**—Acetyl chloride (5 drops) was added to a solution of 18 mg (0.13 mmol) of 2,1-benzisoxazolone in 10 drops of dioxane. The solution was gently warmed over a flame and then cooled. Water was added (crystals formed) and the mixture was extracted with ether. The residue from evaporation of the ether was precipitated from an alcoholic solution with water to give 9.4 mg (44%) of white crystals: mp 116–118° (lit.[10] mp 117.5–118.5°); ir ($CHCl_3$) 3040 (w), 1786 (s), 1704 (s), 1613 (w), 1477 (m), 1464 (s), 1379 (s),1350 (m), 1332 (s), 1299 (w), 1153 (w), 1112 (w), 1074 (w), 1042 (w), 980 cm^{-1} (m, broad); mass spectrum, direct probe (since the peak at *m/e* 43, the acetyl cation, was extremely intense and off-scale, the values in parentheses are percentages of the 135 peak) 178 (6.3), 177 (53.1), 136 (21), 135 (100), 104 (28), 91 (32), 79 (95), 77 (14), 76 (65), 75 (16), 74 (17), 64 (49), 63 (37), 62 (16), 52 (52), 51 (24), 50 (73), 44 (97), 43 (off scale).

Reduction of 2,1-Benzisoxazolone.—2,1-Benzisoxazolone (65.8 mg, 0.488 mmol) was added in small portions to a slurry of 4.1 mg of 10% Pd/C in a solution of 97 mg (2.6 mmol) of sodium borohydride in 3.2 ml of water and 0.28 ml of methanol in an ice bath. After the solution had been stirred for 15 min, the catalyst was removed by filtration, the basic solution was extracted with chloroform (five 1-ml portions), acidified to *ca.* pH 3 with 18% hydrochloric acid, and then extracted again. Evaporation of the solvent from the combined, dried ($MgSO_4$) extract left 50.0 mg (76%) of off-white crystals, mp 143–147°, the infrared spectrum of which matched that reported[17] for anthranilic acid. Sublimation at 100° (0.5 Torr) yielded material of mp 146.5–147.0 (lit.[18] mp 144.9–145.4°; lit.[19] mp 144–145°).

Registry No.—**1**, 2018-71-5; **2**, 118-92-3; **3**, 6526-66-5; **4**, 33047-10-8; **5**, 31499-90-8; **5** *N*-acetyl derivative, 33047-12-0.

Acknowledgments.—We wish to thank the National Institutes of Health for providing the LKB 9000 combined gas chromatograph–mass spectrometer (Grant RR 00273), and Mr. John Naworal for recording the mass spectra.

The Reaction Rates of Alkyl Dihydroxybenzoates in a Nucleophilic Fused Salt[1]

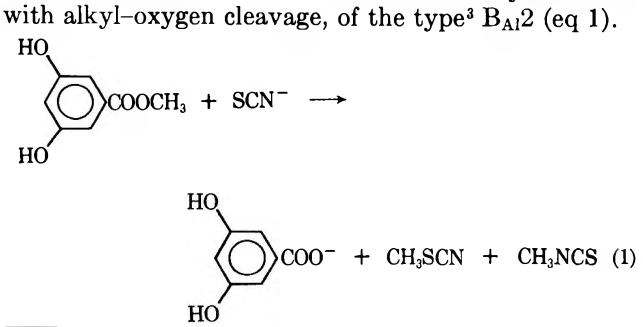
ELIZABETH W. THOMAS AND THOMAS I. CROWELL*

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901

Received September 29, 1971

Methyl and ethyl 3,5-dihydroxybenzoates, in molten potassium–sodium thiocyanate eutectic, react by a pseudo-first-order $B_{Al}2$ displacement on the alkyl group to form alkyl thiocyanates and isothiocyanates. The methyl ester, which reacts 49 times as fast as the ethyl at 150°, shows an activation energy of 26 kcal/mol. The product compositions are 96% MeSCN, 4% MeNCS and 54% EtSCN, 46% EtNCS. Methyl 2,4-dihydroxybenzoate reacts similarly except that the 2,4-dihydroxybenzoate ion immediately decarboxylates, evolving 0.5 mol of carbon dioxide per mole of ester and following the rate equation $\ln a/(a - 2x) = 2kt$. Neither the *o*-hydroxyl group nor the decarboxylation accelerates the displacement, as this ester reacts slightly more slowly than the 3,5-dihydroxy compound. The isotope effect is small ($k_{OH}/k_{OD} = 0.97$).

Noting the high nucleophilicity and low melting point of potassium thiocyanate, we initiated a study of nucleophilic displacement reactions in this molten salt, an ionic, aprotic medium which represents the upper concentration limit of a solution. Suitable substrates, undergoing simple displacement reactions with moderate rates at elevated temperatures and containing hydroxyl groups to confer solubility by hydrogen bonding with the solvent[2] are difficult to devise. Benzoic esters with two phenolic hydroxyl groups, however, have these properties. For example, methyl 3,5-dihydroxybenzoate reacts with thiocyanate ion with alkyl–oxygen cleavage, of the type[3] $B_{Al}2$ (eq 1).



Nucleophilic displacements at the saturated carbon atom in ester hydrolysis or alcoholysis can be observed only under the following conditions: (1) special structural features favor alkyl–oxygen cleavage as in the reaction of β-lactones with water[4] or methanol;[5] (2) the competing attack at the carbonyl group ($B_{Ac}2$) is hindered as in methyl 2,4,6-tri-*tert*-butyl benzoate[6] or is designed to be a symmetrical transesterification;[7] (3) the nucleophile is unreactive toward carbonyl groups. The very few examples of this last case include the cleavage of simple methyl esters by trimethylamine[8] and by lithium halides in pyridine[9a] or 2,4,5-collidine.[9b] Thiocyanate ion also belongs to this small group of nucleophiles preferentially attacking the carbon atom of the alkyl group in esters, effecting a slow displacement of the carboxylate ion. Packham and

(1) Preliminary communication: E. M. Wadsworth and T. I. Crowell, *Tetrahedron Lett.*, 1085 (1970). Research supported by the U. S. Army Research Office (Durham).

(2) T. I. Crowell and P. Hillery, *J. Org. Chem.*, **30**, 1339 (1965).

(3) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed, Cornell University Press, Ithaca, N. Y., 1969, p 1142.

(4) W. A. Cowdrey, E. D. Hughes, C. K. Ingold, S. Masterman, and A. D. Scott, *J. Chem. Soc.*, 1264 (1937); A. R. Olsen and R. J. Miller, *J. Amer. Chem. Soc.*, **60**, 2687 (1938).

(5) T. L. Gresham, *et al.*, *ibid.*, **70**, 1004 (1948); P. D. Bartlett and P. N. Rylander, *ibid.*, **73**, 4273 (1951).

(6) L. R. C. Barclay, N. D. Hall, and G. A. Cooke, *Can. J. Chem.*, **40**, 1981 (1962).

(7) J. F. Bunnett, M. M. Robison, and F. C. Pennington, *J. Amer. Chem. Soc.*, **72**, 2378 (1950); R. A. Sneen and A. R. Rosenberg, *J. Org. Chem.*, **26**, 2099 (1961).

(8) R. Willstätter and W. Kahn, *Ber.*, **35**, 2757 (1902); L. P. Hammett and H. L. Pfluger, *J. Amer. Chem. Soc.*, **55**, 4079 (1933).

(9) (a) E. Taschner and B. Liberek, *Rocz. Chem.*, **30**, 323 (1956); (b) F. Elsinger, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, **43**, 113 (1960).

Rackley[10] obtained methyl isothiocyanate in 25% yield from the heterogeneous system, methyl acetate–fused NaSCN–KSCN at 300°. This paper describes homogeneous kinetic studies of eq 1 and related reactions in fused KSCN–NaSCN eutectic at 140–160°.

Experimental Section

A Colura Ultra-Thermostat circulating bath, filled with Dow-Corning 210 silicone oil, maintained temperature ±0.2°.

Solvent.—The sodium thiocyanate–potassium thiocyanate (25–75 mol %) binary eutectic[11] melting at 133° was prepared from the reagent grade salts (minimum assay 99.3 and 99.7%) which were dried at 110° for 15 hr, then combined, melted in a beaker, and mixed. The melt was poured into an open dish, allowed to cool in a desiccator, pulverized in a drybox, and dried under vacuum at room temperature. For each kinetic run, 10 g of the molten salt was dried at 10^{-3} Torr at the temperature of the run for at least 24 hr. Karl Fisher titration showed the water content of the eutectic to be 0.2% after this treatment. When deuterated esters were to be used as substrates, the eutectic was wet with D_2O before the drying procedure.

Methyl 2,4-Dihydroxybenzoate.—To 35 g (0.23 mol) of 2,4-dihydroxybenzoic acid was added 40 g (1.25 mol) of methanol and 4 g of concentrated sulfuric acid. After 30 hr at reflux, excess methanol and water were distilled off and the residual liquid (about 25 ml) was neutralized to pH 7 with sodium carbonate solution. The precipitated ester was extracted with ether. The tan solid obtained on evaporation of the extracts was recrystallized from benzene as white crystals (21.4 g, 56%): mp 116–117° (lit.[12] 117–118°); homogeneous by tlc; ir (KBr) 3360 (OH stretch), 1640 (carbonyl), 1275 (C–O stretch), 1625 (aromatic ring stretch), 1370 cm^{-1} (methyl C–H bend); nmr (acetone-d_6) methyl singlet 3.46 ppm from TMS.

The other alkyl dihydroxybenzoates, prepared by similar procedures but with 3–5-hr reflux periods, were ethyl 2,4-dihydroxybenzoate, 41% yield, mp 69–70.5° (lit.[13] 69–70°); methyl 3,5-dihydroxybenzoate, 70%, mp 167–168° (lit.[14] 163–165°); and ethyl 3,5-dihydroxybenzoate, 32%, mp 127–128° (lit.[15] 128.5). Isopropyl 3,5-dihydroxybenzoate was vacuum distilled. A fraction obtained at 185–190° (0.3 Torr), which contained both starting acid and product (tlc), was dissolved in benzene–acetone (95:5%), chromatographed on a silica gel (0.2–0.5 mm, 20 g) column, and eluted with benzene–acetone (95:5 then 90:10%). The ester containing fractions were combined and evaporated under reduced pressure to a viscous oil which could not be solidified: yield 0.77 g (6%); ir (DMSO-d_6) 3450–3550 (OH stretch), 1720 (C=O), 1610 (aromatic ring), 1245 cm^{-1} (CO); nmr (DMSO-d_6) methyl doublet δ 1.30, methine multiplet δ 5.13.

Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.17. Found: C, 61.16; H, 6.28.

Sodium 2,4-dihydroxybenzoate was prepared by neutralizing the acid with 0.2 *M* sodium hydroxide and evaporating to dryness under vacuum. The monosodium salt of methyl 2,4-dihydroxybenzoate (presumably sodium 3-hydroxy-4-carbomethoxyphenoxide) was obtained similarly from a methanol solution of the ester after adding 1 equiv of sodium methoxide. Methyl 2,4-dideuteroxybenzoate was prepared by heating 0.7 g of methyl 2,4-dihydroxybenzoate in 12.5 ml of D_2O (99.8%) until it dissolved. The solution was cooled and filtered and the process was repeated. The ir spectrum of the vacuum-dried solid showed equally strong OD (KBr, 2440 cm^{-1}; reported[16] for phenol in D_2O, 2432 cm^{-1}) and OH (3370 cm^{-1}) peaks. Taking into account the lower absorption intensity of OD, about 75% exchange was indicated. This product was again heated with D_2O. After the solvent was evaporated under vacuum, the ir spectrum of the ester showed about 87% exchange in the hydroxyl groups. This was confirmed by the nmr spectrum; the aromatic A_2B pattern moreover was similar to that of the undeuterated ester.

Methyl and ethyl thiocyanate[17] and isothiocyanate[18] were prepared by standard methods.

Procedure.—The Pyrex reaction vessel, 22 × 150 mm, containing about 10 g of the thiocyanate eutectic, was immersed in the oil bath and evacuated for the final stage of the drying procedure. It was then opened and 1.5–2.5 mmol of ester was introduced through a funnel and stirred with a heated rod until dissolved (5–15 min).

The reactions of the 3,5-dihydroxybenzoate esters were followed by weighing the mixture of alkyl thiocyanate and isothiocyanate produced. After introduction of the ester, the system was closed and evacuated to a pressure of 20 Torr. The vapor of the products passed through glass tubing (maintained at about 100° by a heating coil to prevent condensation) into a Dry Ice trap. After the desired time interval, a stopcock next to the trap was closed to isolate it temporarily from the reaction and a clean trap was substituted for the first one. The collected product (about 100 mg) was redistilled on the vacuum line, the vapors passing through calcium chloride to remove traces of water, and finally weighed. This procedure, tested on samples of methyl thiocyanate mixed with much more water (50%) than was produced in the kinetic runs, gave results only 2% high.

Methyl 2,4-dihydroxybenzoate, on the other hand, undergoes decarboxylation as displacement by thiocyanate takes place, and is conveniently followed by measuring the volume of carbon dioxide evolved. A cold finger, containing circulated refrigerant at −10°, was located in the reaction vessel to minimize the partial pressure of methyl thiocyanate before it was completely removed by a Dry Ice trap between the reaction vessel and the rest of the vacuum system. After the ester was dissolved in the molten salt, the system was closed and partially evacuated. (Complete evacuation caused bumping and undue sublimation of the ester.) From the volume of the whole system and the pressure measured on a mercury manometer, the quantity of carbon dioxide formed in the reaction could be calculated at any time.

Product Analysis.—Alkyl thiocyanates and isothiocyanates were identified by their ir spectra (KBr) and by gas chromatography. A column of 20% Carbowax 600 on Anakrom ABS 50/60 support (0.25 × 120 in.) was used. The flame ionization detector response was found to be identical for methyl thiocyanate and methyl isothiocyanate, using 1,2-dimethoxyethane as reference compound in the Micro-Tek gas chromatograph. The relative amounts of isomers produced could therefore be calculated from peak areas without further correction. The volatile products from ethyl 3,5-dihydroxybenzoate gave two peaks showing similar retention times to the methyl products and were assumed without calibration to correspond to ethyl thio- and isothiocyanate. The higher proportion of ethyl isothiocyanate (50% as compared to 5% for the methyl esters) was confirmed by the ir spectrum of the mixture.

Methyl 2,4-dihydroxybenzoate was stable for 3 days at 150°. Dissolved in the thiocyanate melt at 150°, this ester slowly evolved carbon dioxide (identified by mass spectrum), methyl thio- and isothiocyanate (identified as above) and, as a sublimate just above the bath oil level, resorcinol (ir in KBr). Sodium 2,4-dihydroxybenzoate was decarboxylated very rapidly in the melt. Methyl and ethyl 3,5-dihydroxybenzoates, however, showed no evolution of noncondensable (−78°) gas, the pressure remaining constant within 7 mm (methyl) and 1 mm (ethyl) as alkyl thiocyanates formed and passed into the Dry Ice trap. This important observation demonstrated the absence of carbon dioxide, methane, ethane, and ethylene and illustrated the convenience of a vacuum system for handling nonvolatile fused salts.

Results

In the reaction of methyl 3,5-dihydroxybenzoate, 90% of the theoretical weight of product was obtained composed of 96% methyl thiocyanate and 4% methyl isothiocyanate. The product from the ethyl ester was 54% ethyl thiocyanate and 46% isothiocyanate.

(10) D. L. Packham and F. A. Rackley, *Chem. Ind. (London)*, 899 (1966).
(11) J. B. Wrzenewsky, *Z. Anorg. Chem.*, **74**, 99 (1912).
(12) A. Baeyer, *Justus Liebigs Ann. Chem.*, **372**, 85 (1910).
(13) R. J. Kaufmann and R. Adams, *J. Amer. Chem. Soc.*, **45**, 1751 (1923).
(14) J. Herzig and S. Epstein, *Monatsh. Chem.*, **29**, 668 (1908).
(15) C. M. Suter and A. W. Weston, *J. Amer. Chem. Soc.*, **61**, 531 (1939).
(16) C. Haas and D. F. Hornig, *J. Chem. Phys.*, **32**, 1767 (1960).
(17) R. L. Shriner, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 366.
(18) E. C. Horning, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 599.

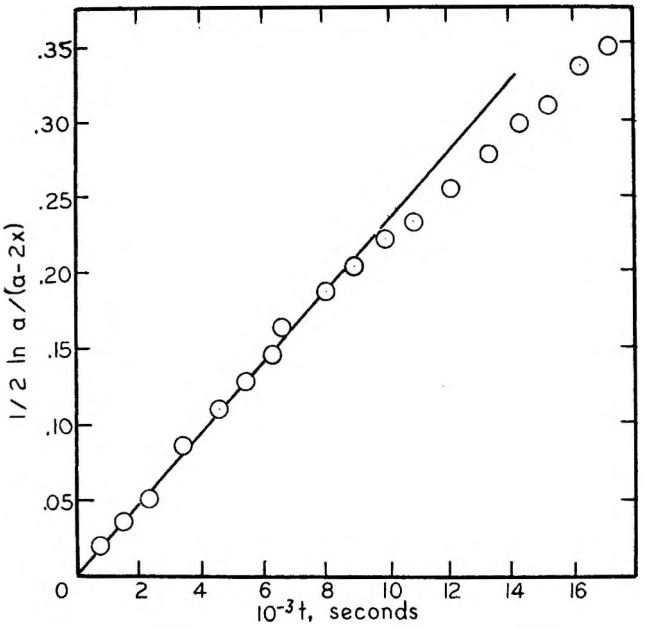


Figure 1.—Kinetic plot for solvolysis of methyl 2,4-dihydroxybenzoate in molten K^+, Na^+/SCN^- at 140.5°.

The rate constants, shown in Table I, were obtained from plots of ln $a/(a - x)$ (linear to 75% reaction)

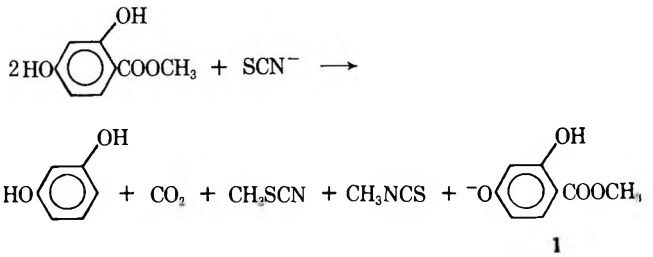
TABLE I

Ester	Temp, °C	No. of runs	10^4k,[a] sec^{-1}	Mean % devn
Me 3,5	140.5	2	1.53	0.5
	150.4	3	3.20	4.7
	160.2	2	6.32	1.3
Et 3,5	150.5	3	0.065	11.7
Me 2,4	140.5	3	0.232	1.3
	150.5	2	0.467[b]	1.3
	160.6	2	0.794	1.1
Me 2,4[c]	150.7	2	0.485	1.0

[a] Mean value of k for given number of runs. [b] This rate constant for thiocyanate displacement is one-half the value given in ref 1 for total ester consumption. [c] Methyl 2,4-dideuterioxybenzoate.

where a is the amount of ester, in millimoles, dissolved in 10 g of melt, and x the millimoles of product at time t. The three-point Arrhenius plot for the methyl ester is linear, the calculated activation energy E_a being 26 kcal/mol and the entropy of activation −16 cal/deg. Isopropyl 3,5-dihydroxybenzoate is insoluble in the melt.

Methyl 2,4-dihydroxybenzoate yielded methyl thio- and isothiocyanate in the same ratio (95.3:4.7) as the 3,5 ester. Carbon dioxide was evolved as the reaction proceeded, apparently approaching 0.5 mol per mole of reactant. The actual yield was 0.46 mol; volatilization of ester from the hot solution probably accounts for the difference. If the reaction proceeds as shown in eq 2 and all the products on the right side except the anion **1** are removed by volatilization, including resorcinol, the failure of half of the substrate to react is explained if **1** is assumed unreactive. The sodium salt of methyl 2,4-dihydroxybenzoate in fact neither dissolved nor reacted in the melt unless it was heated to 198°. (Sodium 2,4-dihydroxybenzoate, however, dissolved and decarboxylated rapidly at 150°.) It is, therefore, proper to plot (1/2) ln $a/(a - 2x)$ *vs.* time,



(2)

since $2x$ is the number of moles of reactant removed when x mol undergo the displacement reaction. A typical plot for reaction of the ester at 140°, followed by carbon dioxide evolution, is shown in Figure 1. The slope, k, is 2.36×10^{-5} sec^{-1} up to 25% reaction. Note that the initial slope of a plot of ln $a/(a - x)$ *vs.* t would have this same value, which simply measures the rate of carbon dioxide evolution from the ester at its initial concentration. Equation 2 is suggested as the reason for deviation from first-order kinetics as the reaction proceeds, but the evaluation of k should not markedly depend on whether or not the interpretation is correct.

All the results are summarized in Table I, including duplicate runs on ester deuterated in the hydroxyl groups. One run at 150.5°, followed gravimetrically, as described for the 3,5 esters, gave a rate constant of 4.2×10^{-5} sec^{-1} before tapering off as it approached 50% reaction.

The Arrhenius plot for methyl 2,4-dihydroxybenzoate is not quite linear: the activation energy is 25 (140–150°), 19 (150–160°), or 22 kcal/mol overall. The corresponding entropy of activation is −29 cal/deg mol.

Ethyl 2,4-dihydroxybenzoate is insouble in the thiocyanate melt.

Discussion

The reaction of the alkyl dihydroxybenzoates appears to be a direct displacement on the alkyl group. The ratio k_{Me}/k_{Et} is 49 for the 3,5 esters at 150–155°, which is in the normal range for SN2 reactions.[19] The absence of ethylene in the products from ethyl 3,5-dihydroxybenzoate shows that ester pyrolysis is not occurring in this medium (the esters alone are stable at the temperatures used) and, together with the absence of methane from the methyl esters, is evidence against the presence of free radicals.

The 2,4-dihydroxy esters might be expected to react more rapidly than those with both the hydroxyl groups in meta positions. If decarboxylation took place simultaneously with displacement, a driving force characteristic of many fragmentation reactions[20] would increase the displacement rate. Furthermore, the ortho hydroxyl group could, by hydrogen bonding or proton transfer, increase the positive charge on the carbonyl carbon atom and consequently the affinity of the adjacent methyl group for the nucleophilic anion. Catalysis of ester hydrolysis by neighboring hydroxyl groups (the Henbest–Kupchan effect[21]) is well known,

(19) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., p 73.

(20) E. M. Kosower, "An Introduction to Physical Organic Chemistry," Wiley, New York, N. Y., pp 94–98.

(21) S. M. Kupchan and W. S. Johnson, *J. Amer. Chem. Soc.*, **78**, 3864 (1956), and subsequent papers; H. B. Henbest and B. J. Lovell, *J. Chem. Soc.*, 1965 (1957).

as is catalysis by the ortho hydroxyl group in the hydrolysis of salicylate esters. Bender has, however, presented convincing evidence that the latter type of catalysis is not general for addition of all nucleophiles to the carbonyl group, only the water molecule.[22]

The fact that methyl 3,5-dihydroxybenzoate undergoes thiocyanate displacement seven times as fast as methyl 2,4-dihydroxybenzoate shows that the factors discussed above are in fact not the most important ones affecting the rate at 140–160° and suggests that the displacement is uncatalyzed and occurs prior to, not simultaneously with, decarboxylation. The difference in the admittedly uncertain activation energies of these two compounds is not large enough to change the rate ratio drastically at other attainable temperatures, the isokinetic temperature falling near room temperature. The isotope effect (k_{OH}/k_{OD} = 0.97 at 150.7°) is also nearly negligible.

The fraction of isothiocyanate formed by the reaction of the ambident nucleophile with the methyl esters, 4–5%, is comparable with similar displacements.[23] The higher proportion (46%) from the ethyl ester is not due to thermal isomerization of ethyl thiocyanate; we found the rate constant for formation of EtNCS from EtSCN in contact with molten eutectic to be only 3×10^{-6} sec^{-1} at 150° (half-life 3 days) and 6×10^{-6} at 170°. The published value[24] for methyl thiocyanate is 8.5×10^{-7} sec^{-1} at 136°. The ethyl thiocyanate, which is collected in the cold trap within a few minutes of its formation, cannot isomerize appreciably in this time. The large amount of iso product must then be formed directly. The evidence does not enable us to determine whether the cause is increased SN1 or "pull–push" character of the displacement[25] or a structural effect on solvation in the neighborhood of the reaction center.

Registry No.—Sodium thiocyanate, 540-72-7; potassium thiocyanate, 333-20-0; methyl 2,4-dihydroxybenzoate, 2150-47-2; methyl 3,5-dihydroxybenzoate, 2150-44-9; ethyl 3,5-dihydroxybenzoate, 4142-98-7; isopropyl 3,5-dihydroxybenzoate, 33046-40-1.

(22) M. L. Bender, F. J. Kézdy, and B. Zerner, *J. Amer. Chem. Soc.*, **85**, 3017 (1963).
(23) A. Fava, A. Iliceto, and S. Bresadola, *ibid.*, **87**, 4791 (1965).
(24) C. N. R. Rao and S. N. Balasubrahmanyam, *Chem. Ind. (London)*, 625 (1960).
(25) N. Kornblum, *et al.*, *J. Amer. Chem. Soc.*, **77**, 6269 (1955).

Fluoronitroaliphatics. VI.[1] Preparation of *N*-(2,2,2-Fluorodinitroethyl)amides

HORST G. ADOLPH

Advanced Chemistry Division, U. S. Naval Ordnance Laboratory, White Oak, Silver Spring, Maryland 20910

Received August 6, 1971

The reaction of 2,2,2-fluorodinitroethylamine with acid chlorides was used to prepare a variety of fluorodinitroethyl-substituted amides, urethanes, and ureas. Urethanes were also prepared by the addition of alcohols to 2,2,2-fluorodinitroethyl isocyanate. The use of the *tert*-butyl group as a protecting group in the synthesis of *N*-(2,2,2-fluorodinitroethyl)amides is described.

N-(2,2,2-Trinitroethyl)amides, urethanes, and ureas, some of which are of interest as explosive ingredients, are generally prepared by amidoalkylation of trinitromethane (eq 5, R = NO_2). The reaction has been carried out by reacting either trinitromethane with a hydroxymethyl amide, or 2,2,2-trinitroethanol with an amide *via* generation of the methylol amide and trinitromethane *in situ*.[2,3,4]

There are apparently no reports in the literature regarding the analogous amidoalkylation of 1,1-dinitroalkanes (R = alkyl). When we attempted to employ this reaction to prepare *N*-(2,2,2-fluorodinitroethyl)-amides (R = F) it failed completely. 2,2,2-Fluorodinitroethanol was unreactive toward a variety of amides as well as urethane and urea, and fluorodinitromethane acted as a demethylolating agent upon hydroxymethyl amides, urethane, and urea. This behavior can be rationalized by examining the equilibria involved in the desired reaction (eq 5).

$$RC(NO_2)_2CH_2OH \rightleftharpoons RC(NO_2)_2^- + CH_2O + H^+ \quad (1)$$

$$RC(NO_2)_2H \rightleftharpoons RC(NO_2)_2^- + H^+ \quad (2)$$

$$R'CONH_2 + CH_2O \rightleftharpoons R'CONHCH_2OH \quad (3)$$

$$R'CONHCH_2OH + H^+ \rightleftharpoons R'CONHCH_2^+ + H_2O \quad (4)$$

$$R'CONHCH_2^+ + R{-}C(NO_2)_2^- \longrightarrow R'CONHCH_2C(NO_2)_2R \quad (5)$$

It follows from the anomalously low acidity of fluorodinitromethane[5,6] that when R = F, in complete contrast to the case where R = NO_2, equilibria 1 and 2 are shifted completely to the left under pH conditions where equilibrium 4 can provide a supply of carbonium ions sufficient for the reaction to proceed at an observable rate.

We recently reported the synthesis of 2,2,2-fluorodinitroethylamine, only the second primary 2,2-dinitroethylamine to be described in the literature, and found it to be an isolable and reasonably stable species.[6] In view of the above difficulties we examined its utility for the preparation of *N*-(2,2,2-fluorodinitroethyl)amides, urethanes, and ureas by reaction with a variety of acid chlorides.

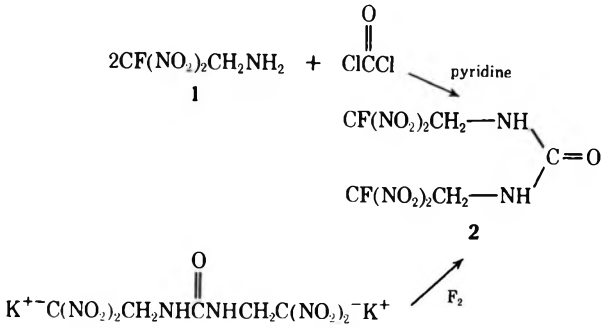
The reaction in methylene chloride solution of acetyl chloride with a 1:1 mixture of 2,2,2-fluorodinitroethylamine (1) and pyridine was straightforward and gave *N*-(2,2,2-fluorodinitroethyl)acetamide in >95% yield. In the reaction of 1 with this and other acid

(1) Part V: H. G. Adolph, *J. Org. Chem.*, **35**, 3188 (1970).
(2) H. Feuer and U. E. Lynch-Hart, *ibid.*, **26**, 391, 587 (1961).
(3) P. Noble, Jr., F. G. Borgardt, and W. L. Reed, *Chem. Rev.*, **61**, 19 (1964).
(4) A. Wetterholm, *Sv. Kem. Tidskr.*, **76**, 628 (1964).
(5) H. G. Adolph and M. J. Kamlet, *J. Amer. Chem. Soc.*, **88**, 4761 (1966).
(6) H. G. Adolph and M. J. Kamlet, *J. Org. Chem.*, **34**, 47 (1969).

chlorides the order of addition of the reactants is of some importance; because of the sensitivity of **1** to acids in the presence of water[6] it is desirable to keep the reaction medium basic until all **1** has reacted, *i.e.*, to add the acid chloride slowly to the mixture of **1** and base. The reaction of **1** with 4,4-dinitroheptanedioyl chloride was carried out in a similar manner. The product, *N*,*N*′-bis(2,2,2-fluorodinitroethyl)-4,4-dinitroheptanedioic amide, was obtained in 57% yield. **1** and oxalyl chloride in a ratio of 2:1 in the presence of 2 equiv of pyridine gave *N*,*N*′-bis(2,2,2-fluorodinitroethyl)oxamide (**10**) in excellent yield. Isolation of the intermediate oxamic acid chloride was not attempted.

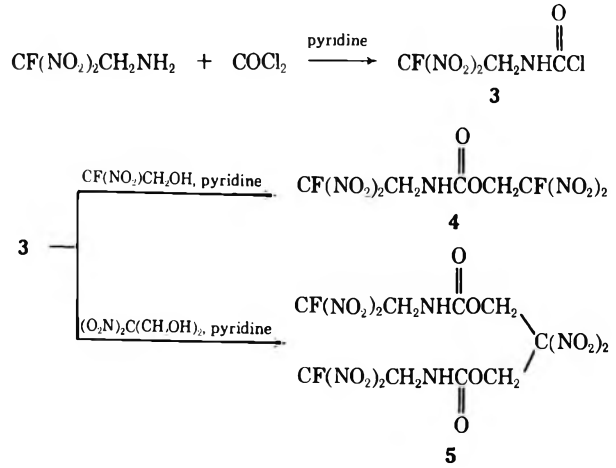
Depending on the ratio of reactants and the nature of the base employed as hydrogen chloride scavenger, the main products of the reaction of **1** with phosgene were *N*,*N*′-bis(2,2,2-fluorodinitroethyl)urea (**2**), *N*-(2,2,-2-fluorodinitroethyl)carbamyl chloride (**3**), and 2,2,2-fluorodinitroethyl isocyanate.

In a ratio of 2:1:2 in benzene or methylene chloride solution, **1**, phosgene, and pyridine reacted readily to give the urea **2**, which had been prepared previously by



the aqueous fluorination of dipotassium *N*,*N*′-bis-(2,2-dinitroethyl)urea.[7]

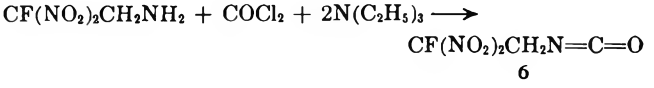
With a 1:phosgene:pyridine ratio of 1:1:1, *N*-(2 2,2-fluorodinitroethyl)carbamyl chloride (**3**), was produced. This material was not obtained pure but was characterized by conversion to the corresponding urethanes on reaction with 2,2,2-fluorodinitroethanol and 2,2-dinitropropane-1,3-diol in the presence of pyridine.



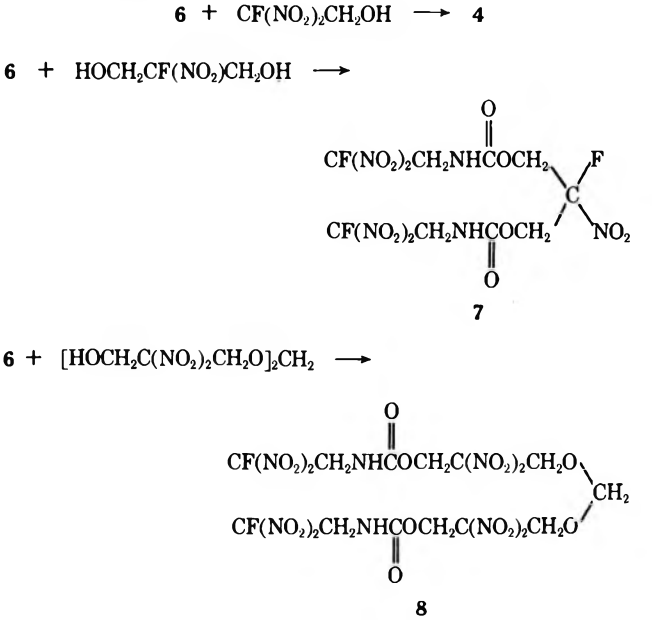
4 was also prepared by the alternate pathway of reacting **1** with 2,2,2-fluorodinitroethyl chloroformate.

(7) M. J. Kamlet and H. G. Adolph, *J. Org. Chem.*, **33**, 3073 (1968).

N-(2,2,2-Fluorodinitroethyl)carbamyl chloride (**3**) did not readily lose hydrogen chloride on further treatment with pyridine, but was converted to 2,2,2-fluorodinitroethyl isocyanate (**6**) on reaction with triethylamine. Alternatively, **1**, phosgene, and triethylamine in a ratio of 1:1:2 in benzene solution reacted at room temperature to give **6** in *ca.* 20% yield.

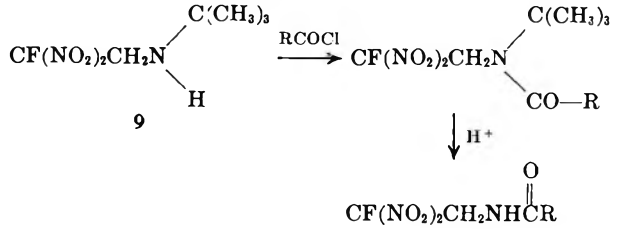


A distillable, colorless liquid, **6** was storable at room temperature for several days. On prolonged contact with triethylamine in benzene, it formed a cyclic trimer, mp *ca.* 150° dec. It underwent addition reactions when treated with a variety of nitrosubstituted alcohols in methylene chloride solution in the presence of catalytic amounts of pyridine.



It has been pointed out[6] that neat 2,2,2-fluorodinitroethylamine is unstable under ambient conditions; even in relatively dilute methylene chloride solution (<25%) appreciable decomposition takes place on extended storage at ambient temperatures. Another problem in treating **1** with acid chlorides on a larger scale is presented by its sensitivity toward acids, particularly in the presence of water, which could lead to vigorous decomposition taking place during the reaction.

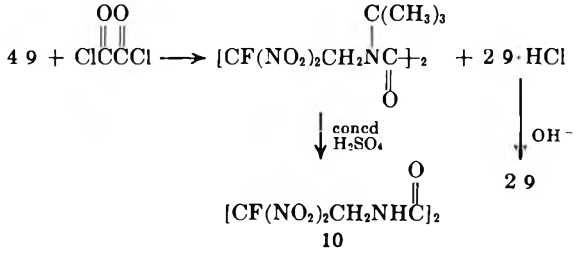
In attempts to circumvent these hazards involved in the direct synthesis of 2,2,2-(fluorodinitroethyl)-amides, an alternative route for their preparation was examined consisting in the acylation of *tert*-butyl-(2,2,2-fluorodinitroethyl)amine (**9**) with acid chlorides



or anhydrides followed by de-*tert*-butylation of the resulting amide by strong acid.

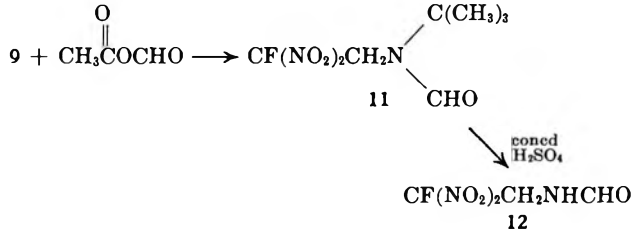
The starting material, **9**, was prepared readily and in almost quantitative yield by addition of *tert*-butylamine to an aqueous solution of 2,2,2-fluorodinitroethanol; the oil that separated was essentially pure **9**. It is stable to extended storage at room temperature and its salts with strong acids are stable in aqueous solution.

9 was found to be less reactive toward acylating agents than **1**, as might be expected because of steric hindrance by the *tert*-butyl substituent. It was also found that in the reaction with a number of acid chlorides, *e.g.*, acetyl chloride and oxalyl chloride, pyridine and trialkylamines were not satisfactory as hydrogen chloride scavengers; these bases reacted with the acid chloride without participation of **9**. The desired amide in the reaction with oxalyl chloride was obtained, however, by using an excess (which was readily recovered) of **9** to neutralize the hydrogen chloride.



Removal of the *tert*-butyl groups in the oxamide was effected by the method of Lacey,[8] stirring a suspension of the material in concentrated sulfuric acid, trifluoroacetic acid, or a mixture of concentrated sulfuric and acetic acids for several hours at room temperature.

N-(2,2,2-Fluorodinitroethyl)formamide (**12**) was also prepared *via* **9** in the manner outlined above. Treating **9** with acetic–formic anhydride gave *tert*-butyl-(2,2,2-fluorodinitroethyl)formamide (**11**) in 71% yield. The *tert*-butyl group in this compound was less readily removed than in other carboxamides. Treatment with trifluoroacetic acid at ambient or reflux temperatures, for example, was ineffective. However, prolonged action of concentrated sulfuric acid converted **11** to **12** in moderate yield.



Experimental Section

Caution. Many compounds described herein are explosive in nature and appropriate care should be taken in their handling. Precautions recommended in working with fluorodinitromethyl compounds, especially 2,2,2-fluorodinitroethanol, have been described elsewhere.[7] Neat 2,2,2-fluorodinitroethylamine (**1**) must be handled with extreme care.[6]

Melting and boiling points are uncorrected; elemental analyses were by Galbraith Laboratories, Inc., Knoxville, Tenn. Nmr spectra were obtained on a Varian HA-100 spectrometer; chemical shifts are relative to TMS as internal standard.

Preparation of Amides from 2,2,2-Fluorodinitroethylamine (1) and Acid Chlorides. General Procedure.—**1** was prepared as described in ref 6. For the initial preparation of an unknown amide distilled **1** (caution, see above) was used; for subsequent preparations the methylene chloride solution of crude **1** as obtained from the reaction of 2,2,2-fluorodinitroethanol with ammonia was found satisfactory; a 70% yield of **1** from 2,2,2-fluorodinitroethanol was assumed in the latter preparations.

The methylene chloride solution of **1** (15–20 g/100 ml) was cooled in an ice bath and pyridine, the calculated amount plus 10% excess, was added with stirring. With continued cooling, a solution of the acid chloride in methylene chloride was added and the mixture was stirred, initially in an ice bath, later at room temperature, for 2 to 15 hr depending on the reactivity of the acid chloride. The methylene chloride solution was then washed with small amounts of dilute sulfuric acid and water, dried, and freed from solvent, and the crude amide was recrystallized from the appropriate solvent.

***N*-(2,2,2-Fluorodinitroethyl)acetamide.**—The crude amide was difficult to crystallize without seed crystals. These were obtained by depositing a small quantity of crude amide on a short column of silica (G. F. Smith, Columbus, Ohio), washing with methylene chloride, eluting with 1:1 methylene chloride–ether, and freeing the main product containing fraction from solvent. The remaining oil crystallized on standing.

Using seed crystals, the crude amide was recrystallized from chloroform–hexane (2:1), mp 57–58°, yield (based on 2,2,2-fluorodinitroethanol) 71%.

Anal. Calcd for $C_4H_6FN_3O_5$: N, 21.53; F, 9.74; mol wt, 195.1. Found: N, 21.2, 21.4; F, 10.0, 10.1; mol wt (in CH_3CN), 190.

***N*,*N*′-Bis(2,2,2-fluorodinitroethyl)-4,4-dinitroheptanedioic Amide.**—4,4-Dinitroheptanedioyl chloride was prepared by the procedure of Herzog, *et al.*[9] The reaction mixture was refluxed for 3 hr and poured into dilute sulfuric acid, the solvent was allowed to evaporate, and the solid product was recrystallized from ethylene dichloride–dimethoxyethane. From 4.85 g of acid chloride there was obtained 6.5 g of crude amide. After repeated fractional crystallization the product melted at 170.5–171.5°, nmr (CD_3CN) δ 2.63 (sym m), 4.65 (pair of d, J_{HF} = 16, J_{NH-H} = 6.5 cps).

Anal. Calcd for $C_{11}H_{14}F_2N_8O_{14}$: C, 25.39; H, 2.71; F, 7.30. Found: C, 25.3; 25.3; H, 2.6, 2.7; F, 7.6, 7.7.

***N*,*N*′-Bis(2,2,2-fluorodinitroethyl)urea (2).**—The reaction mixture obtained by the slow addition of a solution of phosgene in methylene chloride to the **1** + pyridine solution was stirred at room temperature overnight and then poured into dilute sulfuric acid. The solid remaining after evaporation of the methylene chloride was filtered and recrystallized from carbon tetrachloride–acetonitrile, mp 218–219°. The yield, based on 2,2,2-fluorodinitroethanol, was 66%. A lower melting polymorph of this material had previously been obtained by aqueous fluorination of dipotassium bis(2,2-dinitroethyl)urea.[7] The two polymorphs showed slight differences in their ir spectra (in KBr), but had identical nmr spectra, nmr (DMSO-d_6) δ 4.60 (pair of d, J_{HF} = 16, J_{NH-H} = 6.5 cps), 7.14 (t).

***N*-(2,2,2-Fluorodinitroethyl)carbamyl Chloride (3).**—To a solution of 11.5 g of phosgene in 50 ml of benzene was added dropwise at 5–10° a solution of 17.7 g of **1** and 9.5 g of pyridine in 30 ml of benzene. After complete addition the mixture was heated to 50° for 1 hr and the solvents were removed *in vacuo*. The residual oil was diluted to 100 ml with methylene chloride and reacted further as described below.

***N*,*O*-Bis(2,2,2-fluorodinitroethyl)carbamate (4).**—To 40 ml of the above solution of crude fluorodinitroethylcarbamyl chloride was added 5.6 g of 2,2,2-fluorodinitroethanol[6,7] and, dropwise and with cooling in an ice bath, 3.1 g of pyridine. The mixture was stirred at room temperature for 2 hr, diluted with 100 ml of methylene chloride, washed with dilute sulfuric acid, dried, and concentrated. Repeated chilling, filtration, and concentration of the mother liquor gave several fractions of **4** containing diminishing amounts of **2** as impurity. The crude yield totaled 3 g. The product was purified by recrystallization from methylene chloride–hexane: mp 63–64°; nmr (CD_3CN) δ 4.54 (pair of d,

(8) R. N. Lacey, *J. Chem. Soc.*, 1633 (1960).

(9) L. Herzog, M. H. Gold, and R. D. Geckler, *J. Amer. Chem. Soc.*, **73**, 749 (1951).

J_{HF} = 16, J_{NH-H} = 6.5 cps), 5.28 (d, J_{HF} = 16 cps), 6.74 (broad t).

Anal. Calcd for $C_5H_5F_2N_5O_{10}$: C, 18.04; H, 1.51; F, 11.40. Found: C, 17.8; H, 1.5; F, 11.3.

1,13-Difluoro-1,1,7,7,13,13-hexanitro-3,11-diaza-5,9-dioxatridecane-4,10-dione (5).—The above solution of crude fluorodinitroethylcarbamyl chloride (60 ml) was treated with 4.6 g of 2,2-dinitropropane-1,3-diol and 4.6 g of pyridine in the manner described for 4. The methylene chloride solution of the crude product was concentrated until crystallization started. A second crop was obtained by addition of hexane to the mother liquor of the first crop; total yield 4.5 g. The product was contaminated with 2, which is less soluble than 5 and could be removed by fractional crystallization from methylene chloride–hexane. A purer sample of 5 was obtained by addition of 2,2-dinitropropane-1,3-diol to fluorodinitroethyl isocyanate (see below), mp 128.5–130.5°, nmr (acetone-d_6) δ 4.53 (pair of d, J_{HF} = 16, J_{NH-H} = 6.5 cps), 5.02 (s), NH not reported.

Anal. Calcd for $C_9H_{10}F_2N_8O_{16}$: C, 20.62; H, 1.92; F, 7.25; N, 21.37; mol wt, 524.23. Found: C, 20.8; H, 2.0; F, 7.1; N, 21.4; mol wt (acetone), 528.

4 by Reaction of 2,2,2-Fluorodinitroethylamine with 2,2,2-Fluorodinitroethyl Chloroformate.—2,2,2-Fluorodinitroethyl chloroformate was prepared *in situ* as follows. To an ice-cooled solution of 15.4 g of 2,2,2-fluorodinitroethanol[6,7] and *ca.* 12 g of phosgene in 100 ml of methylene chloride was added dropwise 9 g of pyridine. The mixture was stirred at ambient temperature for 3–4 hr, then washed rapidly with ice-cold dilute sulfuric acid, and dried, and the solvent and excess phosgene were removed *in vacuo*. The remaining oil was taken up in 25 ml of methylene chloride and added dropwise and with stirring and cooling to an ice-cold solution of 11 g of 1 and 6.3 g of pyridine in 100 ml of methylene chloride. The mixture was stirred overnight at room temperature and freed from solvent, and the residue was digested with dilute sulfuric acid. The crude product was recrystallized from methylene chloride–hexane to give 21 g (88.6% based on 1) of 4.

2,2,2-Fluorodinitroethyl Isocyanate (6).—To a solution of 6 g of phosgene in 50 ml of methylene chloride was added dropwise at 0–5° and with stirring a solution of 9.2 g of 1 and 6.2 g of triethylamine in 25 ml of methylene chloride. After the exothermic reaction had subsided, another 6.2 g of triethylamine was added dropwise, and the mixture was stirred at room temperature for 1 hr, filtered rapidly, and freed from solvent *in vacuo*. The liquid portion of the remaining semisolid material was dissolved in methylene chloride–hexane (1:1), and the solution was filtered and concentrated. Vacuum distillation of the remaining oil gave 2 g of 6 as a pale yellow liquid, bp *ca.* 45° (0.1 mm), exhibiting a single peak in the glpc chromatogram and a strong band in the ir at 2250 cm^{-1}. The compound was characterized further by the following reactions with nitro alcohols.

Addition to 6 of 2,2,2-Fluorodinitroethanol, 2,2-Dinitropropane-1,3-diol, 2,2,8,8-Tetranitro-4,6-dioxa-1,9-nonanediol, and 2-Fluoro-2-nitropropane-1,3-diol.—The alcohol was added at room temperature to a methylene chloride solution of 6. When necessary, ether was added until the mixture was homogeneous. A few drops of pyridine were added and the mixture was stirred at room temperature overnight. The product was isolated by filtration or removal of the solvents. 4 and 5 prepared in this manner were identical with samples obtained from the reaction of fluorodinitroethyl carbamyl chloride (3) with the corresponding alcohol and pyridine. The two additional carbamates prepared from 6 are described below.

1,19-Difluoro-1,1,7,7,13,13,19,19-octanitro-3,17-diaza-5,9,11,15-tetraoxa-4,16-nonadecanedione (8).—The crude product from 1.8 g of 6 and 1.7 g of 2,2,8,8-tetranitro-4,6-dioxa-1,9-nonanediol[10] weighed 3.4 g. It was taken up in methylene chloride, filtered through a short column of silica (G. F. Smith, Columbus, Ohio) to remove colored material, and recrystallized from methylene chloride: mp 94–96°; nmr (CD_3CN) δ 4.55 (pair of d, J_{HF} = 16, J_{NH-H} = 6.5 cps), 4.46, 4.79, 5.04 (three s), 6.63 (broad peak, NH).

Anal. Calcd for $C_{13}H_{16}F_2N_{10}O_{22}$: C, 22.23; H, 2.30; F, 5.41. Found: C, 22.5; 22.4; H, 2.2, 2.1; F, 5.2, 5.3.

1,7,13-Trifluoro-1,1,7,13,13-pentanitro-3,11-diaza-5,9-dioxa-4,10-tridecanedione (7).—From 1.8 g of 6 and 0.7 g of 2-fluoro-2-nitro-1,3-propanediol[11] there was obtained 2.3 g of crude product. After recrystallization from ethylene dichloride–acetonitrile and drying at 80° (0.1 mm) for 2 days the material melted at 135–137°, resolidified when kept at this temperature, and melted again at 156–157°: nmr (CD_3CN) δ 4.53 (pair of d, J_{HF} = 16, J_{NH-H} = 6.5 cps), 4.61, 4.66, 4.81 (three s),[12] NH not reported.

Anal. Calcd for $C_9H_{10}F_3N_7O_{14}$: C, 21.75; H, 2.03; F, 11.46; N, 19.71. Found: C, 21.8, 21.7; H, 2.0, 2.1; F, 11.8, 11.7; N, 19.6, 19.6.

***N,N'*-Bis(2,2,2-fluorodinitroethyl)oxamide (10).**—A mixture of 100 g of 2,2,2-fluorodinitroethanol,[6,7] 100 ml of water, and 100 ml of methylene chloride was cooled in an ice bath, 70 g of 28% aqueous ammonia was added gradually, and the mixture was stirred for 0.5 hr at ice bath temperature and 6 hr at 25–30°. The phases were separated, the aqueous phase was extracted with 200 ml of methylene chloride, and the combined methylene chloride solutions were washed with 100 ml of 0.1 *N* NaOH and dried ($MgSO_4$). This solution of crude 1 was filtered and cooled in an ice bath; 36.3 g of pyridine was added, then slowly a solution of 29 g of oxalyl chloride in 200 ml of methylene chloride. Toward the end of the acid chloride addition the mixture was allowed to warm to *ca.* 40°. Methylene chloride (100 ml) was added and stirring was continued for another 7 hr. The precipitate was filtered off, washed with methylene chloride, and digested with dilute sulfuric acid to remove ammonium salts. The crude product weighed 68.5 g (58.6%). After two recrystallizations from acetic acid it melted at 224–225°: nmr (moist DMSO-d_6) δ 4.73 (pair of d, J_{HF} = 16, J_{NH-H} = 6.5 cps), 9.75 (t).

Anal. Calcd for $C_6H_6F_2N_6O_{10}$: F, 10.55; N, 23.34; mol wt, 360.16. Found: F, 10.8, 10.5; N, 22.5, 22.8; mol wt, 379, 346.

***N*-*tert*-Butyl-*N*-(2,2,2-fluorodinitroethyl)amine (9).**—*tert*-Butylamine (8.5 g) was added with stirring and cooling to a solution of 15 g of 2,2,2-fluorodinitroethanol in 60 ml of water and the mixture was stirred at room temperature for 2 hr. The oil was separated and dried with a small amount of magnesium sulfate. It was shown by nmr to be pure 9 and was used for further reactions without purification. The yield was essentially quantitative: bp 54–55° (0.5 mm); nmr ($CDCl_3$) δ 1.05 (s), 1.23 (broad peak, NH), 3,81 (d, J_{HF} = 16 cps).

Preparation of 10 *via* 9.—A solution of 16.8 g of 9 in 50 ml of methylene chloride was cooled to 5–10° and 2.6 g of oxalyl chloride in 10 ml of methylene chloride was added. The mixture was stirred for 1 hr at room temperature, heated to reflux for 6 hr, and poured into dilute sulfuric acid, and the organic solvent was allowed to evaporate. Filtration gave 8.7 g of crude *N,N'*-(*tert*-butyl)-*N,N'*-bis(2,2,2-fluorodinitroethyl)oxamide, mp 159–160°. The filtrate was made alkaline and extracted with methylene chloride. Upon removal of the solvent from the extract 8.3 g of 9 was recovered.

A mixture of 10 g of the crude oxamide, 18 ml of acetic acid, and 12 ml of concentrated sulfuric acid was stirred for 2 hr at ambient temperature, ice and water was added, and the solid was filtered off to give 7.5 g of crude 10. After recrystallization from acetic acid the material was identical with a sample prepared from 1 as described above.

***N*-(2,2,2-Fluorodinitroethyl)formamide (12) *via* 9.**—A mixture of 10.5 g of 9 and 30 ml of formic acid was cooled, 30 ml of acetic anhydride was added, and the mixture was stirred overnight. On drowning the reaction mixture in water and filtering off the precipitate there was obtained 8.5 g (71.4%) of *N*-(*tert*-butyl)-*N*-(2,2,2-fluorodinitroethyl)formamide (11).

Nine grams of 11 was added to 15 ml of concentrated sulfuric acid, and the mixture was stirred for 6 hr at 25–30°, drowned on crushed ice, and the solution diluted to 125 ml with water. Charcoal was added to remove a brown, oily material and the solution was filtered, saturated with sodium sulfate, and extracted with five 50-ml portions of ether. Drying ($MgSO_4$) and removing the solvent gave 5 g of crude 12. The product was degassed and distilled in a molecular still at 80–90° (0.1 mm). Nmr and glpc analysis indicated the distillate to be about 95% pure, nmr (CD_3CN) δ 4.64 (pair of d, J_{HF} = 16, J_{NH-H} = 6.5 cps), 7.22 (broad peak, NH), 8.16 (s).

(10) T. N. Hall and K. G. Shipp, U. S. Patent 3,288,863 (Nov 29, 1966).

(11) L. T. Eremenko and G. V. Oreshko, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 380 (1965).

(12) See K. Baum, *J. Org. Chem.*, **35**, 846 (1970), for a discussion of anomalies in the nmr spectra of 2-fluoro-2-nitroalkanols.

Anal. Calcd for $C_3H_4FN_3O_5$: C, 19.91; H, 2.23; F, 10.49; N, 23.21. Found: C, 20.6, 20.5; H, 2.7, 2.6; F, 9.8, 10.1; N, 23.0, 23.0.

Registry No.—**1**, 18139-02-1; **2**, 17003-80-4; **4**, 33046-31-0; **5**, 33191-89-8; **6**, 33046-32-1; **7**, 33147-03-4; **8**, 33046-33-2; **9**, 33046-34-3; **10**, 33191-90-1; **12**, 33046-35-4; *N*-(2,2,2-fluorodinitroethyl)acetamide, 22691-71-0; *N*,*N*′-bis(2,2,2-fluorodinitroethyl)-4,4-dimtroheptanedioic amide, 33046-37-6; *N*,*N*′-di(*tert*-butyl)-*N*,*N*′-bis(2,2,2-fluorodinitroethyl)oxamide, 33046-38-7.

Acknowledgment.—The work described here was carried out under NOL Task IR-144, "Explosives Chemistry."

Reactions of Nitromethane with Hexafluorobenzene at 550°

ELLIS K. FIELDS*

Amoco Chemicals Corporation, Naperville, Illinois 60540

SEYMOUR MEYERSON

Standard Oil Company, Naperville, Illinois 60540

Received June 25, 1971

Nitromethane reacts with hexafluorobenzene at 550° to give products that differ greatly in nature from those with benzene under the same conditions. Pentafluorotoluene and pentafluorophenol are the major products, together with varying amounts of pentafluoroanisole, pentafluorobenzaldehyde, and decafluorobiphenyl. With *p*-difluorobenzene, nitromethane gives *p*-fluorophenol as the only major product. The driving force in reactions of nitromethane with fluorinated aromatics may be the formation of nitrosyl and nitryl fluorides.

Nitromethane reacts with benzene at 500–550° to give aniline, *N*-methylaniline, and biphenyl as major products, together with minor amounts of toluene, anisole, phenol, and *N*-benzylideneaniline.[1] The deuterium content of products from labeled reagents indicated that *N*-methylaniline formed by insertion in benzene of methylnitrene from nitromethane, and aniline by subsequent loss of CH_2 from *N*-methylaniline.[2] Apart from biphenyl, a product derived entirely from benzene, nitrogen compounds comprised about 79% of the total products. It was of interest to find if nitromethane would give analogous products with substituted benzenes. We therefore allowed nitromethane to react with hexafluorobenzene at 550° and determined the products by mass spectrometry, gas chromatography, and directly coupled gas chromatography–mass spectrometry.

Experimental Section

Hexafluorobenzene was from Aldrich Chemical Company. It analyzed 98% hexafluorobenzene and 1% each of penta- and tetrafluorobenzenes. The pentafluoro derivatives of toluene, anisole, aniline, benzaldehyde, and decafluorobiphenyl were from Pierce Chemical Company. Nitromethane was Eastman Reagent Grade, distilled prior to use. The apparatus, procedure, and analytical methods are fully described in previous publications.[3]

In a typical experiment a mixture of 10.72 ml (0.2 mol) of nitromethane and 118 ml (1.0 mol) of hexafluorobenzene was pumped into a Vycor tube filled with Vycor chips at 550° in a stream of argon flowing at 20 ml/min. Liquid products were condensed in a bulb at 0°; gases were collected in gas bulbs for mass spectral analysis. Distillation of the liquid products recovered 171 g, almost all hexafluorobenzene, at 78–80°, and left 12.6 g of a higher boiling residue whose composition is shown in Table II, along with the composition of gases generated in the reaction.

Results and Discussion

Products from the reaction of nitromethane with hexafluorobenzene determined by gas chromatography are listed in Table I. These included various amounts of unknowns, whose molecular weights were determined by mass spectrometry; these are listed in Table II, along with the composition of gaseous products.

TABLE I

PRODUCTS FROM NITROMETHANE AND HEXAFLUOROBENZENE[a]

	Products[b]			
Nitromethane, mol	1	0.5	0.2	0.1
Weight of products boiling over 100°, g	26	27	12.6	7.0
Pentafluorotoluene	37.5	53.0	56.0	60.0
Pentafluorophenol	33.0	23.0	20.7	3.0
Pentafluoroanisole	5.9	9.8	9.9	12.7
Pentafluorobenzaldehyde	6.6	3.2	3.0	4.6
Decafluorobiphenyl	6.8	4.7	3.6	2.9
Unknowns	10.2	6.3	6.8	16.8

[a] Conditions: 1 mol hexafluorobenzene; 550°; contact time, 20 sec; argon, 20 ml/min. [b] Weight percent by gas chromatography.

The two major products were pentafluorotoluene and pentafluorophenol, with pentafluoroanisole prominent among the less abundant ones. In addition, mass spectrometry showed a compound of molecular weight 180, corresponding to tetrafluoroanisole, tetrafluorobenzyl alcohol, or tetrafluorocresol. Its spectrum is compatible with the structure $CH_3C_6F_4OH$. A pair of peaks of about equal intensities at masses 179 and 180 resembles corresponding pairs in the spectra of $C_6F_5CH_3$[4,5] and $C_6F_4HCH_3$,[5] and thus suggests a methyl group on a fluorinated benzene ring. Masses of other fragments (probable derivations) follow: 161 ($M^+ - F$), 151 ($M^+ - CHO$), 150 ([$M^+ - H$] –

(1) E. K. Fields and S. Meyerson, *Chem. Commun.*, 494 (1967).

(2) E. K. Fields and S. Meyerson, *Amer. Chem. Soc. Div. Petrol. Chem. Prepr.*, **16**, No. 1, B96 (1971).

(3) E. K. Fields and S. Meyerson, *Accounts Chem. Res.*, **2**, 273 (1969), and references cited therein.

(4) J. R. Majer, *Advan. Fluorine Chem.*, **2**, 55 (1961).

(5) L. D. Smithson, A. K. Bhattacharya, and C. Tamborski, *Org. Mass Spectrom.*, **4**, 1 (1970).

TABLE II

PRODUCTS FROM NITROMETHANE AND HEXAFLUOROBENZENE[a]

Liquids	Rel concn[b]
Compound of molecular weight 180	33
Pentafluorotoluene	100
Pentafluorophenol	55
Pentafluoroanisole	24
Pentafluorobenzaldehyde	3
Tetrafluoroxylene	10
Hexafluorotoluene	5
Methyl octafluorobiphenyl	4
Nonafluorobiphenyl[c]	3
Methyl nonafluorobiphenyl	4
Decafluorobiphenyl	6
Decafluoromethylbiphenyl	4
Gases	**Mol %[d]**
Nitric oxide	37.1
Carbon monoxide	30.6
Carbon dioxide	13.3
Silicon tetrafluoride	11.2
Nitrogen	3.5
Methane	2.6
Hydrogen cyanide	1.0
Ethylene	0.7

[a] Conditions: mole ratio, nitromethane to hexafluorobenzene, 1:5; 550°; contact time, 20 sec; argon, 20 ml/min. [b] Relative intensities in the low-voltage mass spectrum normalized to pentafluorotoluene = 100; identities confirmed by directly coupled gas chromatography–mass spectrometry. [c] This might arise, at least partly, from the pentafluorobenzene impurity in the hexafluorobenzene. [d] Determined by mass spectrometry.

TABLE III

COMPARISON OF PRODUCTS FROM NITROMETHANE WITH BENZENE AND WITH HEXAFLUOROBENZENE[a]

	C_6X_6, X = H	C_6X_6, X = F
Liquids	Weight %[b]	
$C_6X_6CH_3$	0.5	56
$C_6X_5NH_2$	12.3	
C_6X_6OH	1.6	20.7
$C_6X_5OCH_3$	2.6	9,9
C_6X_5CHO	Trace	3.0
$C_6X_5NHCH_3$	5.5	
$C_6X_5C_6X_5$	69.7	3.6
$C_6X_5C_6X_4NH_2$	2.3	
$C_6X_5CH{=}NC_6X_5$	1.6	
Unidentified	3.9	6.8
Total weight of liquid products, g	5.2	12.6
Gases	**Mol %[c]**	
Nitric oxide	42.1	37.1
Carbon monoxide	24.3	30.6
Carbon dioxide	2.5	13.3
Silicon tetrafluoride		11.2
Nitrogen	12.9	3.5
Methane	14.2	2.6
Hydrogen cyanide	0.4	1.0
Ethylene	1.8	0.7
Hydrogen	1.8	

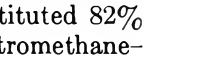
[a] Conditions: 0.2 mol of nitromethane, 1.0 mol C_6X_6; contact time, 20 sec; argon, 20 ml/min. [b] Determined by gas chromatography. [c] Determined by mass spectrometry.

CHO), 136 ($M^+ - C_2FH$), 132 ([$M^+ - CHO$] − F or $M^+ - CHOF$).

The identities of the two most abundant products, $C_6F_5CH_3$ and C_6F_5OH, in conjunction with a little tetrafluorophenol, furnish additional supporting evidence for ascribing the tetrafluorocresol structure to the product of molecular weight 180.

A striking contrast in the reactions of nitromethane with benzene and hexafluorobenzene is demonstrated in Table III. Aniline and biphenyl constituted 82% by weight of the liquid products in the nitromethane–benzene reaction; no pentafluoroaniline, and only 3.6% of decafluorobiphenyl formed in the nitromethane–hexafluorobenzene reaction. None of the liquid products from hexafluorobenzene contained nitrogen. Toluene and phenol constituted only 0.5 and 1.6% by weight, respectively, of the products from benzene, whereas the corresponding fluorinated toluene and phenol amounted to 56 and 20.7%, respectively, from hexafluorobenzene. Among the gases, methane constituted 14.2% from the benzene reaction, only 2.6% from the hexafluorobenzene reaction.

The sharply different product distributions can be rationalized in terms of the greater susceptibility of C_6F_6 than of C_6H_6 to nucleophilic attack,[6] even though the reactive intermediates in the gas phase are doubtless free radicals rather than ions. The electron-donating character of a methyl substituent, which might be translated into nucleophilicity of the methyl radical, would favor attack on C_6F_6 over that on C_6H_6. A measure of the extent of such preference is implied in the difference between the resultant bond-dissociation energies, $D(C_6F_5{-}CH_3) - D(C_6H_5{-}CH_3)$, which has been estimated at about 25 kcal/mol.[4] The high yield of pentafluorophenol, with no evidence for intermediate $C_6F_5NO_2$ formation, could be accounted for by NO_2 attack *via* an oxygen atom to form C_6F_5ONO as an intermediate, paralleling the formation of CH_3ONO in the photolysis of CH_3NO_2 by recombination of $CH_3\cdot$ and NO_2 through an oxygen atom.[7] The canonical structure i would appear to be a better nucleophile than



i ii

ii. Support for this view can be drawn from the consistently lower ionization potentials of alkyl nitrites than of the isomeric nitroalkanes.[8]

Nitromethane at high temperature, alone or in the presence of benzene, decomposes to methyl radical and NO_2; the methyl radical abstracts hydrogen from nitromethane and goes to methane.[2]

$$CH_3NO_2 \longrightarrow CH_3\cdot + NO_2$$

$$CH_3\cdot + CH_3NO_2 \longrightarrow CH_4 + \cdot CH_2NO_2$$

The major overall reaction with hexafluorobenzene is

$$C_6F_6 + CH_3NO_2 \longrightarrow C_6F_5CH_3 + NO_2F$$

Apparently methyl radical is captured so rapidly by hexafluorobenzene that it cannot abstract hydrogen

(6) J. A. Young, *J. Chem. Educ.*, **47**, 733 (1970); W. A. Sheppard and C. M. Sharts, "Organic Fluorine Chemistry," W. A. Benjamin, New York, N. Y., 1969, Chapter 8.

(7) G. C. Pimentel and G. Rollefson, "Formation and Trapping of Free Radicals," Academic Press, New York, N. Y., 1960, Chapter 4; R. E. Rebbert and N. Slagg, *Bull. Soc. Chim. Belg.*, **71**, 709 (1962); B. H. J. Bielski and R. B. Timmons, *J. Phys. Chem.*, **78**, 347 (1964).

(8) The differences for the methyl, ethyl, *n*-propyl, and isopropyl compounds all fall in the range of 0.4 to 0.6 eV. For the ionization-potential data, see R. W. Kiser, "Introduction to Mass Spectrometry and Its Applications," Prentice-Hall, Englewood Cliffs, N. J., 1965, Appendix IV; M. J. S. Dewar, M. Shanshal, and S. D. Worley, *J. Amer. Chem. Soc.*, **91**, 3590 (1969).

from nitromethane to give methane, as it does in the presence of benzene. Further, pentafluorotoluene is not attacked so readily by radicals as is toluene, at least in the presence of excess hexafluorobenzene.

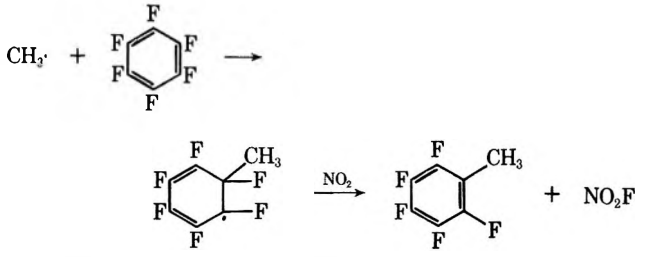
The role of NO_2 is also quite different in the two reactions. It abstracts a hydrogen from benzene to give phenyl radical, which forms biphenyl by arylating benzene or by dimerizing.

$$NO_2 + C_6H_6 \longrightarrow HNO_2 + C_6H_5\cdot$$

$$C_6H_5\cdot + C_6H_6 \xrightarrow{-[H]} C_6H_5C_6H_5$$

$$2\,C_6H_5\cdot \longrightarrow C_6H_5C_6H_5$$

NO_2 does not readily abstract a fluorine atom from hexafluorobenzene, for there was little decafluorobiphenyl. Rather it appears to take a fluorine atom from the intermediate cyclohexadienyl free radical formed by addition of methyl radical to hexafluorobenzene.



Methoxyl radical, a possible contributing precursor of pentafluorophenol, may arise from a prior nitro–nitrite rearrangement

$$CH_3NO_2 \longrightarrow CH_3ONO \longrightarrow CH_3O\cdot + NO$$

or dissociation and recombination, as in the known photochemical sequence[7]

$$CH_3NO_2 \longrightarrow CH_3\cdot + NO_2 \longrightarrow CH_3ONO \longrightarrow CH_3O\cdot + NO$$

followed by

$$CH_3O\cdot + C_6F_6 \xrightarrow{NO} CH_3OC_6F_5 + NOF$$

Such a nitro–nitrite rearrangement was strongly evident in the thermal decomposition of nitrobenzene, but took place to a much lesser extent in thermal decomposition of nitromethane and in its reaction with benzene. Pentafluorophenol may form from pentafluoroanisole by loss of either CH_2 or $CH_3\cdot$.

$$C_6F_5OCH_3 \xrightarrow{-CH_2} C_6F_5OH$$

$$C_6F_5OCH_3 \xrightarrow{-CH_3\cdot} C_6F_5O\cdot \xrightarrow{[H]} C_6F_5OH$$

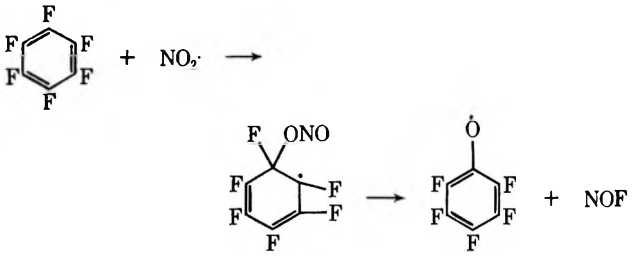
In reactions of anisole with nitrobenzene at 600°, as well as in the decomposition of anisole alone at that temperature, some of the products are most readily explained on the basis of carbene formation and insertion.[9]

Aromatic nitro compounds give phenols upon decomposition at elevated temperatures.[3] However, the path to pentafluorophenol through formation of pentafluoronitrobenzene or perhaps pentafluorophenyl nitrite directly, not involving prior dissociation of nitromethane,

$$C_6F_6 + CH_3NO_2 \longrightarrow \begin{matrix} C_6F_5NO_2 \\ C_6F_5ONO \end{matrix} + CH_3F$$

$$C_6F_5NO_2 \longrightarrow C_6F_5ONO \xrightarrow{-NO} C_6F_5O\cdot \xrightarrow{[H]} C_6F_5OH$$

appears to be excluded by the absence of methyl fluoride from the products. An alternative mechanism for pentafluorophenol is addition of NO_2 through the oxygen atom to hexafluorobenzene, followed by loss of NOF.



Pentafluorophenoxy radical then abstracts a hydrogen from nitromethane to give pentafluorophenol.

Most of the gaseous products may be accounted for by these reactions.

$$NO_2F + CH_3NO_2 \longrightarrow HF + CH_2(NO_2)_2$$

$$4HF + SiO_2 \longrightarrow SiF_4 + 2H_2O$$

$$CH_2(NO_2)_2 \longrightarrow CO + H_2O + 2NO$$

$$CH_2(NO_2)_2 \longrightarrow CO_2 + H_2O + {}^1/_2N_2 + NO$$

Nitryl fluoride is a good nitrating agent;[10] dinitromethane decomposes readily at temperatures around 100°,[11] though the products have not been described. The formation of less nitrogen than demanded by the equations above indicates that other paths to CO_2 may exist.[12]

Some HF and subsequently SiF_4, as well as pentafluorobenzaldehyde, may also arise by the following process.

$$C_6F_6 + CH_3NO_2 \longrightarrow C_6F_5CH_2NO_2 + HF$$

$$C_6F_5CH_2NO_2 \longrightarrow C_6F_5CHO + HNO$$

Although C_6F_6 is thermally stable, being recovered unchanged after 30 sec at 700°,[13] we found that it reacted readily at elevated temperatures with organic compounds containing hydrogen atoms, even aromatic hydrogen, such as in chlorobenzene.[9]

$$C_6F_6 + C_6H_5Cl \xrightarrow[20\ sec]{700°} C_6F_5C_6H_4Cl + HF$$

Other products arose solely from chlorobenzene: biphenyl, chloro- and dichlorobiphenyl, and chloronaphthalene, the latter presumably derived from benzyne.[14] The driving force in these reactions of hexafluorobenzene apparently comes from the formation of HF.

(9) E. K. Fields and S. Meyerson, unpublished results.

(10) S. J. Kuhn and G. A. Olah, *J. Amer. Chem. Soc.*, **83**, 4564 (1961).

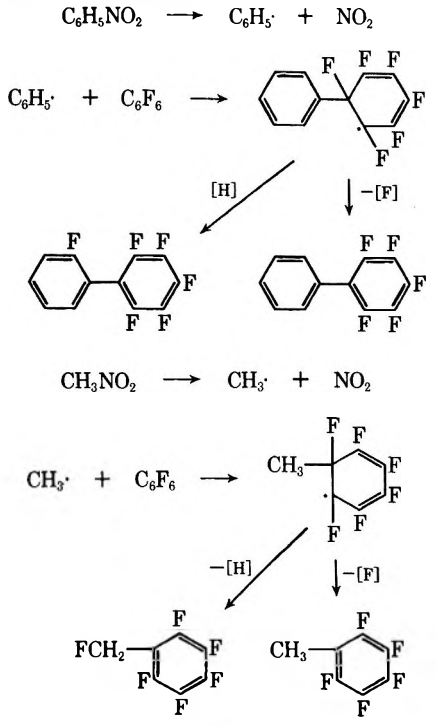
(11) P. Duden, *Ber.*, **26**, 3004 (1893).

(12) A referee has pointed out that both NO_2F and NOF attack glass readily to form SiF_4. In addition, NOF forms a white solid with glass, which may explain the formation of less nitrogen than demanded by the equations.

(13) E. K. Fields and S. Meyerson, *J. Org. Chem.*, **32**, 3114 (1967).

(14) E. K. Fields and S. Meyerson, *J. Amer. Chem. Soc.*, **88**, 3388 (1966).

Hexafluorotoluene listed in Table II could form by carbene insertion, or by exchange of fluorine and hydrogen atoms in the intermediate cyclohexadienyl free radical, paralleling that in the reaction of phenyl radical derived from nitrobenzene with hexafluorobenzene.[13]



Decafluoromethylbiphenyl may form in a similar fashion.

Pentafluorotoluene has been made from hexafluorobenzene with methyllithium in 16% yield.[15] Pentafluorophenol has been prepared in 20% yield, along with dihydroxytetrafluorobenzenes, by the reaction of hexafluorobenzene with aqueous potassium hydroxide at 175° under pressure.[16] Pentafluorophenol has also been made by the reaction of pentafluorophenyllithium with trimethyl borate and oxidation of the dimethyl pentafluorophenyl borate with hydrogen peroxide. The overall yield was 39%.[17]

Our reaction of nitromethane with hexafluorobenzene provides a useful preparative method for pentafluorotoluene and pentafluorophenol. By varying the mole ratio of the two reactants from 0.1:1 up to 1:1, the reaction can give pentafluorotoluene with little pentafluorophenol, or about equal amounts of the two products, in a one-step reaction.

(15) British Patent 887,691, to National Polychemicals, Inc. (Jan 24, 1962); M. W. Buxton and J. C. Tatlow to Imperial Smelting Corp., British Patent 977,961, (Dec 16, 1964).

(16) W. J. Pummer and L. A. Wall, *J. Res. Nat. Bur. Stand.*, **A68**, (3), 277 (1964).

(17) G. M. Brooke, B. S. Furniso, W. K. R. Musgrave, and M. A. Zuasem, *Tetrahedron Lett.*, 2991 (1965).

As shown in Table III, the nature of the products and relative amounts of analogous products in the reactions of nitromethane with benzene and hexafluorobenzene differed sharply. We therefore examined the reaction of nitromethane with a compound containing both hydrogen and fluorine atoms, *p*-difluorobenzene. The products of the reaction are listed in Table IV.

TABLE IV

PRODUCTS FROM NITROMETHANE AND *p*-DIFLUOROBENZENE[a]

Product	Rel concn[b]
Fluorotoluene	2
Fluorophenol	100
N-Methylfluoroaniline	1
Fluoroanisole	8
Difluorotoluene	3
Difluorophenol	3
N-Methyldifluoroaniline	4
Difluorobiphenyl	3
Trifluorobiphenyl	15
Tetrafluorobiphenyl	13

[a] Conditions: 1 mol of *p*-difluorobenzene, 0.2 mol of nitromethane; 550°; contact time, 20 sec; N_2, 20 ml/min. Total weight of products boiling above 95°, 17.7 g. [b] Relative intensities in the low-voltage (7.5 V nominal) mass spectrum, normalized to fluorophenol = 100.

The major product by far is fluorophenol; the ratio of its concentration to that of fluoroanisole, 12:1, suggests that the fluoroanisole arose from methylation of fluorophenol, rather than fluorophenol from fluoroanisole by loss of CH_2. Little fluorotoluene or difluorotoluene formed, in contrast to the reaction of nitromethane and hexafluorobenzene in identical mole ratios, which gave 2.8 times as much pentafluorotoluene as pentafluorophenol.

Displacement of a fluorine atom was preferred over that of a hydrogen atom by a ratio of 33:1, even though *p*-difluorobenzene has twice as many hydrogen as fluorine atoms. The driving force may be formation of NOF rather than NOH in the overall reaction

$$C_6H_4F_2 + CH_3NO_2 \longrightarrow C_6H_4FOH + NOF + CH_2$$

The behavior of nitromethane at 550° seems to be strongly influenced by the nature of added reagents. We are presently examining its reactions at different concentrations with a variety of benzene derivatives, as well as with pyridine and thiophene.

Registry No.—Nitromethane, 75-52-5; hexafluorobenzene, 392-56-3; benzene, 71-43-2; *p*-difluorobenzene, 540-36-3.

Acknowledgment.—The authors are happy to acknowledge the assistance of Dr. D. K. Albert of American Oil with gas chromatographic analyses.

Oxidation of 2,4,6-Trimethylheptane

DALE E. VAN SICKLE

Research Laboratories, Tennessee Eastman Company, Division of Eastman Kodak Company, Kingsport, Tennessee 37662

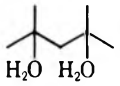
Received July 27, 1971

2,4,6-Trimethylheptane (TMH), a model compound for polypropylene, was autoxidized at 100 and 120°; the kinetic behavior of the reaction was studied, and the major products of the reaction were identified. The synthesis of alcohols, formed as oxidation products (after reduction of the primary product hydroperoxides), is also described. Intramolecular propagation seems to be the dominant reaction pathway in TMH oxidation. The yield of the major product, 2,4,6-trimethyl-2,4,6-heptanetriyl trihydroperoxide, was never greater than ~80% and decreased markedly with increased conversion. At the higher conversions, fragmentation of the hydrocarbon skeleton evidently occurred to give lower molecular weight products which were not identified in the gas chromatographic analysis. Thus, oxygen balances became progressively poorer at higher conversions.

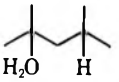
One approach to the study of polymer reactions is the study of model compound reactions. The low-molecular-weight products from the model compound reactions can be isolated and identified in a straightforward manner, whereas identification of products from polymer reactions must be done mainly by spectroscopy.

In polypropylene, the alternate placement of methyl groups along the polymer chain seems to impart special susceptibility to autoxidation. This placement then give a sequence of tertiary hydrogens down the polymer chain adjacent to the methylene group in each repeating unit. A model compound which duplicates this hydrogen sequence in a limited way is 2,4,6-trimethylheptane (TMH). The oxidation of TMH has been reported,[1] but the products were not identified. A more recent article[2] mentioned oxidation of 2,4,6-trimethylnonane but gave no details.

The most relevant works on autoxidation of alkanes containing alternating tertiary hydrogens are by Rust[3] and, more recently, Mill[4] and Montorsi who showed that the principal product of 2,4-dimethylpentane autoxidation is the dihydroperoxide **1**. The ratio of

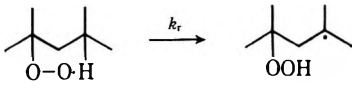


1



2

monohydroperoxide **2** to the dihydroperoxide **1** was 1:7, and the combined yields of **1** and **2** accounted for more than 90% of the consumed oxygen. An intermediate step, which is apparently unique to the alternating tertiary center alkanes, involves intramolecular transfer of a hydrogen atom to an alkyl peroxy radical.[4]



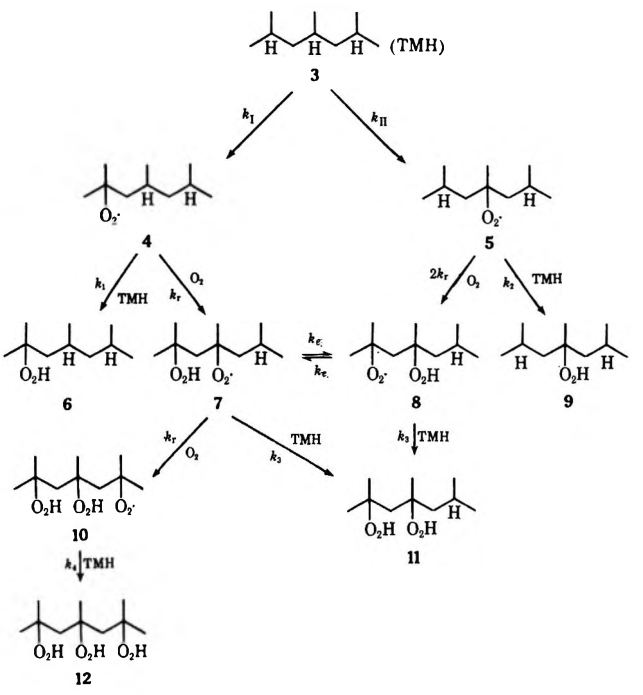
The objective of this research was to determine the generality of intramolecularly propagated oxidation in hydrocarbons by measuring the yields of mono-, di-, and trihydroperoxides formed in the autoxidation of TMH. Sufficient knowledge about the intramolecularly propagated oxidation may suggest whether it is an important propagation step in the autoxidation of polypropylene, where the alternating sequence of tertiary centers is practically infinite.

(1) A. C. Buchachenko, K. Y. Kaganskaya, and M. B. Nieman, *Kinet. Katal.*, **2**, 38, 149 (1961).
(2) J. C. W. Chien, *J. Phys. Chem.*, **71**, 2247 (1967).
(3) F. Rust, *J. Amer. Chem. Soc.*, **79**, 4000 (1957).
(4) T. Mill and G. Montorsi, Abstracts, 161st National Meeting of the American Chemical Society, March 28, 1971, Petr. No. 8.

Results and Discussion

Kinetics of TMH Autoxidation.—This oxidation is apparently too complex to describe with a reasonably concise list of equations. Table I lists the pertinent data obtained, and Scheme I lists the proposed important transformations.

SCHEME I



It was assumed that a steady-state concentration of the various peroxy radicals (**4**, **5**, **7**, **8**, and **10**) attack the substrate TMH at the tertiary hydrogens to form alkyl radicals which, after being scavenged by oxygen, are converted to the peroxy radicals **4** and **5**. From this point, a series of competitions occur between intramolecular hydrogen abstraction (rearrangement) (k_r) or intermolecular reaction (k_i, i = 1, 2, 3, 4) with more TMH. The final hydroperoxide products are the species **6**, **9**, **11**, **12** which, after triphenylphosphine treatment, give the monohydric alcohols, diols, and triol by glpc analysis.

TABLE I

RATES AND PRODUCTS OF TRIMETHYLHEPTANE OXIDATION AT 100°

Expt no.	TMH, mmol	Soln vol, ml[a]	[TMH], M	[tert-Bu_2O_2], M	Oxidn rate × 10^6,[b] M min^{-1}	O_2 consumed, mmol	Time, min	O_2H Yield—mmol[c]	O_2H Yield—O_2 consumed, %	Yield of products, mmol[d]—Monohydric alcohols[e]	Diols[f]	Triol	Other[g]
34[h]	124.1	26.3	4.72	0.0085[i]	44	1.94	1703	1.41	73				
141	104.8	22.9	4.58	0.0066	62	4.22	1370	2.46	58	0.054	0.048	0.25	0.343[j]
62	100.6	21.9	4.58	0.0091	66	0.97	510	0.79	81	0.023	0.022	0.137	0.11
138	109.1	23.7	4.58	0.0102	72	1.01	505	0.77	77	0.01	0.019	0.076	0.07[k]
105	108.5	23.7	4.58	0.0280	96	1.37	465	0.96	70	0.019	0.026	0.158	0.11
111	106.3	23.3	4.58	0.0607	142	1.28	365	0.94	73	0.018	0.024	0.15	0.13
147[l]	110.7	24.8	4.46	0.0000	193	1.48	150	1.02	69				
59[l]	98.7	22.1	4.46	0.0142	650	1.23	70	0.91	74	0.024	0.029	0.18	0.18
144[l]	138.1	39.5	3.50[m]	0.0119	209	1.72	220	1.14	66				
101[l]	96.0	41.0	2.30[m]	0.0108	94	1.49	382	0.76	52	0.022	0.075	0.145	0.19
108[l]	117.8	80.3	1.46[m]	0.0109	72	2.18	465	0.98	45	0.01	0.011	0.11	0.11
130[n]	108.1	23.9	4.57	0.0324	55	1.30	715	0.84[o]	65	0.11	0.11	0.17	1.83;[p] 0.13[q]
133[q]	88.7	20.8	4.26	0.0404	96	1.40	651	1.09	78	0.02	0.025	0.14	0.26;[r] 0.06[q]

[a] At reaction temperature. [b] Initial rate, mol $l.^{-1}$ min^{-1}. [c] Iodometric titration.[5] [d] By glpc after triphenylphosphine reduction. [e] 2,4,6-Trimethyl-2- and -4-heptanols. [f] 2,4,6-Trimethyl-2,4- and, if any, -2,6-heptanediols. [g] Summation of five to ten unidentified peaks, mol wt of 170 assumed. [h] 80°. [i] 1,1′-Azodicyclohexanecarbonitrile (ADC). [j] 0.44 mequiv of acid present (from NaOH titration). [k] 0.012 mequiv of acid present. [l] 120°. [m] Benzene solutions. [n] Tetralin hydroperoxide concentration = 1.675 mol = 0.07 M. [o] Net hydroperoxide formed (total titre = 167 mmol). [p] Tetralone and tetralol found following triphenylphosphine reduction. [q] Cumene concentration = 9.36 mmol = 0.45 M. [r] Cumyl alcohol.

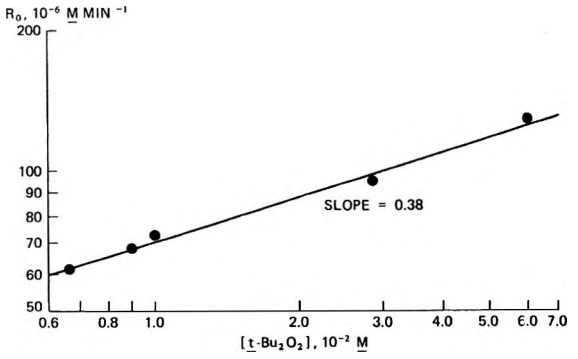


Figure 1.—Oxidation rate dependence on initiation rate.

It was of interest to see whether the oxidation rate dependence conformed to simple rate laws, applicable to many oxidations, where kinetic chain lengths are long, of the form

$$R_o = -dO_2/dt = (R_i/2k_t)^{1/2}k_p[RH] \quad (1)$$

where R_o = rate of oxidation, R_i = rate of initiation, k_p = rate constant for propagation, k_t = rate constant for termination, and [RH] = concentration of substrate.[6] Kinetic chain lengths for the TMH oxidations of Table I are estimated to range from 100 to 10. The TMH oxidation system is too complex to make an exact steady-state analysis tractable, but a simple law such as eq 1 might be approximated. For instance, Mill and Montorsi[4] made an analysis of the dimethylpentane system and, with certain simplifying assumptions, obtained an expression for the oxidation rate.

$$R_o = (R_i/2ak_t)^{1/2}k_p[RH]\left[\frac{k_p'[RH]}{k_r} + 2\right] + \frac{R_i}{2a}\left[\frac{k_p'[RH]}{k_r} + 1/2\right] \quad (2)$$

Both k_p and k_p' are propagation rate constants for the two principal peroxy radicals present and a is the fraction of termination from the reaction of two peroxy radicals. On the assumption that the first term of eq 2 dominates and that $2 \gg k_p'[RH]/k_r$, eq 2 reduces to eq 3, which is the same as eq 1 except for the factor of 2 (when $a = 1$).

$$R_o = 2(R_i/2ak_t)^{1/2}k_p[RH] \quad (3)$$

For TMH the oxidation rate (R_o) dependence on the initiation rate (R_i) was determined by the usual log–log plot of R_o against initiator concentration which is proportional to R_i. The results are shown in Figure 1. There is some scatter in the data but no point lies more than 8–10% from the line which was drawn. The slope of the line is 0.38, significantly lower than the 0.50 expected. The outcome is somewhat surprising, since most oxidations show initiator dependence orders from 0.5 to 1.0.

Orders in initiation rate of 1/3 can be predicted from certain models of oxidation mechanisms, which involve a dominating amount of nonterminating peroxy radical interaction ($a \ll 1$) and subsequent cleavage of the alkoxy radicals formed.

$$2RO_2\cdot \longrightarrow 2RO\cdot + O_2$$
$$RO\cdot \longrightarrow R'\cdot + R'' = O$$

Although the TMH oxidation to hydroperoxides is far from quantitative, an explanation for the odd initiator dependence lies in the existence of a second source of initiation.

The temperature dependence of the reaction was estimated from experiments 34, 138, and 59 by correcting the initial rates to unit hydrocarbon concentration and unit initiation rate and assuming eq 1 to be valid. Rates of initiation were calculated from eq 4.

$$R_i = 2k_d[tert\text{-}Bu_2O_2] \quad (4)$$

The values of k_d used were extrapolations of previously published data.[7,8] The results are summarized in

(5) R. D. Mair and A. J. Graupner, *Anal. Chem.*, **36**, 194 (1964).
(6) L. Bateman, *Quart. Rev., Chem. Soc.*, **8**, 147 (1954).
(7) D. E. Van Sickle, F. R. Mayo, and R. M. Arluck, *J. Amer. Chem. Soc.*, **87**, 4832 (1965).
(8) L. Batt and S. W. Benson, *J. Chem. Phys.*, **30**, 895 (1962).

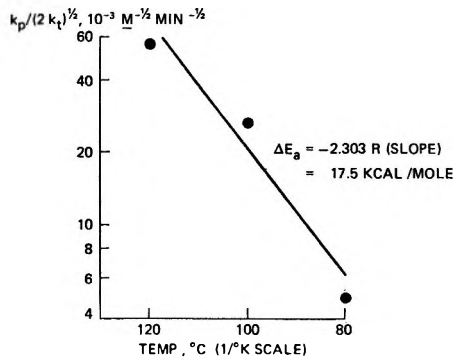


Figure 2.—Temperature dependence of TMH oxidation.

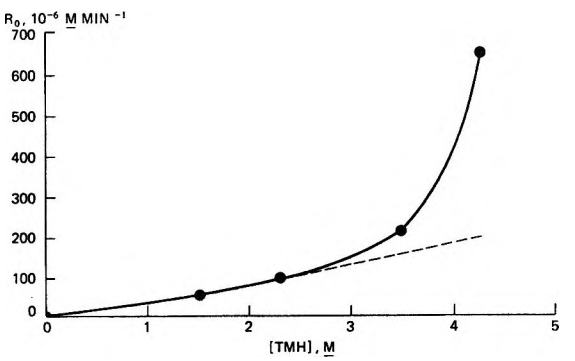


Figure 3.—Hydrocarbon concentration dependence of TMH oxidation.

Table II, and the $R_o/R_i^{1/2}$ [TMH] values were subjected to the usual Arrhenius plot (Figure 2). There

TABLE II
TEMPERATURE DEPENDENCE OF TMH OXIDATION RATE

Expt no.	Temp, °C	$R_o \times 10^6$, M min^{-1} [a]	$R_i \times 10^6$, M min^{-1} [b]	[TMH], M	$R_o/R_i^{1/2}$ [TMH]	$R_o/R_i^{0.38}$ [TMH]
34	80	44	5.01	4.72	4.1	9.53
138	100	72	0.76	4.58	18.2	33.1
59	120	650	13.3	4.46	40.0	100.5

[a] From Table I. [b] Calculated from eq 7 (100 and 120°) or $k_d = 2ek'_d$ [ADC] (80°); k_d for *tert*-Bu_2O_2 = 3.66×10^{-5} min^{-1} (100°)[8] and 4.67×10^{-4} min^{-1} (120°);[8] k'_d for ADC = 4.97×10^{-4} min^{-1} (80°).[7]

is some scatter, but the visually determined "best line" has a slope which corresponds to an activation energy of 16.5 kcal/mol, which appears to be too large. Correction of the rates to a 0.38 power dependency in R_i removes most of the scatter (actually curvature), but the line retains the same slope. For the closely related 2,4-dimethylpentane, a value for $E_p - {}^1/_2E_t$ of 10.7 kcal/mol was reported;[3] and for the simplest system, isobutane, the reported value was 12 kcal/mol.[9] For most systems, the value of E_p alone is not higher than 10 kcal/mol.[10] Measurement of the absolute value of the propagation rate constant for TMH at different temperatures indicated a E_p of only 9.1 kcal/mol.[1] It appears that there was a second source of initiation, either a direct thermal initiation or very early hydroperoxide decomposition, which was not accounted for in estimating composite rate constants in Table II.

Experiment 147 with neat TMH and no initiator at 120° indicated that thermal initiation began immediately and that the initiation rate rapidly accelerated with the consumption of oxygen, presumably as a result of hydroperoxide decomposition. Therefore, it seems probable that the earliest measurable rates of the experiments with di-*tert*-butyl peroxide present were enhanced by either thermal initiation or autocatalysis.

The effect of benzene dilution of TMH oxidation mixtures was twofold. First, the apparent initial oxidation rate decreased rapidly when a small amount of benzene was added; then it apparently became proportional to the TMH concentration. A plot of R_o *vs.* TMH concentration is shown in Figure 3. The second effect of benzene dilution of TMH oxidation mixtures was on autocatalysis. In experiment 59, with pure TMH, the oxidation rate accelerated with conversion and the final rate was 50% higher than the initial rate. In experiment 144, where the TMH concentration was reduced by only 21%, no autocatalysis was observed and the final rate equaled the initial rate. The inhibition of autocatalysis by benzene dilution was noted,[7] but not explained. Simple preservation of the hydroperoxide is not the answer, since hydroperoxide yields progressively decreased with increased benzene dilution of the TMH. The reduced hydroperoxide yield may result partly from low kinetic chain lengths at the highest benzene dilutions.

Products of TMH Oxidation.—It was initially hoped that the oxidation of TMH would be sufficiently similar to that of 2,4-dimethylpentane so that an extension of Mill[4] and Montorsi's kinetic analysis could be used in this study. The difficulties encountered in the product analysis seem to obviate this possibility. First, at no time during the oxidation was the hydroperoxide yield (relative to oxygen absorbed) greater than ~80%. Hydroperoxide yields of 2,4-dimethylpentane oxidations were greater than 90% and were relatively insensitive to conversion (the hydroperoxide yields were nearly 90% at 10–15% conversion).[3] TMH, in contrast, gave the highest hydroperoxide yield at less than 1% conversion and the yield dropped sharply to 58% at 4% conversion. The yield of carboxylic acid rose as per cent conversion rose, which may have been the result of attack on the hydroperoxide or accelerated thermal decomposition.

Another surprising factor was the large preponderance of the trihydroperoxide with only small amounts of mono- and dihydroperoxide present at any time. The relative amounts of mono-, di-, and trihydroperoxide were not appreciably changed by benzene dilution, except that more unidentified side products were formed, perhaps at the expense of the trihydroperoxide.

The most disconcerting part of the product analysis was the amount of alcohols found compared to the amount of hydroperoxide titrated. Thus, for experiment 62, the theoretical amount of hydroperoxide associated with the alcohols found was 3(0.14) + 2(0.02) + 1(0.02) = 0.48 mmol, but the actual amount titrated was 0.79 mmol. For experiment 59, the values were 0.62 mmol (theoretical) *vs.* 0.91 mmol (actual). Before the glpc responses were calibrated, it appeared that alcohol yields satisfactorily matched the hydroperoxide titre, but repeated glpc experiments with weighed alcohols and internal standard (dimethyl succinate) showed that the alcohol shortages were real.

(9) D. L. Allara, T. Mill, D. G. Hendry, and F. R. Mayo, *Advan. Chem. Ser.*, **76**, 40 (1968).
(10) D. G. Hendry, *J. Amer. Chem. Soc.*, **89**, 5433 (1967).

The triphenylphosphine reduction procedure was changed in experiment 138 to include 1.5 hr of reaction on a steam bath prior to the distillation to concentrate the products. This procedure apparently further reduced the yield of triol relative to titrated hydroperoxide. At this point, one can only speculate that either the triphenylphosphine reduction was inefficient, with some hydroperoxide being converted to products other than the expected alcohols, or the unidentified products of the glpc trace corresponded to hydroperoxidic products with more than one hydroperoxide group per mole of the unidentified materials.

The quantity listed in the "other" column of Table I is an estimation of the material corresponding to the area of approximately 12 peaks in the chromatograph trace. For neat TMH, only one of these unidentified peaks had substantial area (less area than that of the diol). Elution time of this peak was between those of the diol and triol, and its area seemed to increase as product solutions were allowed to stand at room temperature. Whatever the products of the TMH hydroperoxide decomposition were, some apparently were low molecular weight and were obscured by the large peak of unreacted TMH in the glpc analysis.

The last two experiments (130 and 133) of Table I were attempts to change the product ratios by adding an agent more active in transfer than the TMH substrate. Tetralin hydroperoxide (0.07 M), which is a very efficient transfer agent for peroxy radicals,[11] did not prevent the trihydroperoxide from becoming the major product of the oxidation, although the relative yields of mono- and dihydroperoxides were increased. Cumene had scarcely any effect on the product ratios, although the amount of cumyl alcohol detected indicated substantial participation of cumene in the oxidation. The experiment with tetralin hydroperoxide resulted in a good balance of the net hydroperoxide formed and the yields of TMH alcohols, but the experiment with cumene again resulted in an alcohol shortage [0.75 mmol of OH (theoretical) *vs.* 1.09 mmol of O_2H (actual)].

From Scheme I and the data of Table I qualitative conclusions can be made regarding the relative values of some of the rate constants involved. In Scheme I, the rate constants k_I and k_{II} include include the sum of the steady-state concentrations of all the peroxy radicals of the system. Since the intention is to form ratios of rates of formation of products, this steady-state sum need not be explicitly determined. Also, it was assumed that the alkyl radicals formed were quickly scavenged by oxygen and did not enter into propagation reactions. Then the steady state equations for the peroxy radical intermediates are as follows.

$$\frac{d[4]}{dt} = k_I[TMH] - k_i[4][TMH] - k_r[4] = 0 \quad (5)$$

$$\frac{d[5]}{dt} = k_{II}[TMH] - k_2[5][TMH] - 2k_r[5] = 0 \quad (6)$$

$$\frac{d[7]}{dt} = k_e[8] + k_r[4] - (k_3[TMH] + k_r + k_e)[7] = 0 \quad (7)$$

$$\frac{d[8]}{dt} = k_e[7] + 2k_r[5] - (k_3[TMH] + k_e)[8] = 0 \quad (8)$$

$$\frac{d[10]}{dt} = k_r[7] - k_4[TMH][10] = 0 \quad (9)$$

These five independent equations and five unknowns can be solved directly, but the algebraic expressions become complicated. However, substantial simplification results from the use of the product analyses which indicated $k_4 \gg k_i$ [TMH] (i = 1, 2, 3, 4); that is, intramolecular propagation is favored over intermolecular transfer. The steady state concentrations are

$$[4] = \frac{k_I[TMH]}{k_r} \quad (10)$$

$$[5] = \frac{k_{II}[TMH]}{2k_r} \quad (11)$$

$$[7] = \frac{k_r[4] + k_e[8]}{k_r + k_e} = \frac{(k_{II} + k_I)[TMH]}{k_r} \quad (12)$$

$$[8] = \frac{2k_r[5] + k_e[7]}{k_e} = \frac{k_{II}[TMH]}{k_e} + \frac{(k_{II} + k_I)[TMH]}{k_r} \quad (13)$$

$$[10] = \frac{k_r[7]}{k_4[TMH]} = \frac{(k_{II} + k_I)}{k_4} \quad (14)$$

The rates of diol and triol formation are

$$\frac{d(11)}{dt} = k_3[TMH]([7] + [8]) \quad (15)$$

$$\frac{d(12)}{dt} = k_4[TMH][10] \quad (16)$$

so that the ratio of their rates of formation is

$$\frac{d(11)}{d(12)} = \frac{k_3([7] + [8])}{k_4[10]} = \frac{k_3[TMH]}{(k_I + k_{II})}\left[\frac{2(k_I + k_{II})}{k_r} + \frac{k_{II}}{k_e}\right] \quad (17)$$

If it is assumed that $k_I = 2k_{II}$ and that $k_e \gg k_r$ (not an unreasonable assumption based on rates reported for analogous intermolecular processes[12]), then eq 17 becomes

$$\frac{d(11)}{d(12)} = \frac{2k_3[TMH]}{k_r} \quad (18)$$

Thus, from the data of experiment 62, a typical value for the ratio of intermolecular to intramolecular propagation would be

$$\frac{k_3}{k_r} = \frac{[d(11)/d(12)]}{2[TMH]} = \frac{[0.02/0.14]}{(2)(4.6)} = 0.015\,M^{-1} \quad (19)$$

For 2,4-dimethylpentane, where only one competition exists between intermolecular (k_p) and intramolecular (k_r) propagation, a value of $k_p/k_r = 0.013$ was reported; this is in unexpectedly good agreement with the TMH results. The small difference of the values is in the right direction but of insufficient magnitude to clearly indicate that the dihydroperoxide of TMH maintains high stability relative to the trihydroperoxide. The data of Table I and the reported results for 2,4-dimethylpentane[4] indicate little or no temperature dependence for the k_i/k_r ratios.

Conclusions

Like 2,4-dimethylpentane, TMH preferentially oxidizes by an intramolecular propagation reaction. The intramolecular propagation is, in fact, much faster than the intermolecular transfer reaction, and very reactive transfer agents are required to intercept the intramolecular reaction. (The intramolecular prop-

(11) K. U. Ingold, *Accounts Chem. Res.*, **2**, 1 (1969).

(12) J. A. Howard, W. J. Schwalm, and K. U. Ingold, *Advan. Chem. Ser.*, **75**, 6 (1967).

agation reaction appears to be general for 1,3,5-methyl substituted alkanes.) These results may be relevant to the polypropylene stabilization problem, where it is necessary to interrupt the intramolecularly propagated oxidation of a 1,3,5...substituted polymer chain with an inhibitor. In the viscous polymer system, collisions between inhibitor and polymer are greatly restricted, and it is surprising that low levels of inhibitor are effective.

As the number of intramolecularly situated hydroperoxy groups in the product increase, significant differences in the oxidation system occur. Neat isobutane[9] and 2,4-dimethylpentane[4] oxidize with little or no autocatalysis, and hydroperoxide yields are regularly greater than 90% of consumed oxygen. Neat TMH oxidizes with substantial autocatalysis (at 120°) which is easily inhibited with a small quantity of benzene, and hydroperoxide yields are approximately 70%. Moderately concentrated benzene solutions of polypropylene (up to 3.98 *M* in monomer units) oxidize with some autocatalysis,[13] and the hydroperoxide yield at 1% conversion is ~40%. Apparently the propensity of the hydroperoxides to decompose is related to the number of hydroperoxide groups at adjacent positions and increases significantly as the number of groups in the cluster increases.

Experimental Section

Materials.—2,4,6-Trimethylheptane (99% pure) was purchased from Chemical Samples Co., Columbus, Ohio. It was passed over neutral alumina just prior to use. Eastman reagent grade cumene was carefully fractionated [bp 153° (733.4 mm)] to remove an impurity detected by glpc. Tetralin hydroperoxide was synthesized and purified by a reported procedure.[14] 1,1′-Azodicyclohexanecarbonitrile obtained from Chemical Procurement Laboratories was recrystallized from acetone–methanol. Di-*tert*-butyl peroxide (*tert*-Bu_2O_2) (99% pure) was purchased from Wallace and Tiernan, Inc., Lucidol Div. "Chromatoquality" benzene was purchased from Matheson Coleman and Bell. Eastman reagent grade triphenylphosphine was sublimed before use. 2,4,6-Trimethyl-1,6-heptadien-4-ol was purchased from Chemical Samples Co.

Of the five monohydric alcohols, diols, and triols expected as oxidation products (following reduction[15] of the corresponding hydroperoxides with triphenylphosphine), only the two monohydric alcohols have been described previously. All five alcohols were synthesized for use as glpc standards.

2,4,6-Trimethyl-4-heptanol.—2,4,6-Trimethyl-1,6-heptadien-4-ol (10 g) was hydrogenated at room temperature in 50 ml of ethanol with 1 g of 5% Pd on charcoal catalyst until no more hydrogen was adsorbed. Filtration and distillation of the ethanol solvent left an oil (2,4,6-trimethylheptanol) which distilled at 84° (23 mm) [lit.[16] bp 86–87° (26 mm)]. The nmr spectrum of the product confirmed the proposed structure.

2,4,6-Trimethyl-2-heptanol.—4,6-Dimethyl-2-heptanone [bp 107–108° (101 mm)] was isolated in 97% purity (as measured by glpc) from technical diisobutyl ketone by careful fractionation. The structure of the distillate was confirmed by nmr. The dimethylheptanone (20 g, 0.152 mol) was treated with excess methylmagnesium bromide in diethyl ether. Removal of the ether from the dried product solution left an oil which distilled at 60° (3 mm) [lit.[17] bp 80° (25 mm)]; yield was 18 g (75%). An nmr spectrum confirmed the structure.

2,4,6-Trimethyl-2,4-heptanediol.—This material was synthesized from ethyl 3,5-dimethyl-3-hydroxyhexanoate, which was prepared by a Reformatsky reaction according to the procedure of Surzur.[18] Methyl isopropyl ketone, ethyl bromoacetate, and zinc were treated as described by the procedure[18] to give the hydroxy ester in 52% yield [lit.[18] bp 101° (76 mm)]. The hydroxy ester (20 g, 0.106 mol) was treated with excess methylmagnesium bromide in ether by stirring at reflux overnight. The usual work-up procedure with dilute sulfuric acid afforded an ether solution of product which, after drying and distillation, yielded 8 g (43%) of diol: bp 118–123° (0.5 mm); ir max 3350, 2900–3000, 1470, 1415, 1380, 1185, 1042, 870, and 759 cm^{-1}; nmr ($CDCl_3$) δ 0.9 (d, 6, terminal methyl protons), 1.1–1.5 (m, 11), 1.65 (d, 2, center methylene protons), 4.35 (d, 2, hydroxy protons), and one proton (isopropyl) not resolved.

2,4,6-Trimethyl-2,6-heptanediol.—3-Methylglutaric acid obtained from Columbia Organic Chemical Co. was converted to the diethyl ester, bp 94–95° (3.1 mm). Reaction of 5 g (0.025 mol) of the ester with an excess (~0.3 mol) of methylmagnesium bromide in ether yielded ~5 g of a crude oil. The oil partially crystallized on standing, but could not be distilled without dehydrating to an unsaturated alcohol. No solvent was found which would satisfactorily serve for recrystallization of the crude product, but, after long-term sublimation of the crude product, white crystals were obtained: mp 64–66°; ir max 3240, 2970–2850, 1380, 1367, 1185, 1064, 979, 952, 932, 891, 858, and 774 cm^{-1}; nmr ($CDCl_3$) δ 1.00 (d, 3, center methylene protons), 1.20 (s, 12, terminal methyl protons), 1.3–2.0 (m, 5, secondary and tertiary protons), 3.4 (s, 2, hydroxy protons).

2,4,6-Trimethyl-2,4,6-heptanetriol.—2,6-Dihydroxy-2,6-dimethyl-4-heptanone (5 g, 0.0333 mol) obtained from K & K Laboratories, Inc) was treated with an excess of methylmagnesium bromide in ether by refluxing overnight. Work-up of the reaction mixture was accomplished by the cautious addition of 1 *N* sulfuric acid, followed by continuous ether extraction of the aqueous phase. Concentration of the dried ether solution of products gave a heavy oil (~5 g) which could not be crystallized. Analysis of the oil by glpc (20% silicone SE-30 on Chromosorb P, 6 ft × 0.25 in.) indicated that some of the starting ketone was present, but that a major product (with the longest retention time in the trace) constituted about $^2/_3$ of the total. This major product was isolated by repetitive preparatory glpc in sufficient quantity for spectral analysis and use as an authentic sample of triol to add to product solutions from TMH oxidations: ir max 3350, 2980, 2940, 1470, 1415, 1380, 1192, 1060, 935, 867 and 771 cm^{-1}; nmr ($CDCl_3$) δ 1.2–1.4 (d, 12, terminal methyl protons), 1.43 (s, 3, center methyl protons), 1.73 (m, 4, methylene protons), 5.08 (s, 3, hydroxyl protons).

Oxidation Procedure.—Most of the details of autoxidizing liquid samples have been described.[7] Solutions of the TMH, initiator, and any cooxidant were made in the reaction bulbs. Normally, ~20 ml of solution was prepared in bulbs of ~31 ml capacity. Reaction progress was followed and the rates were calculated as described.[7] After the reaction mixture was cooled, the gas vented, and the bulb detached, 5 ml of propyl acetate was added to redissolve a second phase which separated when cooled.

Analysis.—Two small portions of the product solution were titrated[5] for hydroperoxide. Based on the titration results, a 10–20% excess of triphenylphosphine was added to the reaction mixture and allowed to stand for at least 1 hr to ensure complete reduction of the hydroperoxides.

Direct glpc analysis of the reduced solution did not give well-resolved separations; so the products were concentrated by removing most of the unreacted TMH *in vacuo* (5 mm at 40°). The pot residue was transferred quantitatively to a sample vial with a small amount of acetone; a known amount of dimethyl succinate or eicosane was added as an internal standard, and the solution was analyzed by glpc (5% nitrile–silicone XE-60 on Chromosorb Z, 6 ft × 0.125 in., temperature 60–200°, Aerograph 600 D). The glpc investigation of the distillate indicated that no significant amount of products was carried over. The response of the chromatograph to the 2,4,6-trimethyl-2,4-heptanediol and 2,4,6-trimethyl-2,4,6-heptanetriol relative to

(13) D. E. Van Sickle, paper presented at the 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 12–17, 1971.

(14) A. Robertson and W. A. Waters, *J. Chem. Soc.*, 1578 (1948).

(15) D. B. Denney, W. F. Goodyear, and B. Goldstein, *J. Amer. Chem. Soc.*, **82**, 1393 (1960).

(16) A. D. Petrov, V. I. Sushchinskii, and L. D. Konoval-chikov, *Zh. Obshch. Khim.*, **25**, 1566 (1955); *Chem. Abstr.*, **53**, 4474*g* (1956).

(17) E. A. Braude and J. A. Coles, *J. Chem. Soc.*, 1524 (1952).

(18) J. M. Surzur, *Bull. Soc. Chim. Fr.*, 1625 (1956).

the internal standard, was determined and the appropriate correction factor was applied. This correction factor (same for both polyols) was assumed to be applicable to the unidentified peaks in the glpc trace. The 2,4- and 2,6-diols eluted simultaneously by the chromatographic technique used in this study.

Registry No.—**3**, 2613-61-8; 2,4,6-trimethyl-2,4-heptanediol, 33070-42-7; 2,4,6-trimethyl-2,6-heptanediol, 33070-43-8; 2,4,6-trimethyl-2,4,6-heptanetriol, 33070-44-9.

Lithium–Ammonia Reduction of Benzaldehydes to Toluenes

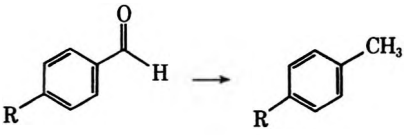
STAN S. HALL,* ANNE P. BARTELS, AND ARLENE M. ENGMAN[1]

Department of Chemistry, Rutgers University, Newark, New Jersey 07102

Received August 16, 1971

Two methods are reported for the reduction of benzaldehydes to toluenes in lithium–ammonia solutions. By these methods *p-tert*-butylbenzaldehyde, *p*-isopropylbenzaldehyde, *p*-methylbenzaldehyde, and benzaldehyde were reduced to *p-tert*-butyltoluene, *p*-cymene, *p*-xylene, and toluene, respectively. Both methods take advantage of good proton sources to minimize a serious competitive reaction which leads to dimers. Mechanistic implications are discussed.

The only reported reduction of an aldehyde in metal–ammonia solutions is that of vanillin to vanillyl alcohol plus a dimer in potassium–ammonia.[2] Presumably the reduction of aldehydes in liquid ammonia has been avoided because aldehydes readily condense with ammonia.[3] We have found that aromatic aldehydes are amenable to metal–ammonia conditions and wish to describe two useful methods for their reduction to toluenes.



R = *tert*-C_4H_9, *iso*-C_3H_7, CH_3, H

Recently we reported conditions for the reduction of aromatic ketones to aromatic hydrocarbons in lithium–ammonia (THF) solutions.[4] Extensions of this work to aromatic aldehydes[5] led to the following observations: (1) the aromatic aldehydes were reduced substantially faster than aromatic ketones; (2) trace amounts of cobalt had no noticeable reduction rate enhancement effect as was observed with aromatic ketones; and (3) aromatic aldehydes dimerize much more readily than aromatic ketones.[6]

The formation of dimers made the method inutile for our purposes as a synthetic reaction and consequently a modified method was sought which would minimize their formation. Since dimers had not been observed in the reduction of benzyl alcohols when subjected to these conditions,[7] thus excluding the possibility of dimer formation from the benzyl radical **5**, we assumed the ketyl radical **2a** to be the source of dimers.[8,9] It was reasoned that if the ketyl radical **2b** would be formed in the presence of a good proton source, such as *tert*-butyl alcohol or ammonium chloride, it might be quickly protonated forming the alkoxy radical **3**, which in turn would be rapidly reduced to the benzyl alkoxide **4**. The net effect should be a substantial decrease in the amount of dimer formed. Following this presupposition, two useful methods were developed and are described. The product toluene normally represented more than 90% of the chromatographable material and was usually isolated pure in at least 80% yield using either method.

Method A involves the addition of a solution of the benzaldehyde and *tert*-butyl alcohol in THF to a refluxing lithium–ammonia solution, followed by an ammonium chloride quench. Substituting sodium benzoate[10] for the ammonium chloride yielded mainly the toluene along with lesser amounts of the benzyl alcohol and aldehyde (*ca.* 5:1.5:1) indicating that the ammonium chloride quench is necessary to complete the reduction.

(1) National Science Foundation Undergraduate Research Participant, summer 1971.

(2) K. Freudenberg, W. Lautsch, and G. Piazolo, *Chem. Ber.*, **74**, 1879 (1941).

(3) (a) R. L. Augustine, Ed., "Reduction," Marcel Dekker, New York, N. Y., 1968, p 116; (b) H. Smith, "Organic Reactions in Liquid Ammonia. Chemistry in Nonaqueous Ionizing Solvents," Vol. I, Part 2, Wiley, New York, N. Y., 1963, pp 123 and 216.

(4) S. S. Hall, S. D. Lipsky, F. J. McEnroe, and A. P. Bartels, *J. Org. Chem.*, **36**, 2588 (1971).

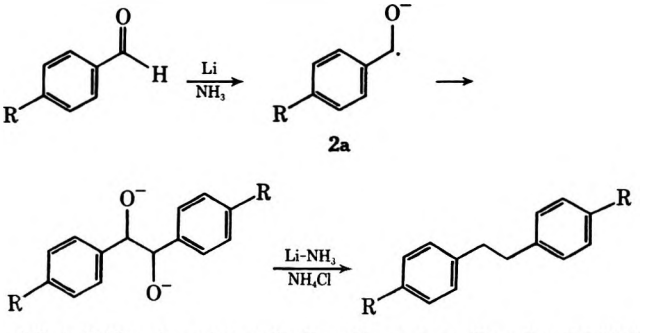
(5) The benzaldehyde in THF was added slowly (*ca.* 20 min) to a lithium–ammonia (THF) solution. After 20 min at reflux the mixture was cautiously quenched with excess ammonium chloride.

(6) The following interesting toluene/aromatic hydrocarbon dimer (2) ratio was observed for *p-tert*-butylbenzaldehyde, *p*-isopropylbenzaldehyde, *p*-methylbenzaldehyde, and benzaldehyde, respectively: 82/18, 77/23, 60/40, and 56/44. After analysis by glc the monomer–dimer aromatic hydrocarbon mixture was eluted from an alumina column with petroleum ether (bp 38–58°) and then distilled apart at reduced pressures. Spectral data (ir, nmr, and mass spectra) indicated the major dimer to be a 1,2-diarylethane. Perhaps the most revealing were the mass spectra. For example, 1,2-*p*,*p*'-dicumylethane from *p*-isopropylbenzaldehyde, *m/e* (rel intensity) 133 (100), 266 (8, M+). In addition, the major dimer from the reduction of benzaldehyde was compared with an authentic sample of 1,2-diphenylethane.

(7) (a) S. S. Hall, S. D. Lipsky, and G. H. Small, *Tetrahedron Lett.*, 1853 (1971); (b) G. H. Small, unpublished results.

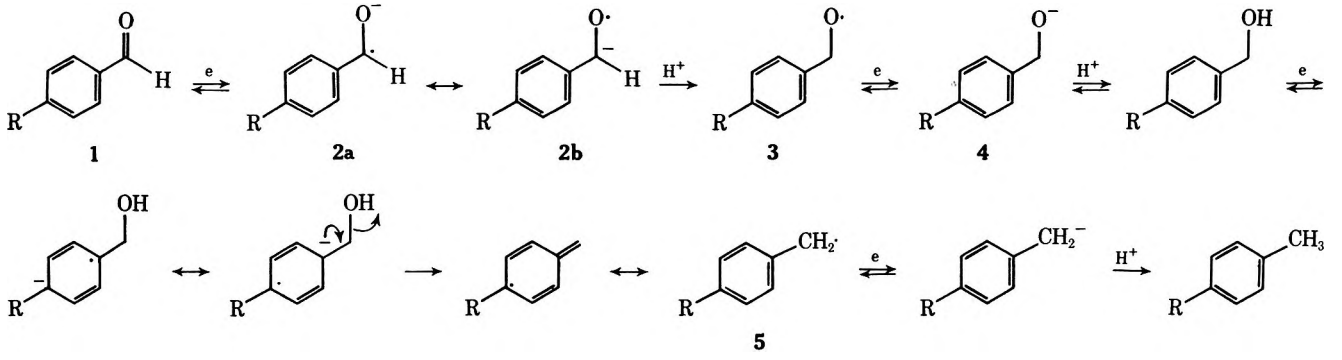
(8) (a) W. E. Bachmann, *J. Amer. Chem. Soc.*, **55**, 1179 (1933); (b) C. B. Wooster, *ibid.*, **59**, 377 (1937).

(9) We assumed the major dimer to be formed according to the following general scheme *via* a bimolecular reduction.

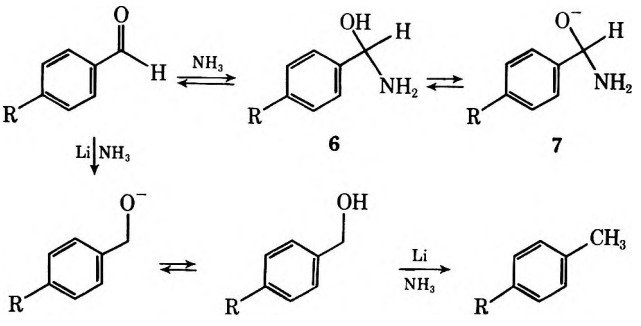


(10) A. P. Krapcho and A. A. Brothner-By, *J. Amer. Chem. Soc.*, **81**, 3658 (1959).

SCHEME I



Method B was designed to take advantage of the condensation reaction between the aldehyde and ammonia to form a hydrobenzamide.[3] The general procedure is to allow the aldehyde to react with the ammonia, then add lithium and quench the mixture with ammonium chloride. When sodium benzoate[10] was used as the quenching agent a 1:1 mixture of the toluene and the benzaldehyde was formed.[11] This result suggests that in liquid ammonia there is an equilibrium between the free aldehyde and hydrobenzamide 6. When the lithium is added the free aldehyde is quickly reduced to the alkoxide, protonated by the hydrobenzamide 6, and then is reduced further to the aromatic hydrocarbon. The resulting anion 7 of the hydro-



benzamide probably resists reduction until the ammonium chloride is added regenerating the aldehyde, which is then rapidly reduced to a toluene before all the lithium is destroyed. In contrast, quenching with sodium benzoate would destroy the excess reducing agent and then during normal work-up the benzaldehyde would be regenerated.

Although both methods are satisfactory, we tend to favor method A for the reduction of benzaldehyde and alkylbenzaldehydes since less high molecular weight material seems to be formed (see Experimental Section).

Our suggestions for the mechanism of the reduction are outlined in Scheme I. The mechanism incorporates the reduction of a carbonyl group to an alcohol[12] and a benzyl alcohol to a toluene[13] and is analogous to that proposed for the reduction of aromatic ketones to aromatic hydrocarbons.[4]

(11) Prolonged equilibration of the aldehyde in liquid ammonia before the addition of lithium did not alter this result.

(12) See ref 3a, pp 97–98.

(13) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, pp 74–75.

Experimental Section[14]

Lithium–Ammonia Reduction.—Precautions for the exclusion of impurities (moisture, air, peroxides, contaminate metals, or metal salts) were scrupulously observed. All reductions were carried out under a static nitrogen (prepurified) atmosphere and anhydrous ammonia was distilled into the reaction vessel. Tetrahydrofuran (THF) was filtered through an alumina column, and then refluxed and distilled from $LiAlH_4$ just prior to use. Lithium wire (0.01% Na, Ventron Corp.) was wiped free of oil and washed with petroleum ether (bp 38–58°) immediately before use. All product toluenes gave satisfactory spectral and analytical data; and in the reductions of benzaldehyde, *p*-methylbenzaldehyde, and *p*-isopropylbenzaldehyde, the products were also compared with authentic samples of toluene, *p*-xylene, and *p*-cymene, respectively. The reduction of *p*-isopropylbenzaldehyde and *p-tert*-butylbenzaldehyde are described to illustrate each method.

Method A. *p*-Cymene.—To a mixture containing 20 ml of ammonia, 10 ml of THF, and 175 mg (25 mg-atoms, 10 pieces) of lithium was added dropwise (*ca.* 20 min)[15] a solution of 0.79 g (5 mmol) of *p*-isopropylbenzaldehyde and 0.46 g (6.25 mmol) of *tert*-butyl alcohol in 10 ml of THF. Almost immediately the excess lithium was consumed by the rather rapid addition (*ca.* 5 min) of excess ammonium chloride (*ca.* 5 g)[16] and the ammonia was allowed to evaporate. After the residue had been partitioned between aqueous NaCl and Et_2O, the organic layer was dried and concentrated. Analysis by glc indicated a 98% yield of *p*-cymene and a 2% yield of dimers (2). After chromatography (alumina, petroleum ether) a pale yellow liquid (0.60 g, 90%) was isolated which was identical with an authentic sample of *p*-cymene.

Method B. *p-tert*-Butyltoluene.—To a solution containing 20 ml of ammonia and 10 ml of THF was added a solution of 0.81 g (5 mmol) of *p-tert*-butylbenzaldehyde in 10 ml of THF. After 30 min 210 mg (30 mg-atoms, 12 pieces) of lithium was added. Once the dark blue solution was established,[17] excess ammonium chloride (*ca.* 4.5 g) was rather rapidly added (*ca.* 5 min)[16] and the ammonia was allowed to evaporate. After the residue had been partitioned between aqueous NaCl and Et_2O, the organic layer was dried and concentrated. Analysis by glc indicated a 94% yield of *p-tert*-butyltoluene along with a 2% yield of dimers (2) and a 4% yield of unknown high molecular weight material (1 major and 2 minor peaks). After chromatography (alumina, petroleum ether) a pale yellow liquid (0.66 g,

(14) Spectral measurements were determined with the following instruments: ir, Beckman Model IR-10; nmr, Varian Associates Model A-60; mass spectra, Perkin-Elmer Model 270 with a Varian Associates Model 620/i computer attachment. Gas chromatographic analyses (glc) were performed on a Hewlett-Packard Model 5750 research chromatograph (flame detector) using a 6 ft × 1/8 in. 10% silicon gum rubber UCC-W-982 (methylvinyl) on 80–100 Chromosorb W. Separations and purifications were attained on absorption alumina (80–200 mesh) columns. Further purification, for analytical purposes, was accomplished by flash distilling the samples at reduced pressure.

(15) The rate of addition should be slow enough to maintain a dark blue solution.

(16) For a convenient method of adding the quenching agent see ref 4.

(17) We normally waited for *ca.* 20 min, although this length of time does not seem to be necessary.

89%) was isolated: nmr τ 8.71 (s, 9 H), 7.71 (s, 3 H), 2.98 (d, 2 H, J = 8 Hz), 2.77 (d, 2 H, J = 8 Hz); mass spectrum m/e (rel intensity) 39 (21), 40 (21), 41 (42), 77 (16), 91 (26), 93 (26), 105 (50), 133 (100), 148 (20, M^+).

Anal. (flash distilled, 14 mm). Calcd for $C_{11}H_{16}$: C, 89.12; H, 10.88. Found: C, 89.26; H, 10.86.

Registry No.—Lithium, 7439-93-2; ammonia, 7664-41-7; *p*-isopropylbenzaldehyde, 122-03-2; *p*-cymene, 99-87-6; *p-tert*-butyltoluene, 98-51-1; *p-tert*-butyl benzaldehyde, 939-97-9.

Acknowledgments.—The authors are grateful to Miss Rose Marie Luethy and Mr. Paul P. Vallon, Givaudan Corp., Clifton, N. J., for the mass spectra, and to Dr. Franz J. Scheidl, Hoffmann–La Roche Inc., Nutley, N. J., for the microanalyses.

The Origin of the Paramagnetic Species in Lignin Solutions. Autoreduction of 2,6-Dimethoxybenzoquinone and Related Quinones to Radical Anions in Alkaline Solution

J. D. FITZPATRICK AND CORNELIUS STEELINK*[1]

Department of Chemistry, University of Arizona, Tucson, Arizona 85721

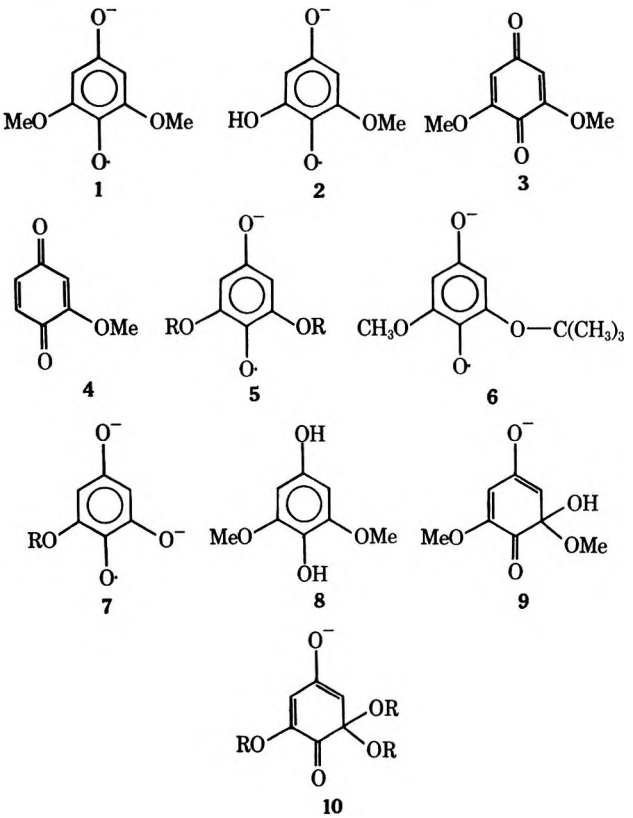
Received July 14, 1971

The lignin model compound, 2,6-dimethoxybenzoquinone (**3**), is spontaneously reduced to stable semiquinone radical anions by alkaline solutions of water or alcohol. This behavior parallels that of hardwood lignins. Rapid replacement of the methoxyl groups by alkoxide ion occurs in alkanolic solvents; steric factors play an important role in this exchange. The primary reaction intermediate appears to be a cyclohexadienone adduct of quinone and nucleophile; its concentration is rate determining. A mechanism for the reaction is proposed.

Lignin, the ubiquitous component of terrestrial plants, has been shown to be paramagnetic.[2-5] The paramagnetism of lignin preparations increases with extent of chemical and enzymatic degradation.[5] Hardwood lignins, which contain a high proportion of 3,5-dimethoxy-4-hydroxyphenyl elements, have a higher spin content than analogous softwood lignins (whose chief structural elements are 4-hydroxy-3-methoxyphenyl groups). Alkali lignins show the highest radical content of all preparations.

When hardwood lignin preparations are dissolved in dilute aqueous base, a paramagnetic species is formed. This has been identified as 2,6-dimethoxy-*p*-benzosemiquinone (**1**).[6] In strong base, a second radical (**2**) appears.[6] All commercial hardwood lignins, such as kraft and Meadol, yield **1** and **2**. Brauns native and Bjorkman hardwood lignins yield low concentrations of **1**, as does Indulin (predominantly a softwood product).

We have found that hot water extracts of commercial alkali lignins contain appreciable amounts of 2,6-dimethoxyquinone (**3**) and small quantities of vanillin, syringaldehyde, and polymeric material. No 2-methoxybenzoquinone (**4**) was found. Native hardwood lignins do not yield any of the above with hot water. However, when refluxed with 1.0 M NaOH in air, they form vanillin, syringaldehyde, and traces of **3**. Since **3** appears to be the sole structural precursor of the paramagnetic species (apparently formed during a Dakin-type cleavage of native lignin during the pulping process),[7] we decided to investigate its behavior in a variety of basic solvents. The behavior of **3** may have relevance for other systems. Redox reactions of **3** have been implicated in plant resistance to fungal attack;[8a] its formation in plants may have arisen by a Dakin cleavage of lignin during attack by oxidases and peroxide.[8b]



1 2 3 4 5 6 7 8 9 10

Results

Reduction of Quinone 3 in Alkanolic Solvents.—When 10^{-3} M solutions of **3** were mixed with anhydrous alkanols and sodium ethoxide, strong esr signals were observed for 2,6-dialkoxybenzosemiquinones (**5**). Sec-

(1) Presented at the 161st National Meeting of the American Chemical Society, Los Angeles, Calif., March 29, 1971.

(2) C. Steelink, *Advan. Chem. Ser.*, **59**, 51 (1966).

(3) C. Steelink, T. Reid, and G. Tollin, *J. Amer. Chem. Soc.*, **85**, 4048 (1963).

(4) T. N. Kleinert, *Tappi*, **50**, 120 (1967).

(5) C. Steelink, *Geochim. Cosmochim. Acta*, **28**, 1615 (1964).

(6) J. D. Fitzpatrick and Cornelius Steelink, *Tetrahedron Lett.*, 5041 (1969).

(7) K. Kratzl, W. Schafer, P. Claus, J. Gratzl, and P. Schilling, *Monatsh. Chem.*, **98**, 891 (1967).

(8) (a) M. E. Mace and T. T. Hebert, *Phytopathology*, **53**, 692 (1967); (b) E. S. Caldwell and C. Steelink, *Biochim. Biophys. Acta*, **184**, 420 (1969).

TABLE I

HYPERFINE SPLITTING CONSTANTS (IN GAUSS) OF SEMIQUINONE ANIONS

Semiquinone	Solvent	Base	A^H_{OR}	A^H_{ring}
2,6-Dimethoxy-*p*-benzosemiquinone (1)	Anhydrous methyl alcohol	0.1 *M* NaOMe	0.75	1.50
2,6-Dimethoxy-*p*-benzosemiquinone (1)	50% *tert*-butyl alcohol in water	0.1 *M* NaOH	0.77	1.50
2,6-Diethoxy-*p*-benzosemiquinone (5)	Anhydrous ethyl alcohol	0.1 *M* NaOEt	0.80	1.60
2,6-Diethoxy-*p*-benzosemiquinone (5)	Anhydrous ethyl alcohol	0.1 *M* NaOH	0.87	1.50
2,6-Diethoxy-*p*-benzosemiquinone (5)	80% Ethyl alcohol–20% water	0.1 *M* NaOH	0.90	1.46
2,6-Diethoxy-*p*-benzosemiquinone (5)	50% Ethyl alcohol–50% water	0.1 *M* NaOH	0.94	1.42
2,6-Diethoxy-*p*-benzosemiquinone (5)	25% Ethyl alcohol–75% water	0.1 *M* NaOH	0.96	1.41
2,6-Diethoxy-*p*-benzosemiquinone (5)	10% Ethyl alcohol–90% water	0.1 *M* NaOH	0.97	1.38
2-Hydroxy-6-ethoxy-*p*-benzosemiquinone (7)	Anhydrous ethyl alcohol	1.0 *M* NaOEt	0.68	2.80, 0.6[a]
2,6-Diisopropyl-*p*-benzosemiquinone (5)	Anhydrous isopropyl alcohol	0.1 *M* NaO-*i*-Pr	0.45	1.65
2,6-Diisopropyl-*p*-benzosemiquinone (5)	50% Isopropyl alcohol–50% water	0.1 *M* NaOH	0.50	1.40
2-Hydroxy-6-isopropoxy-*p*-benzosemiquinone (7)	Anhydrous isopropyl alcohol	1.0 *M* NaO-*i*-Pr	0.40	2.90, 0.15[a]
2-Hydroxy-6-methoxy-*p*-benzosemiquinone (2)	Anhydrous *tert*-butyl alcohol	0.1 *M* NaO-*tert*-Bu	0.60	2.90, 0.28[a]
p-Benzosemiquinone[b]	Anhydrous methyl alcohol	0.1 *M* NaOH		2.40
2-Methoxy-*p*-benzosemiquinone[c]	Water	pH 9.18 buffer	0.85	3.65, 1.95, 0.54

[a] Ring protons not specifically assigned. [b] Included in table as a reference compound. [c] Prepared by dissolving 2-methoxybenzoquinone in buffer. Unstable at higher pH values.

ondary radicals of type **7** appeared soon after mixing in 0.1–1.0 *M* NaOR. The exception to this group of alkanols was *tert*-butyl alcohol; in this case, there was evidence for the transitory existence of radical **6**, which rapidly gave way to radical **2**. At higher concentrations of NaOR, only the secondary radical **7** was observed. Again, the exception was encountered with *tert*-butyl alcohol, which showed only radical **2**. Thus, complete and fast alkoxy exchange occurred within all systems except *tert*-butyl alcohol. The esr results are summarized in Table I.

When NaOH was substituted for the NaOR in the alkanol solvents, only radicals of type **5** were observed for all alcohols except *tert*-butyl alcohol. In the latter case, only radical **1** was observed, indicating that no ether exchange had occurred. The coupling constants for **1** agreed with those reported by Hewgill.[9]

To assess the effect of solvent type on the exchange reaction, we used a variety of aqueous alcohol mixtures. In 50% water–alcohol, quinone **3** yielded radical **5**, identical with that found in 100% alcohol (with the exception of *tert*-butyl alcohol, which gives radical **1**). In this solvent system, complete ether exchange occurred. In an attempt to find the lower limit of alcohol content at which exchange did not occur, we used successively more dilute alcoholic solutions in water. Even at 10% ethanol in water, complete exchange of OEt with OMe took place.

Further studies showed that each alcohol exhibited a threshold value or minimum concentration at which the OR–OMe exchange would occur. This is illustrated in Figure 1. For primary alcohols, a 5% solution of alcohol in water exhibits the presence of both radicals **1** and **5**, a concentration at which partial exchange occurs. With secondary and tertiary alcohols, no exchange was observed and only radical **1** was present.

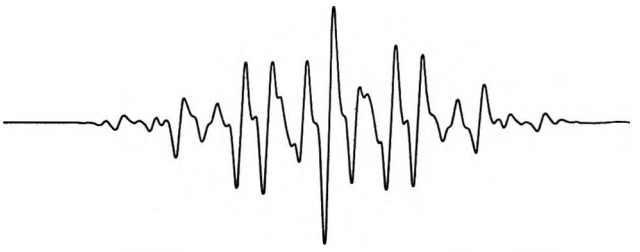


Figure 1.—Esr spectrum of 2,6-dimethoxybenzoquinone in 5% ethanol and 0.10 *M* NaOH. Both radicals **1** and **5** are present.

The effect of solvent polarity on the coupling constants was pronounced. With increasing polarity, there was a regular decrease of the ring proton coupling and an increase of the alkoxyl proton constants. Apparently, semiquinone **5** underwent asymmetric solvation (or hydrogen bonding) to a considerably larger extent than alkyl-substituted benzosemiquinone anions.[10]

In the above reactions, the principal nucleophile appears to be an alkoxide ion, even though the concentration of water and OH^- is much greater. This is not unexpected, since the equilibrium

$$ROH + OH^- \rightleftharpoons RO^- + H_2O$$

(9) F. R. Hewgill and L. R. Mullins, *J. Chem. Soc. B*, 1155 (1969).

(10) T. A. Claxton and D. McWilliams, *Trans. Faraday Soc.*, **64**, 2593 (1968).

contains appreciable amounts of alkoxide ion even at 5% alcohol concentration. A simple calculation[11] for a 5% aqueous solution of a typical alcohol shows that more than 10^{-2} *M* alkoxide is present in solutions containing 0.1 *M* NaOH.

Reduction of Quinone 3 in Aqueous Base. A. Esr Spectra.—When quinone **3** was dissolved in aqueous base, an esr signal was generated. The signal reached a maximum intensity slowly (1–24 hr) depending on pH, and then decayed. At high pH values, a new signal emerged, that of radical **2**. The maximum concentration of semiquinone anion was 10 mol % of the original quinone, as measured against a standard solution of 2,2,6,6-tetramethylpiperidine-1-oxyl. This behavior of quinone **3** parallels that of hardwood lignins in aqueous base.

The intensity of the esr signal is pH dependent. Radicals were generated at pH values as low as 9. At pH 10 and 1×10^{-3} *M* quinone, there appears to be an incubation period of about 10 min before radical **1** signal appears.[12] Thereafter, a slow increase in radical concentration occurs until a maximum is reached. This is followed by a slow decay. At higher pH, the primary radical is supplanted by a secondary radical **2** whose concentration is usually greater than that of the primary radical. Thus, at pH 12.45, radical **1** reached its maximum concentration in 1.0 hr; radical **2** reached its maximum concentration in 4.0 hr. The secondary radical **2** has a longer half-life than the primary. The entire time sequence is shortened at higher pH. At pH 14, the primary radical is not even observed.

The color of the quinone solution changed dramatically when mixed with base. The yellow color of the quinone was instantly discharged on contact with base. Thereafter, the sequence of color changes was colorless–pink–red. At the end of 24 hr, the solution was red-brown. Only 2% of the original quinone **3** was recovered from the red-brown reaction mixture.

The formation of primary and secondary radical species from hydroquinones has been detected by esr spectroscopy.[13,14] The kinetics of formation of radical species from unsubstituted benzoquinone has been studied by optical spectroscopy;[15,16] these studies were based on flow techniques for rapid reactions. Our system appeared to behave by a different mechanism, and take place at a much slower rate. Therefore, our measurements (see below) were made in a static system.

B. Optical Spectra.—In the above, it was shown that hydroxide ion (or alkoxide ion) causes the reduction of quinones as well as displacing the methoxyl group from the ring. To further elucidate the mechanism of this reaction, we found it necessary to examine some of the species in the reaction mixture by ultraviolet and visible spectrophotometry. These studies were restricted to aqueous solutions, since a few observations in ethanolic solution indicated similar behavior to aqueous solutions.

When quinone **3** (1×10^{-3} *M*) was mixed with pH 11 aqueous buffer solution, and the reaction was scanned by ultraviolet spectrophotometry over a period of 3 hr, a set of spectra was obtained as shown in Figure 2. At higher pH values, similar sets of spectra were obtained. In these cases, the 245 nm band was much more intense with respect to the 210 and 300 nm bands, as well as in absolute intensity. The 300 nm band was shifted toward higher wavelengths at higher pH values.

The existence of two isobestic points (at 227 and 278 nm) indicated that a single product, or a number of products with identical chromophores, were formed from the decay of the 245 nm band. Since the reduction of quinone **3** could yield semiquinone anion radicals, hydroquinone anions, and dianions, as well as the quinone itself, we decided to determine the absorption maxima of some of these species. The maxima are recorded in Table II.

TABLE II
ABSORPTION MAXIMA OF VARIOUS COMPOUNDS IN WATER SOLUTION

Compd	λ_{max}, nm	ϵ
2,6-Dimethoxybenzosemiquinone (in pH 12, buffer)	210	(110)[a]
	315	(40)[a]
	430	(5.8)[a]
	550	(0.90)[a]
2,6-Dimethoxyquinone	288	8.9×10^3
	395	3.8×10^2
2,6-Dimethoxyhydroquinone	284	3.9×10^3
2,6-Dimethoxyhydroquinone dianion (in 0.01 *M* NaOH and $Na_2S_2O_4$)	210	1.4×10^4
	318	4.0×10^3

[a] Relative intensities.

The spectrum of radical **1** was obtained by two methods. (1) A solution of hydroquinone **8** in base was oxidized with oxygen. The rates of increase in signal intensity of the esr spectrum were compared with the increase of peaks in the optical spectrum, run under identical conditions. (2) Equimolar mixtures of quinone **3** and hydroquinone **8** were placed in aqueous base. A very strong stable spectrum was observed in the optical and esr regions. Peaks at 550 (weak), 427, 317 (broad), and 210 nm were recorded and are in accordance with values reported for similar systems.[17,18] The anion of hydroquinone **8** was prepared in basic solution containing sodium hydrosulfite. It was noted (Table II) that the broad peak at 317 nm could arise from all three species: **1**, **3**, and **8** anions.

It is obvious that the 245 nm band is not characteristic of any of the compounds listed in Table II. A first-order plot was obtained for the decay of this band over a 3-hr period. The rate constant was independent of pH over a broad range (Table III). At pH values above 13, however, the constant did increase slightly. When the concentration of quinone was varied over a twofold range, rate data were obtained which were consistent with first-order kinetics. At pH values of 10 or less, the reaction was too slow to permit

(11) E. J. King, "Acid Base Equilibria," Topic 15 in the International Encyclopedia of Physical Chemistry and Chemical Physics, Macmillan, New York, N. Y., 1965, p 284.

(12) This may be due to scavenging of the initially formed radical by dissolved oxygen which had not been completely removed.

(13) J. Pilar, I. Buben, and J. Pospisil, *Tetrahedron Lett.*, 4303 (1968).

(14) T. J. Stone and W. A. Waters, *J. Chem. Soc.*, 1488 (1965).

(15) M. Eigen and P. Matthies, *Chem. Ber.*, **94**, 3309 (1961).

(16) M. Sasaki, *Nippon Kagaku Zasshi*, **90**, 1231 (1969).

(17) Y. Harada and H. Inokuchi, *Mol. Phys.*, **8**, 265 (1963).

(18) H. Diebler, M. Eigen, and P. Mathies, *Z. Electrochem.*, **65**, 634 (1961).

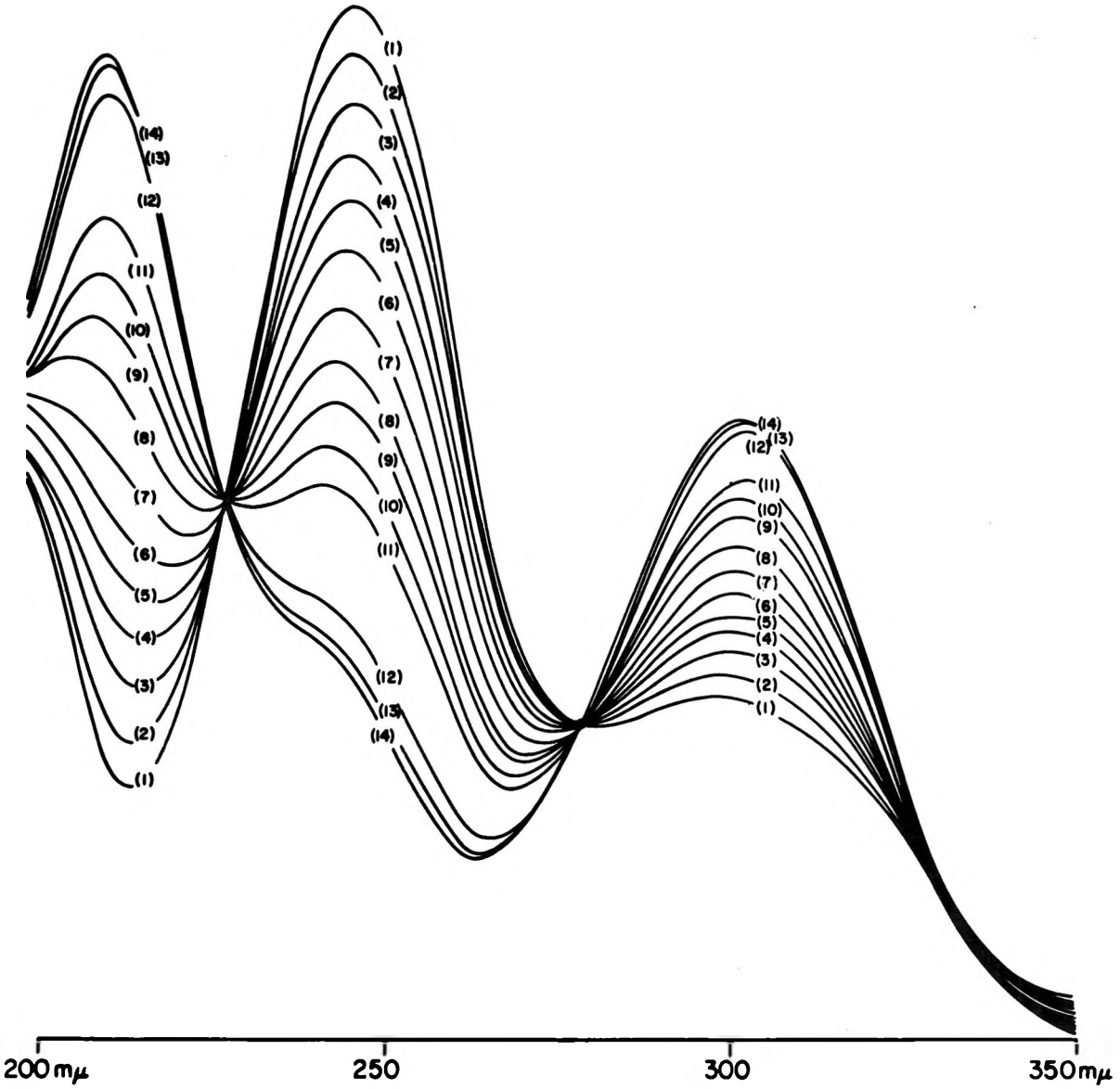


Figure 2.—Ultraviolet absorption spectrum of 2,6-dimethoxybenzoquinone (1×10^{-3} *M*) in 0.01 *M* NaOH. Time after mixing quinone **3** and base: (1) 2 min, (2) 7 min, (3) 12 min, (4) 17 min, (5) 22 min, (6) 28 min, (7) 37 min, (8) 47 min, (9) 57 min, (10) 67 min, (11) 77 min, (12) 137 min, (13) 177 min, (14) 197 min.

TABLE III
FIRST-ORDER RATE CONSTANTS

Species	Initial concn of quinone, *M*	Solvent	*k*, min^{-1}
245 nm band (decay)	7.5×10^{-4}	pH 12, buffer	0.022
	5×10^{-4}	pH 12, buffer	0.022
	1×10^{-3}	0.01 *M* NaOH	0.015
	1×10^{-3}	0.001 *M* NaOH	0.012
Radical 1 (formation)	1×10^{-3}	pH 9.18, buffer	0.011
	1×10^{-3}	0.01 *M* NaOH	0.008
	1×10^{-3}	pH 12.45	0.006

detectable changes over a 30-min scan, although small esr signals were present. At low pH values, the quinone spectrum was dominant.

During the decrease of the 245 nm band, increases were observed for bands at 210, 280–315, and 500 nm. These bands could represent one or more phenolate anions, dianions, or radical anions. They did not lend themselves to ready kinetic analysis.

On the basis of its spectral characteristics, we assigned the structure **9** to the species absorbing at 245 nm. Adducts such as **9** have been reported for quinones;[15,19] cyclohexadienone compounds have absorption maxima in this spectral region.[20–23]

The 210 nm band could represent phenolate anion or anion radical; the broad band at 280–315 nm could contain contributions from phenolate anion, radical anion, and quinone. The band at 550 nm probably represents decay products of the semiquinone radical. None of these bands lent themselves readily to kinetic analysis.

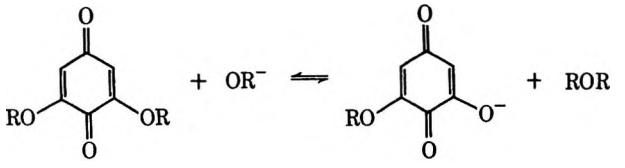
When esr measurements were taken of this reaction sequence under conditions identical with those monitored by optical spectroscopy, a first-order increase in radical species was obtained. The first-order rate for

(19) C. A. Bishop and L. K. J. Tong, *J. Amer. Chem. Soc.*, **87**, 50 (1965).
(20) H. W. Wanzlick and U. Jahnke, *Chem. Ber.*, **101**, 3744 (1968).
(21) C. J. R. Adderley and F. R. Hewgill, *J. Chem. Soc. C*, 2771 (1968).
(22) H. Musso and D. Maassen, *Justus Liebigs Ann. Chem.*, **689**, 94 (1965).
(23) H. Musso and D. Bormann, *Chem. Ber.*, **98**, 2774 (1965).

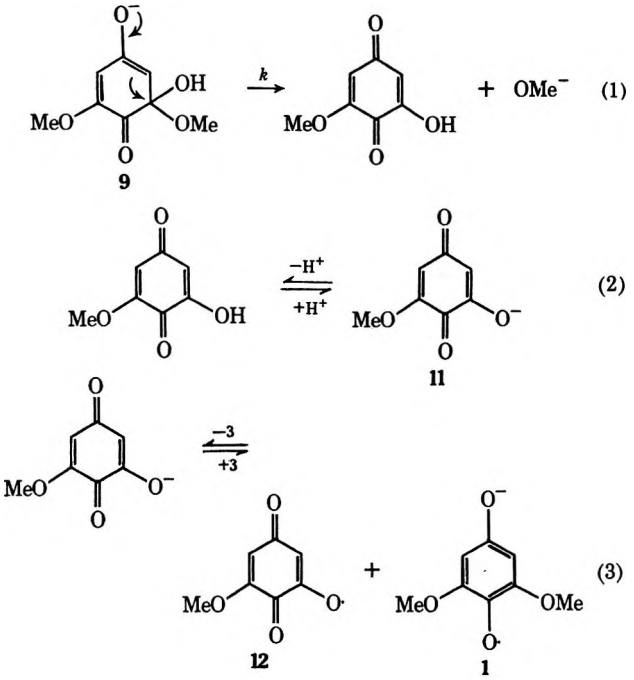
the increase of radical 1 approximated that of the 245 nm band.

Discussion

These results indicate that the formation of semiquinone radicals of types 1 and 5 is preceded by a rapid equilibrium between quinone 3 and OH^- (or OR^-) and adducts such as 9[16] or 10.[9] In most alkanolic solvents, replacement of both methoxyl groups from 3 occurs rapidly to yield adduct 10 with the exception of attack by bulky nucleophiles. At very high concentrations of OR^-, direct attack on the OR group may compete with nuclear attack.



To account for the appearance of radical 1 from quinone 3, we propose the following mechanism in which the decomposition of adduct 9 (or 10) is rate controlling. This is similar to a mechanism proposed by Eigen[15] for unsubstituted benzoquinone, but differs in the identity of the rate-controlling species.



The compounds 11 and 12 absorb in the 500–550 nm region and their presence would account for the simultaneous appearance of red substances with the appearance of radical species. Radical 12 would decay rapidly; radical 1 is stable. Equilibria 2 and 3 would be expected to form high concentration of products.

This reaction is considerably slower than that reported for the unsubstituted benzoquinone.[15] This may be due to the inability of 9 to enolize rapidly to a reducing species, as was the case for the Eigen and Mathies[15] intermediate.

Conclusion

This quinone–base system appears to be a reasonable model for the behavior of hardwood lignins under basic conditions. Quinone 3 arises from the oxidative degradation of 3,5-dimethoxy-4-hydroxyphenyl moieties in lignin. Quinone 4 would be expected to arise from the degradation of the 4-hydroxy-3-methoxyphenyl moieties, which are also present in hardwood lignins. However, its absence from the reaction mixtures and esr spectra is not unexpected, due to its known instability in aqueous alkaline media.[24,25]

One might predict that a variety of substituted quinones could be found in commercial hardwood lignin solutions, whose structures would depend on the nucleophiles present in the alkaline solutions. Certain applications of the paramagnetic character of lignin preparations, such as potential radical initiators, have already been suggested.[26] The role of alkoxy-substituted quinones in disease resistance of plants may be due to the spontaneous generation of radical intermediates under mildly basic conditions. The activity of the carcinostatic antibiotic Mitomycin C (a substituted benzoquinone) also appears to be the result of its semiquinone radical anion.[27]

Experimental Section

Materials.—2,6-Dimethoxy-*p*-benzoquinone, mp 257–258° (lit.[28] 255°), was prepared from 2,6-dimethoxyphenol by lead tetraacetate oxidation. 2-Methoxy-*p*-benzoquinone, mp 147–148° (lit.[29] 144–145°), was prepared by a chromic acid oxidation[30] of 2-methoxyhydroquinone, which was prepared by a Dakin oxidation of vanillin.[31]

Spectra.—All esr measurements were made in a flat quartz cell in the cavity of an E-3 Varian spectrometer. The instrument operated at 9.5 GHz with a frequency modulation of 100 kHz. In those cases where it was desired to exclude air, there was attached to the cell a special glass mixing device, consisting of two chambers, one of which contained the weighed quantity of solid substrate and the other of which contained the alkaline solution of buffer. Before mixing, the apparatus was flushed with nitrogen and the solution was deaerated by bubbling nitrogen through it for 15 min. The apparatus was then stoppered. It was not feasible to use a solution of the quinone because of its limited solubility in water.

Ultraviolet and visible spectra were measured in a Cary Model 14 spectrophotometer.

Esr Spectra of Alkanolic Solutions.—A 2.5×10^{-3} M solution of quinone 3 in 0.1 *M* sodium ethoxide was prepared by diluting a 5×10^{-3} *M* solution of quinone with an equal volume of 0.2 *M* sodium ethoxide in ethanol. The latter was made by dissolving the appropriate amount of sodium metal in ethanol. This mixture gave a signal for the primary radical 5. When 1.0 *M* sodium ethoxide was used, a signal for radical 7 was obtained. The same conditions were used to generate radicals 5 and 7 from isopropyl alcohol *n*-propyl alcohol. When the solvent was *tert*-butyl alcohol, with 0.2 *M* potassium *tert*-butoxide, a radical with only one methoxyl exchanged was observed. With 1.0 *M* potassium *tert*-butoxide, distorted spectra were obtained.

Radical signals could be observed in the presence of air, if a sufficiently high concentration of quinone were used (usually

(24) V. Sundman and K. Haro, *Finska Kemistsamfundets Medd.*, **75**, 111 (1966).

(25) W. Flaig, *Chem. Geol.*, **3**, 161 (1968).

(26) T. N. Kleinert, *Holzforsch. Holzverwert.*, **22**, 94 (1970).

(27) C. Nagata and A. Matsuyuma, "Progress in Antimicrobial and Anticancer Chemotherapy," Vol. II, University Park Press, Baltimore, 1970, pp 423–425.

(28) H. D. Becker, *J. Org. Chem.*, **30**, 982 (1965).

(29) T. Fukuzumi, *Bull. Agr. Chem. Soc. Jap.*, **24**, 278 (1960).

(30) A. I. Vogel, "A Textbook of Practical Organic Chemistry," 3rd ed, Wiley, New York, N. Y., 1956, p 745.

(31) H. D. Dakin *Amer. Chem. J.*, **42**, 477 (1909).

about 5×10^{-3} M). At lower concentrations, there was enough dissolved oxygen to scavenge any semiquinone radicals which were formed.

Thin Layer Chromatography of Lignin Extracts.—Brauns native lignin samples such as aspen and Black Spruce[32] (0.1 g) were refluxed for 2 hr (with and without oxygen) in 5 ml of 1.0 M NaOH and neutralized with dilute HCl, followed by extraction with ethyl ether. The concentrated ether extracts were chromatographed on silica gel plates using benzene–ethanol (4:1) by volume) or the organic layer from a mixture of n-butyl alcohol–acetic acid–water (4:1:5 by volume) as developing solvents. The spots were visualized with 2,4-dinitrophenylhydrazine. The first solvent mixture proved best for separation of syringaldehyde from vanillin, while the latter mixture gave better separation of 2,6-dimethoxybenzoquinone from the other two components.

Commercial (alkali) lignin samples such as Meadol and kraft were extracted by boiling water followed by chloroform extraction of the aqueous solutions, or by extracting the solid lignin samples directly with chloroform. The concentrated chloroform extracts were chromatographed using the above developing solvents.

Synthesis of the Semiquinone of 2-Hydroxy-6-methoxybenzoquinone (2).—The structure of the secondary radical **2** was previously confirmed[6] by the Fremy's salt oxidation of the monomethyl ether of phloroglucinol to 2-hydroxy-6-methoxybenzoquinone, and treatment of this compound with alkali to give the corresponding semiquinone.

In the present work, this structure was further confirmed by preparation of 5-iodovanillin by the method of Pepper[33] and conversion to 5-hydroxyvanillin[34] followed by a Dakin oxidation to 2-hydroxy-6-methoxybenzohydroquinone. On treatment with alkali and air, this gives the esr spectrum of **2**.

Kinetic Studies. A. All esr rate studies were carried out under nitrogen in the apparatus described above. After the substrate and buffer were mixed, the spectrum was scanned at definite time intervals and the intensity of the central line of the spectrum was taken as a measure of radical concentration.

B.—Optical rate studies were made by dissolving definite quantities of the quinone in commercial (phosphate and borate) buffer solutions, which had been deaerated with nitrogen for 0.5 hr before mixing. Scanning of the quinone–base mixture was started as soon as the quinone had completely dissolved.

Ether Exchange.—In a typical experiment, quinone **3** (200 mg) was dissolved in 100 ml of ethanol containing 0.01 mol of NaOH. After 3 min of stirring, the red reaction mixture was poured into 200 ml of ice water, acidified, and extracted with chloroform. The pale yellow solid isolated from the chloroform solution was identified as 2,6-diethoxy-p-benzoquinone: mp 125–126° (lit.[9] 126–127°); nmr ($CDCl_3$) δ 1.40 (t, 6), 3.90 (q, 4), 5.75 (d, 2). When the latter was dissolved in CD_3OD in an nmr tube, and a small quantity of solid NaOH was added, instant exchange of ethoxyl groups with CD_3O^- was observed.

Registry No.—**1**, 33070-34-7; **2**, 33070-35-8; **3**, 530-55-2; **5** (R = Et), 33070-36-9; **5** (R = i-Pr), 33070-37-0; **7** (R = Et), 33070-38-1; **7** (R = i-Pr), 33070-39-2; **8**, 15233-65-5; **9**, 33122-24-6; 2-methoxy-p-benzoquinone, 33070-40-5; 2,6-dimethoxyhydroquinone dianion, 33070-41-6.

Acknowledgment.—The authors acknowledge the generous support of a National Science Foundation Institutional Grant to the Department and the Petroleum Research Fund for this work.

(32) Kindly supplied by Dr. F. E. Brauns, Bellingham, Wash.

(33) L. W. Crawford, E. V. Eaton, and J. M. Pepper, *Can. J. Chem.*, **34**, 1562 (1956).

(34) S. K. Banerjee, M. Manolopoulo, and J. M. Pepper, *ibid.*, **40**, 2175 (1962).

Substituent Chemical Shift Correlations. Proton Magnetic Resonance Chemical Shifts for N,N,N-Trimethylphenylammonium Iodides[1a]

Gary R. Wiley[1b] and Sidney I. Miller*

Department of Chemistry, Illinois Institute of Technology, Chicago, Illinois 60616

Received May 18, 1971

N-Methyl pmr chemical shifts of 21 meta- or para-substituted N,N,N-trimethylphenylammonium (TMA) iodides were determined in deuterium oxide and acetonitrile. Infinite dilution shifts were obtained from expressions of the type (M = mol/l.) δ (D_2O), Hz = $\delta^0_0 + (28.61 \pm 6.19)M$ and δ (CH_3CN), Hz = $\delta^0_0 + (166.5 \pm 5.7)M - (2240 \pm 2.16)M^2$. The corresponding Hammett correlations were δ^0 (D_2O), Hz = $5.857\sigma + 217.86$ ($r = 0.85$, $N = 17$) and δ^0 (CH_3CN), Hz = $5.123\sigma + 211.0$ ($r = 0.89$, $N = 12$); one Swain–Lupton surface for our meta-substituted TMA's was given by δ^0 (CH_3CN), ppm = $0.03855F + 0.1074R - 3.548$ ($r = 0.999$, $N = 7$, $\%R = 64$). The proportionality of pmr substituent chemical shifts, or δ–δ relations, between pairs of families was tested. In general, the Hammett and δ–δ linear relations were often poor ($r < 0.9$), while the Swain–Lupton equation was usually good ($r > 0.95$), as judged by the correlation coefficient (r). It can be shown, however, that pmr correlations which depend solely on reactivity constants (σ, F, R) are theoretically deficient and we would discourage their use. The introduction of additional terms, *e.g.*, to correct for substituent magnetic anisotropy, appears to be essential, but the merits of such a hybrid approach are doubtful.

In investigations of the relation between the transmission of electronic effects and substituent chemical shifts (SCS = δ) our group has taken diametrically opposed positions. Initially, we assumed that the usual structure–reactivity correlations of the Hammett (eq 1) or Taft type applied to proton magnetic resonance (pmr) data.[2] Recently, we tested eq 1 on *ca.* 100 systems of the type XC_6H_4–T–H and found that SCS are often poorly represented; that is, correlation coefficients for eq 1 are low ($r < 0.9$).[3] It was also significant that the variations in ρ with the nature of the transmitting group, $-C_6H_4T-$, made little chemical sense.

$$\delta = \rho\sigma + \text{constant} \qquad (1)$$

Originally, the compounds (TMA) seemed interesting, because a novel group, namely positive nitrogen, was involved in relaying substituent effects to the methyl protons.[2] Later, the anilinium family became crucial to a new approach to substituent effects, embodied in the Swain–Lupton relation;[4] F and R measure

(1) (a) Presented in part at the Third Great Lakes Regional Meeting, American Chemical Society, June 1969, and abstracted from the Ph.D. thesis of G. R. W., May 1971, Illinois Institute of Technology; (b) American Chemical Society Petroleum Research Fund (GF-760) and Division of Analytical Chemistry Summer Fellowships are gratefully acknowledged.

(2) S. H. Marcus, W. F. Reynolds, and S. I. Miller, *J. Org. Chem.*, **31**, 1872 (1966).

(3) T. Yokoyama, G. R. Wiley, and S. I. Miller, *ibid.*, **34**, 1859 (1969).

(4) C. G. Swain and E. C. Lupton, Jr., *J. Amer. Chem. Soc.*, **90**, 4328 (1968).

TABLE I

PROPERTIES OF THE N,N,N-TRIMETHYLPHENYLAMMONIUM (TMA) IODIDES[a]

Registry no.	Substituent	Mp or dp, °C[b] Found	Mp or dp, °C[b] Lit.	Iodide, % Found	Iodide, % Calcd	δ⁰ (D_2O),[c] Hz	δ⁰ (CH_3CN),[c] Hz	Ref[a]
98-04-4	H	226.5	228	48.47	48.23	217.98 ± 0.07	211.92 ± 0.06	*d*
	D	227–229		47.2	47.9			*e*
6140-15-4	*p*-CH_3	218–219	216–218	45.84	45.78	216.07 ± 0.01	210.19	*f*
33046-97-8	*m*-CH_3	188–188.5	177–178	45.89	45.78	216.41 ± 0.11	210.61 ± 0.1	*f*
2498-27-3	*m*-OH	185–186.5	179	45.92	45.47	215.83 ± 0.06	209.41 ± 0.09	*g*
455-08-3	*p*-F	232–233		45.69	45.14	218.41 ± 0.04	211.85 ± 0.06	
454-60-4	*m*-F	180.5–182		45.26	45.14	218.83 ± 0.05	212.34	
17311-01-2	*p*-CN	163–164	181	44.43	44.05	221.03 ± 0.04	213.62	*h*
7541-76-6	*p*-CHO	156–157		43.8	43.58	221.91 ± 0.01	214.44 ± 0.03	*i*
17310-99-5	*p*-OCH_3	261–262		43.46	43.28	216.00 ± 0.06	209.81	
2373-41-3	*m*-Cl	191–192	187, 199	42.84	42.64	218.44 ± 0.04	212.14	*j, k*
27853-26-5	*p*-$COCH_3$	179–181		41.01	41.58	220.94 ± 0.02	213.94	
1202-17-1	*p*-$N(CH_3)_2$	289.5–290	246	41.35	41.44	213.72 ± 0.11	207.30	*k*
880-00-2	*p*-COOH	238–239	238	41.4	41.32	220.67 ± 0.06	213.71	*l*
2345-55-3	*m*-COOH	203	204	41.05	41.32	221.08 ± 0.02	214.30	*h*
27389-55-5	*m*-NO_2	198–199	205	42.11	41.19	224.40 ± 0.03	216.60	*m*
33046-24-1	*m*-NO_2[n]	248		30.77	30.60	224.40 ± 0.03	216.60	
33046-25-2	*p*-Br	192	184	37.26	37.10	217.82 ± 0.10	211.01	*o*
2350-78-9	*p*-NNC_6H_5	184	184	34.54	34.56	228.38	215.76	*p*
31061-59-3	*m*-O^-					211.83 ± 0.02	208.33	*q*
33039-70-2	*p*-$N(CH_3)_2H^+$					221.32 ± 0.07	214.05	*r*
33192-03-9	*m*-CO_2^-					219.91 ± 0.03	213.18	*q*
33046-28-5	*p*-CO_2^-					219.23	*s*	*q*

[a] The citation is to a method of preparation and/or melting point. [b] These are generally decomposition ranges; see text. [c] In general, ±0.15 Hz is a good estimate of uncertainty in δ^0, the value at infinite dilution. Where a ± value is given these are standard deviations in the least squares evaluation of δ^0. [d] G. Funatsukuri, Japanese Patent 5059 (1960); also reported in *Chem. Abstr.*, **55**, 1663 (1961). [e] The salt contained 1.6 D on the ring and was prepared from *N,N*-dimethylaniline (R. J. Preto, Ph.D. dissertation, Illinois Institute of Technology, 1967). [f] K. T. Tsuboyama and M. Yanagita, *Sci. Pap. Inst. Phys. Chem. Res., Tokyo*, **53**, 337 (1959). [g] S. Oae and C. C. Price, *J. Amer. Chem. Soc.*, **80**, 3425 (1958). [h] W. Tadros and A. B. Sakla, *J. Chem. Soc.*, 1116 (1954). [i] H. B. Hass and M. L. Bender, *J. Amer. Chem. Soc.*, **71**, 1767 (1949). [j] I. Heilbron, A. H. Cook, H. M. Bunbury, and D. H. Hey, Ed., "Dictionary of Organic Compounds," 4th ed, Oxford University Press, New York, N. Y., 1965. [k] A. Campbell Ling and F. H. Kendall, *J. Chem. Soc. B*, 440 (1967). [l] A. Zaki and W. Tadros, *J. Chem. Soc.*, 562 (1941). [m] Z. Rappoport, Ed., "Handbook of Tables for Organic Compound Identification," 3rd ed, The Chemical Rubber Co., Cleveland, Ohio, 1967. [n] This is the bromide salt. [o] V. Wolf, *Justus Liebigs Ann. Chem.*, **592**, 222 (1955). [p] R. Möhlau, *Chem. Ber.*, **17**, 1490 (1884). [q] One drop of diethylamine was added to the parent TMA in the nmr tube; an additional drop did not alter the chemical shift. [r] One drop of dilute acid (10 1 solvent–concentrated H_2SO_4, by volume) was added to the parent TMA. [s] The solubility was too low.

the field and resonance capabilities of substituent X and f and r are weighting factors appropriate to the system, the property (y) examined, the conditions, etc.

$$y = fF + rR + \text{constant} \quad (2)$$

An essential feature of the approach is that $R \equiv 0$ for $(CH_3)_3N^+$ as a substituent.[4] Our test of relation 2, both on our SCS and those of other families, disclosed some basic theoretical problems. We then went on to examine a relatively new correlative approach to SCS, which is completely independent of measures of reactivity, *e.g.*, σ, F, R, etc. This is

$$\delta_1 = s\delta_2 + \text{constant} \quad (3)$$

in which the SCS of two different families are compared directly. Meanwhile, the difficulties in using either eq 1, 2, or their analogs have been recognized by a Japanese group and it is attempting to provide rather different approaches to correlating pmr data.[5]

Experimental Section

Materials.—The *N,N,N*-trimethylphenylammonium (TMA) iodides were all known compounds, except as indicated in Table I. They were generally prepared by direct reaction of available dimethylanilines with excess methyl iodide in benzene or ether at *ca.* 25°. In a few cases, the analogous bromides were prepared. All of the salts were recrystallized to constant melting point or decomposition point (dp). Careful control in the rate of heating (2°/min) allowed good reproducibility of these characteristic temperatures. The use of sealed, evacuated capillaries offered no special advantage, judging from the behavior of the *m*- and *p*-fluoro-TMA; for, although these compounds now melted rather than decomposed, the melting points were only 3–4° lower than the decomposition points in open capillaries. All temperatures are uncorrected. They were determined with a Thomas-Hoover "Unimelt" (oil bath) or in a Mel-Temp (metal block) apparatus when temperatures over 240° were encountered. The TMA's were analyzed titrimetrically with standard silver nitrate to the eosin end point (Table I) and nmr proton counts were usually taken. Purity checks by ir and pmr spectra were also made.

Acetonitrile (Baker Analyzed Reagent) with 1% tetramethylsilane (TMS) added was stored in a nitrogen atmosphere in the dark over 4A molecular sieves. This treatment removed water, the only impurity which we could detect at the ~0.01% level. Deuterium oxide (Merck) containing 1% sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) was used directly. Pmr spectra of the solvents as well as ir spectra of acetonitrile showed no change over the course of the study.

Pmr Spectra.—All samples were run on a Varian A-60 spectrometer modified by an A-60A variable temperature probe insert and operating at ±0.020 MHz. Chemical shifts (δ), relative to 1% internal TMS in acetonitrile and relative to 1% internal DSS in deuterium oxide, were measured by a side band (juxtaposition) technique. The audio-oscillator (HP200CD) was monitored by a frequency counter (HP5216A) operated in the period mode. Averages of several hundred periods were used to determine the side-band frequency. Oscillator and/or spectrometer drift were monitored and found negligible. The sweep width was calibrated on each use of the spectrometer, and the

(5) H. Yamada, Y. Tsuno, and Y. Yukawa, *Bull. Chem. Soc. Jap.*, **43**, 1459 (1970).

smallest sweep width setting (50 Hz) was used to allow direct reading of the chart paper to ± 0.01 Hz.

Repeated measurements were made on sealed standard samples to check probe temperature and instrument reproducibility at various times. The probe temperature was 37 ± 2°. The presence or absence of oxygen in the solutions had no observable effect on the methyl resonances of TMA. A check on the temperature dependence (20–40°) and of added water (mole fraction <0.13) in acetonitrile indicated that these factors could only introduce deviations within the error limits on δ of TMA.

Fresh solutions of TMA were prepared for each run by weighing the dry salt and diluting to volume. Aliquots were taken for further dilution. All glassware was calibrated. Generally, solutions from at least two weighed samples were used for the measurements of δ. Toward the end of this study, particularly for the deuterium oxide solutions in which the concentration dependence was slight, dilutions of aliquots were made in an nmr tube, with the help of a ruler. An error analysis showed that the concentration errors were negligible in comparison with errors in obtaining δ.

At each concentration, δ was obtained as the mean of six scans, three upfield and three downfield. Extrapolation of δ to infinite dilution (δ^0) was made from dilution plots for each compound. These plots were based on at least three points, that is, six for acetonitrile and four for deuterium oxide. The concentration range studied was low, *ca.* 2×10^{-2}–10^{-3} *M*, to minimize errors in extrapolation to δ^0. All of the dilution shift data are given in the thesis.[1b]

Computations.—Calculations were done on a Wang calculator (Model 362K) with card reader or on an IBM 1620 computer. Struble's program was used for fitting the nonlinear equations.[6]

Results and Discussion

TMA Infinite Dilution Chemical Shifts.—The infinite dilution chemical shifts, δ^0, of the various TMA's studied in acetonitrile and deuterium oxide solutions are reported in Table I. These δ^0 values were determined from dilution shift plots, that is, plots of observed chemical shift *vs.* TMA concentration. It was noted early in the study that the dilution curves of many compounds were very similar in a given solvent (Figure 1). This is also apparent analytically from fits to eq 4 in which the parameters often agree within the expressed error limits for each solvent system.[1b]

$$\delta_{obsd} = \delta^0 + c_1M + c_2M^2 + c_3M^3 \quad (4)$$

Since it was determined that TMA shifts in deuterium oxide were adequately described in terms of a linear dependence in *M*, least squares straight lines were used to determine δ^0. With reference to the similarity of dilution curves, it is interesting to note that 16 TMA, except for those of low solubility (X = *m*-O^-, *m*-CO_2^-, and NNC_6H_5), had the average slope of eq 5.

$$\delta(D_2O) = (28.61 \pm 6.19)M + \delta^0_o \quad (5)$$

In acetonitrile, the concentration dependence was greater. Here the SCS were best fit by a shallow parabolic curve. If, for any compound, insufficient data were available to generate an independent curve, δ^0 was determined by superimposing the data on eq 6.

$$\delta^0(CH_3CN) = \delta^0_o + (166.5 \pm 5.7)M - (2240 \pm 2.16)M^2 \quad (6)$$

A cursory check of salt effects on δ was made. In deuterium oxide solution, *p*-methyl-TMA iodide and *m*-nitro-TMA bromide have the same δ before and after being mixed. Changing the gegenion, *e.g.*, bromide for iodide, or mixing the two leaves the δ of *m*-nitro-TMA unchanged. If, however, large amounts of potassium iodide, *e.g.* 1.0 *M*, are added to *p*-methyl-TMA iodide, a change in δ can be effected, *viz.*, 216.23 to 217.74 Hz. Similar observations were recorded for the solvent acetonitrile. Specifically, a saturated solution of potassium iodide in acetonitrile raised δ in *p*-carboxy-TMA from 214.23 to 218.21 Hz and *m*-carbomethoxy-TMA from 214.68 to 219.78 Hz.

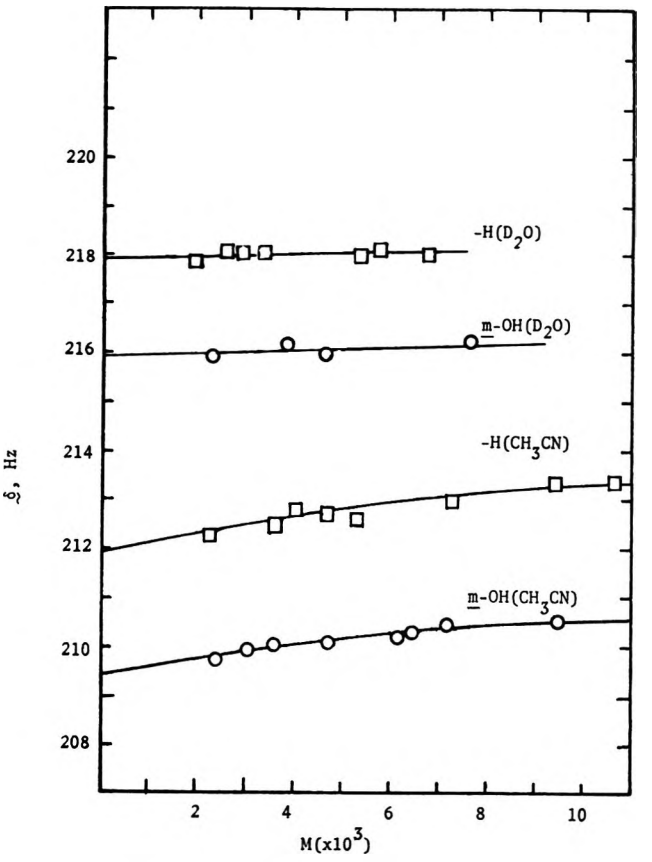


Figure 1.—Representative TMA dilution shift plots.

Other workers have obtained dilution shift curves and gegenion effects similar to ours both for TMA and pyridinium halides and ascribe these both to specific interactions as well as ion–ion association.[7] Certainly, the association of a variety of alkylammonium salts in organic solvents is known:[8] *p*-methyl-TMA iodide is *ca.* 6% associated in water and *ca.* 16% associated in propionitrile in *ca.* 10^{-3} *M* solution at 25°.[9] A salt may also change the medium in more subtle ways which may then be reflected in δ^0 of another solute.[10] In aqueous solutions, for example, δ^0 of water increases or decreases, depending on the salt added.[10] In our system, we can only guess that there are such reciprocal effects between the electrolyte and the solvent. We believe that all of these concentration dependent effects on δ are minimized as [TMA] → 0.

"Reactivity" Correlations.—Out of some 100 systems to which eq 1 has been applied,[2,3] 49 have an average correlation coefficient (*r*) of 0.88. In this respect, the

(6) G. Struble, "Non-linear least squares curve fitting program," IBM 1620 Users Group Library, Statistical Laboratory and Computing Center, University of Oregon, Eugene, Ore.

(7) (a) G. Fraenkel and J. P. Kim, *J. Amer. Chem. Soc.*, **88**, 4203 (1966); (b) W. F. Reynolds and U. R. Priller, *Can. J. Chem.*, **46**, 2787 (1968).

(8) W. A. Adams and K. J. Laidler, *Can. J. Chem.*, **46**, 1977 (1968).

(9) (a) H. J. M. Creighton and D. H. Way, *J. Franklin Inst.*, **186**, 675 (1918); (b) H. J. M. Creighton, *ibid.*, **189**, 641 (1920).

(10) (a) J. Burgess and M. C. R. Symons, *Quart. Rev., Chem. Soc.*, **22**, 276 (1968); (b) J. F. Hinton and E. S. Amis, *Chem. Rev.*, **67**, 367 (1967).

TABLE II

PMR DATA AND THE SWAIN–LUPTON EQUATION[a]

Series	Solvent	N^b	f	r	Constant, ppm	Variance × 10^3	R,[c] %	Ref
4-$XC_6H_4CH{=}CH_2$	C_6H_{12}	7	0.01651	0.1901	6.618	1.465	88	*d*
cis-4-$XC_6H_4CH{=}CHH$	C_6H_{12}	7	0.09695	0.3989	5.630	0.3453	72	*d*
trans-4-$XC_6H_4CH{=}CHH$	C_6H_{12}	7	0.1658	0.3948	5.110	0.09112	60	*d*
4-$XC_6H_4N(CH_3)_3^+$	CH_3CN	8	0.02873	0.08689	3.526	0.1353	65	*e*
	D_2O	9	0.03881	0.1112	3.634	0.1709	64	*e*
3-$XC_6H_4N(CH_3)_3^+$	CH_3CN	7	0.03855	0.1074	3.538	0.1038	64	*e*
	D_2O	8	0.06126	0.1278	3.639	0.2898	57	*e*
4-XC_6H_4OH	DMSO	20	1.059	1.653	9.259	34.57	49	*f*
	DMSO	14	0.9488	1.880	9.309	4.244	55	*f*, *g*
3-XC_6H_4OH	DMSO	7	0.9708	0.6621	9.250	4.003	30	*f*
4-$XC_6H_4CH_2Cl$	CCl_4	6	0.06337	0.1475	4.510	0.5408	59	*h*
3-$XC_6H_4CH_2Cl$	CCl_4	7	0.07331	0.1451	4.507	1.344	55	*h*
4-XC_6H_4H	CCl_4	5	0.5820	0.5321	6.908	4.575	36	*i*
3-XC_6H_4H	CCl_4	5	0.3080	0.2342	7.139	1.416	32	*i*
2-XC_6H_4H	CCl_4	5	0.8040	1.106	7.099	11.39	46	*i*

[a] Equation 2. [b] N is the number of substituents. [c] Resonance contribution, eq 9. [d] Reference 24b. [e] Our work. [f] Reference 16. [g] The six worst points have been deleted from the previous set. [h] Reference 2. [i] S. Castellano, C. Sun, and R. Kostelnik, *Tetrahedron Lett.*, 5205 (1967).

present data on TMA are no exception. Such correlations must be rated as poor, according to standards

$$\delta^0(D_2O) = 5.857\sigma + 217.86 \quad (N = 17, r = 0.85) \quad (7)$$

$$\delta^0(CH_3CN) = 5.123\sigma + 211.0 \quad (N = 12, r = 0.89) \quad (8)$$

generally accepted in the area of structure–reactivity correlations, namely, $r > 0.99$ excellent, $r > 0.95$ satisfactory, $r > 0.90$ fair.[11] Hammett pmr correlations rated from poor ("noncorrelations") to excellent continue to appear.[12] It is unfortunate that some poor correlations are tolerated or accepted, without comment on their validity or significance. A more fundamental issue, to which we shall return shortly, is that even the satisfactory correlations carry a message in the Hammett ρ which is too complex to decipher.[3,5]

At the next level of complexity are the extended structure–reactivity equations, *e.g.*, of Taft and of Yukawa and Tsuno,[13] which take a form analogous to eq 2 here. Equations of this type have occasionally been used for pmr data,[3,5,14,15] and, recently, Charton has used a similar relation to analyze pmr data of ortho-substituted families.[15c] The Yukawa–Tsuno analog of eq 2 does not really give satisfactory results for SCS of side chain protons of the benzyl fluorides[3] or the 1,1-diphenylethylenes.[15a] Because the applicability of eq 2 to pmr data had not been tested in depth and because the Swain–Lupton formalism has apparently achieved the maximum separation of field and resonance effects, we used this equation and substituent constants F and R.[4] In any system, the sensitivity to resonance effects was defined as[4]

$$\%\ R = 100(0.228\ r)/(0.365\ f + 0.228\ r) \quad (9)$$

The results of fitting a few systems to eq 2 are given in Table II. Sets of data sufficient for a test of eq 1 are often inadequate to test eq 2, since different versions of eq 2 apply to meta and para members of a given family. The fit of the data to eq 2 is, of course, better than to eq 1 and it is usually very good, as may be seen from the variances of Table II. The correlation coefficient, as calculated from coefficients of determination,[4] is 0.999 for meta-substituted TMA's in acetonitrile, 0.997 for the ortho proton of monosubstituted benzenes in CCl_4, and 0.994 for the 14 para-substituted phenols in DMSO (20 para-substituted phenols in DMSO have $r = 0.959$). The Hammett correlation for the phenols was excellent (δ *vs.* σ and σ^-, $N = 36$, $r = 0.974$)[16] and is hardly improved in the separate correlations for meta and para substituents. Our TMA data, which give poor Hammett correlations, now give excellent correlation with eq 2. In some sets, the standard deviation is less satisfactory.

Apart from the matter of fit, which might be expected to improve with the higher parameter equation, there is the question of significance. There is no obvious relation of the parameters f and r, or the % R to the basic aryl structure. In some families the "resonance" contribution from the meta and para position hardly differs; this is inexplicable, at least for the present. In fact, we find it both frustrating and amusing that the TMA have a resonance contribution, $R = 64\%$ in Table II, just like any other family, *e.g.*, $R = 59\%$ for benzyl chloride and $R = 49\%$ for phenols. If it is admitted that the TMA cannot make a resonance contribution according to the Swain–Lupton formulation,[4] one might be puzzled. This can be resolved simply by saying that reactivity parameters F and R are theoretically unsuitable for interpreting δ and denying

(11) (a) P. R. Wells, *Chem. Rev.*, **63**, 171 (1963); (b) H. H. Jaffé, *ibid.*, **53**, 191 (1953).

(12) (a) M. Brink and E. Larsson, *Tetrahedron*, **26**, 5535, 5547 (1970); (b) C. H. Yoder, R. H. Tuck, and R. E. Hess, *J. Amer. Chem. Soc.*, **91**, 539 (1969); (c) K. Bowden, M. J. Hanson, and G. R. Taylor, *J. Chem. Soc. B*, 174 (1968); (d) R. W. Daisley and J. Walker, *J. Chem. Soc. B*, 146 (1969); (e) J. R. Dimmock, P. L. Carter, and P. D. Ralph, *J. Chem. Soc. B*, 698 (1968); (f) V. Bekárek, J. Klicnar, F. Kristek, and M. Večeřa, *Collect. Czech. Chem. Commun.*, **33**, 994 (1968); (g) S. Arakawa and M. Hashimoto, *Bull. Chem. Soc. Jap.*, **41**, 1449 (1968); (h) G. P. Schiemenz, *Angew. Chem., Int. Ed. Engl.*, **7**, 544, 545 (1968); (i) I. F. Tupitsyn, N. N. Zatsepina, and A. V. Kirova, *Org. Reactiv.*, **7**, 682 (1970); (j) R. R. Fraser and R. N. Renaud, *Can. J. Chem.*, **49**, 800 (1971); (k) H. Sakurai and M. Ohtsuru, *J. Organometal. Chem.*, **13**, 81 (1968); (l) V. Bekárek, J. Socha, and M. Večeřa, *Collect. Czech. Chem. Commun.*, **33**, 3377 (1968); (m) G. Socrates and M. W. Adlard, *J. Chem. Soc. B.*, 733 (1971).

(13) (a) P. R. Wells, S. Ehrenson, and R. W. Taft, *Progr. Phys. Org. Chem.*, **6**, 147 (1968); (b) Y. Yukawa and Y. Tsuno, *Mem. Inst. Sci. Ind. Res. Osaka Univ.*, **23**, 71 (1966).

(14) J. M. Haigh and D. A. Thornton, *Tetrahedron Lett.*, 2043 (1970).

(15) (a) Y. Yukawa, Y. Tsuno, and H. Yamada, *Mem. Inst. Sci. Ind. Res. Osaka Univ.*, **23**, 79 (1966); (b) Y. Yukawa and H. Yamada, *Nippon Kagaku Zasshi*, **85**, 501 (1964); (c) M. Charton, *J. Org. Chem.*, **36**, 266 (1971).

(16) M. T. Tribble and J. G. Traynham, *J. Amer. Chem. Soc.*, **91**, 379 (1969).

that their correlation has anything but empirical validity. In our view, Charton's analyses of pmr data and the ortho effect is subject to the same limitations.[15c]

δ–δ Correlation.—It appeared to us that a logical precondition for the Hammett or Swain–Lupton correlations, eq 1 and 2, might be closer to the data. That is, δ^0 of one family of compounds might be related to δ^0 of another family (eq 3). Such an approach is inefficient in that it can involve several systems in numerous cross comparisons. The virtue of eq 3, and perhaps its regressive feature too, is that the δ–δ comparison is direct and involves no assumptions, adjustments, or hypotheses.

There have been a few reports on different δ–δ comparisons, *e.g.*, two solutes in a series of solvents,[17] or pairs of chemical shifts within one family of compounds,[18] or SCS of two families under the same conditions.[3,19] Sample plots are given in the thesis[1a] and in the citations.[3,17–19] The results for a number of δ–δ comparisons are given in Table III, where we emphasize r as the criterion of fit; the slope parameter, occasionally given in brackets, seems less important at this stage. That is, if the fits are poor, both the "theory" and applications of eq 3 become superfluous.

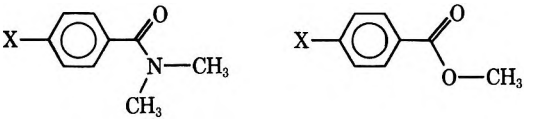
Initially, we found many systems which had significantly larger r (and often N) in their δ–δ than in their Hammett correlations. As we added to the number tested, the average r of the δ–δ relations tended to decline. One could, of course, become selective and reject problem systems. By deleting the families $ArNH_2$ in C_6H_{12} and $ArCH{=}CH_2$ in $CDCl_3$ from Table III, we would immediately raise the average r above 0.90. In so doing, however, we would discard some fair (r = 0.90–0.95) correlations along with the poor (r < 0.90) ones.

Perhaps the most significant point to make about Table III is that there are no large blocks or extended series of values of $r > 0.95$. Thus, even if there were a rationale for eq 3, there is not much practical incentive to speculate on it. Theoretically, the slopes of eq 3 also do not relate to structure in any obvious way; this may be evident, if one considers the toluenes (Table III, column 3) compared with other aryl families, *e.g.*, $ArOCH_3$, ArCHO, $ArSCH_3$, etc., in which the SCS were measured in a single solvent, carbon tetrachloride. All of this is significant, if disappointing, because the pure and unadulterated pmr property is contained in eq 3.

Comments on Pmr Correlations.—At the outset, it would seem desirable to avoid adventitious medium effects or to keep them constant.[12j] In pmr correlations, differential influences of association, *e.g.*, hydrogen bonding or ion pairing, of anisotropy, *e.g.*, aryl solutes and solvents,[20] or of any other concentration-dependent effects are usually minimized when SCS are taken at infinite dilution in an "inert" solvent. Since this has not been a standard practice, discrepancies in published work on the same compounds are not uncommon.[3] As for the choice of a solvent, this is often dictated by other necessities; in any case, there are systems for which even carbon tetrachloride is not inert enough.[21] It is probable that δ^0 of this study are probably free of residual specific effects, because the dilution plots of most compounds were essentially parallel. This was far from the case with the benzyl halides.[3] The existence of unsystematic concentration-dependent effects at infinite dilution should, in fact, be used as an early criterion to disqualify any family from correlations of the type 1–3.

Suppose now that a sufficient and representative number of compounds in a family have been examined. On this point statistical criteria may be explicit, but out of prudence we have recommended $N > 10$.[3] Suppose further that one could settle on the scale to use, *e.g.*, σ, σ^-, σ^+, or F and R, etc. It has been shown previously that, even if eq 1 was acceptable, the magnitude of ρ could not be related in any way to the chemical structure it was intended to characterize.[3] Equally, the demands of precision and significance were not met in general by the δ–δ relation 3. Finally, though the Swain–Lupton surface 2 may store δ^0 well, it is of dubious significance. In short, all three relations appear to have no theoretical basis.

There have been several signs that SCS can be extraordinarily sensitive to their environment. From "outside" of the molecule a change in solvent can change the Hammett ρ substantially and often drastically: for $ArCH_2CH_2\mathbf{H}$, ρ = 6.8 in carbon tetrachloride and 4.6 in acetone; for $ArO\mathbf{H}$, ρ = 67 in carbon tetrachloride and 110 in HMPA.[2,3] From "within" the molecule there are the marked changes in ρ when aryl families differ only in their geometry, *e.g.*, syn and anti anils or cis and trans cinnamic acids.[2,3] Relative motion within the molecular framework leads to obvious effects on SCS, when barriers are high, but even in low barrier systems, *e.g.*



the broadening of δ (~0.8–1.4 Hz) has been observed.[22] In fact, most protons on side chains, except for those in cylindrically symmetrical groups, *e.g.*, CH_3, $N(CH_3)_3^+$, $C(CH_3)_3^+$, or those in rigid or severely hindered systems, will be mobile. Differential mobilities in these families make for variable magnetic effects. All of this suggests that the mutual interaction of a side chain proton with a remote substituent may be incompletely represented in eq 1–3.

Some time ago a phenomenological relation was proposed to account for the chemical shift. Equation 10 contained at least five "contributions" and some of

$$\delta = \sum_i \Delta\delta_i \qquad (10)$$

these were or could be composite.[23] Portions of this equation have been used occasionally in SCS cor-

(17) S. H. Marcus and S. I. Miller, *J. Phys. Chem.*, **73**, 453 (1969).

(18) (a) B. Caddy, M. Martin-Smith, R. K. Norris, S. T. Reid, and S. Sternhell, *Aust. J. Chem.*, **21**, 1853 (1968); (b) Y. Nomura, Y. Takeuchi, and N. Nakagawa, *Tetrahedron Lett.*, 639 (1969); (c) W. Drenth and A. Loewenstein, *Recl. Trav. Chim. Pays-Bas*, **81**, 635 (1962).

(19) (a) C. Brown and D. R. Hogg, *J. Chem. Soc. B*, 1315 (1968). (b) K. D. Bartle, D. W. Jones, and P. M. G. Bavin, *J. Chem. Soc. B*, 388 (1971).

(20) E. M. Engler and P. Laszlo, *J. Amer. Chem. Soc.*, **93**, 1317 (1971).

(21) T. Schaefer, B. Richardson, and R. Schwenk, *Can. J. Chem.*, **46**, 2775 (1968).

(22) G. P. Schiemenz and G. Stein, *Tetrahedron*, **26**, 2007 (1970).

(23) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, 1969, Chapter 2-2.

TABLE III

CORRELATION COEFFICIENTS IN SAMPLE δ–δ RELATIONS (EQUATION 3)

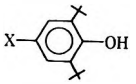
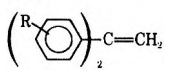
Site x[a,b] (solvent)	Code/ ref[c]	Site y[a,b]: –CH₃ (CCl₄)	–OH (DMSO)[d]	 (CDCl₃)	 (CDCl₃)	 (CDCl₃)	NH₂ (C₆H₁₂)	N⁺(CH₃)₃ (CH₃CN)	SCH₃ (CCl₄)	Avg r × 10³
–N(CH₃)₂	76	[0.94]	[7.80]	0.979	0.960	0.897	0.935	0.990(9)	0.953	958
(CHCl₃)		0.994(7)	0.958(10)							
–OCH₃	*e*	[1.39]	[11.8]							
(CH₃CN)		0.992(11)	0.981(10)	0.972	0.929	0.885	0.903	0.976	0.835	934
–OCH₃	14	[0.83]	[6.8]							
(CCl₄)		0.988(9)	0.956(10)	0.981	0.964	0.888	0.959	0.960	0.870	946
	8	[0.179]	[1.66]							
(CCl₄)		0.986	0.988(8)	0.997	0.972	0.857	0.987	0.979	0.996	970
–SCH₃	16	[1.52]	[11.8]							
(CCl₄)		0.979(9)	0.917(10)	0.992(7)	0.997(7)	0.829(7)	0.463	0.974		876
–N⁺(CH₃)₃	*f*	[2.15]	[16.1]							
(CH₃CN)		0.968(12)	0.917(12)	0.966	0.934	0.765	0.834		0.974	908
–CH₃	2		[7.90]						[0.63]	
(CCl₄)			0.938(13)	0.960(10)	0.947(10)	0.828(10)	0.573	0.968	0.979(9)	885
–N⁺(CH₃)₃	*f*	[1.68]	[13.2]	[2.3]	[1.8]	[0.65]		[0.829]	[1.6]	
(D₂O)		0.967(12)	0.927(12)	0.940(8)	0.888(8)	0.739(8)	0.805	0.989(19)	0.972(6)	903
–CH₂F	*g*	[0.76]	[5.6]							
(CCl₄)		0.982	0.948(10)	0.979	0.957	0.848	0.861	0.987(8)	0.995	945
–CH₂Cl	*g*	[1.30]	[9.07]					[0.57]		
(CCl₄)		0.963	0.854(10)	0.891	0.867	0.887	0.488	0.934(8)	0.874	845
–H	*h*	[0.31]	[2.38]							
(CCl₄)		0.953(7)	0.969(6)							
–OH	9	[0.10]	[0.966]							
(DMSO)		0.950(12)	0.992(11)	0.975	0.863	0.508	0.893	0.905	0.855	868
–OH	*d*	[0.111]		[0.19]	[0.15]	[0.055]	[0.21]	[0.052]	[0.071]	
(DMSO)		0.938(13)		0.977(10)	0.920(10)	0.720(10)	0.704(11)	0.917(12)	0.917(10)	870
–C≡CH	23	[0.61]	[5.08]	[0.89]	[0.67]	[0.29]		[0.31]	[0.39]	
(CCl₄)		0.950(10)	0.997(10)	0.980(8)	0.907(8)	0.753(8)	0.874	0.912(7)	0.881(8)	907
–NH₂	*i*	[0.11]	[1.03]							
(DMSO)		0.871	0.988(11)	0.870	0.854	0.767	0.845	0.789	0.874	857
–NH₂	7	[0.18]	[1.47]	[0.28]	[0.21]	[0.09]		[0.082]	[0.12]	
(CH₃CN)		0.924	0.974(18)	0.952(10)	0.898(10)	0.708(10)	0.849	0.876(9)	0.954(8)	892
	86	[0.90]	[7.25]					[0.43]		
(FSO₃H)		0.959(11)	0.970(11)	0.977	0.921	0.678	0.927	0.984(9)	0.996	926
	*j*	[0.87]	[7.5]					[0.39]		
(SO_2)		0.880	0.961(11)	0.956	0.889	0.556	0.929	0.854(8)	0.984	876
	*k*	[0.443]	[3.68]							
(CCl_4)		0.966	0.967(11)	0.981	0.931	0.663	0.980(11)	0.945	0.833	908
	*l*	[0.60]	[3.26]							
(CH_3COCH_3)		0.953(11)	0.913(11)	0.959	0.931	0.636	0.926	0.941	0.845	888
	11a	[0.80]	[4.33]							
($CHCl_3$)		0.941	0.836(11)	0.918	0.928	0.746	0.728	0.961	0.784	855
—NH₂	6a	[0.21]	[2.4]							
(C_6H_{12})		0.573	0.704(11)	0.953	0.763	0.236		0.834	0.463	647
	66	[0.82]	[6.38]							
($CDCl_3$)		0.950(15)	0.939(13)	0.963	0.935	0.738	0.819	0.946(9)	0.838	891
	41	[1.9]	[14.9]							
($CDCl_3$)		0.794	0.723(13)	0.702	0.783	0.988	0.205	0.756	0.690	705
	*m*	[0.670]	[4.98]							
($CDCl_3$)		0.960(10)	0.977(10)		0.977(12)	0.734(12)	0.953	0.966	0.992(7)	937

TABLE III (*Continued*)

Site x[a,b] (solvent)	Code/ ref[c]	Site y[a,b] –CH₃ (CCl₄)	–OH (DMSO)[d]	 (CDCl₃)	 (CDCl₃)	 (CDCl₃)	NH₂ (C_6H_{12})	$N^+(CH_3)_3$ (CH_3CN)	SCH_3 (CCl_4)	Avg $r \times 10^3$
 (CDCl₃)	*m*	[0.81] 0.947(10)	[5.77] 0.920(10)	0.977(12)		0.814(12)	0.763	0.934	0.975(7)	904
 (CDCl₃)	*m*	[1.17] 0.828	[9.38] 0.720(10)	0.733(12)	0.814(12)		0.236	0.765	0.829(7)	704
–CHO (CCl₄)	5	[0.59] 0.919	[3.43] 0.843(8)	0.944(8)	0.936(8)	0.418(8)	0.872	0.959	0.994(5)	861
average *r*		0.929	0.918	0.946	0.916	0.758	0.830	0.929	0.892	

[a] Each system may be represented as XC_6H_4TH, where H is the site and T the transmitting group. Unless the whole structure is indicated, each system is designated by the site. The average number of substituents was $N = 10$–11, and the range was $N = 6$–16. Each entry consists of the correlation coefficient *r*, sometimes preceded by the slope parameter [*s*] and followed by (N). [b] The sites listed horizontally supply the δ_{yi} values for eq 3; the vertically listed sites supply δ_{xi}. Since δ_y entries are also included among the δ_x entries, citations are given with the latter set. [c] A number in this column refers to systems coded in ref 2 and 3, where citations are also given. [d] Reference 16. [e] R. Tanaka, this laboratory. [f] This study. [g] Reference 3. [h] Footnote *i*, Table II. [i] B. M. Lynch, B. C. MacDonald, and J. G. K. Webb, *Tetrahedron*, **24**, 3595 (1968). [j] D. A. Tomalia and H. Hart, *Tetrahedron Lett.*, 3389 (1966). [k] Reference 15a. [l] M. A. Weinberger, R. M. Heggie, and H. L. Holmes, *Can. J. Chem.*, **43**, 2585 (1965). [m] Gurudata, J. B. Stothers, and J. D. Talman, *Can. J. Chem.*, **45**, 731 (1967).

relation studies.[15,24] Having recognized that their version of eq 2 was inadequate, Yukawa and Tsuno attempted modifications.[15] Most recently, they have taken certain terms from eq 10, and with appropriate scaling have identified two with polar and resonance effects and utilized another to correct for substituent magnetic anisotropy.[5] The latter takes into account the nature and geometry of the substituent and must be applied individually in any given aryl family. For the several meta-substituted aryl families whose SCS were correlated, the number of substituents was rather small ($N \simeq 6$–9). And, as was the case with eq 2, it is difficult to see what the polar term means in terms of the chemical structure and there appear to be problems with halogen substituents. It must be conceded, however, that, according to the goodness of fit, the correlations are impressive ($r > 0.99$).[5]

In order to obtain satisfactory correlations of SCS of an aryl family, at least one more term must be added to eq 2. Whatever virtue simplicity has, we have lost it. The question of using extended and/or modified versions of eq 1–3 *vs.* eq 10 for investigating the effect of structure on δ becomes academic and perhaps irrelevant as the two approaches move closer together.

(24) (a) T. A. Wittstruck and E. N. Trachtenberg, *J. Amer. Chem. Soc.*, **89**, 3803 (1967); (b) G. K. Hamer and W. F. Reynolds, *Can. J. Chem.*, **46**, 3813 (1968).

The Isolation, Structure, Synthesis, and Absolute Configuration of the Cactus Alkaloid Macromerine[1,2]

STANLEY D. BROWN, JOE E. HODGKINS, AND MANFRED G. REINECKE*

Department of Chemistry, Texas Christian University, Fort Worth, Texas 76129

Received July 19, 1971

(−)-Macromerine has been isolated as the major alkaloid of the cactus *Coryphantha macromeris* and its structure determined to be *N*,*N*-dimethyl-2-hydroxy-2-(3′,4′-dimethoxyphenyl)ethylamine (**3**) from spectral and analytical measurements. Two independent syntheses of racemic macromerine and one of (+)-macromerine (**3a**) were developed. The absolute configuration of (−)-macromerine was shown to be *R* by relating it to (*R*)-(−)-adrenaline (**8**).

Coryphantha macromeris is one of the more alkaloidiferous species found in our recent phytochemical surveys of cacti.[3,4] Chromatography of the crude base fraction on alumina affords the crystalline major alkaloid, macromerine, in 0.16% yield.[5] The molecular weight by mass spectroscopy (225) and the elemental analysis point to a molecular formula of $C_{12}H_{19}NO_3$ for macromerine.

The nmr spectrum in $CDCl_3$ indicates the presence of three aromatic hydrogen atoms, two methoxyl groups, an OH group, and two *N*-methyl groups (downfield shift in acid[6]). The presence of the hydroxyl group is substantiated by the infrared spectrum

(1) Taken from the (a) Masters Thesis and (b) Ph.D. Dissertation of S. D. Brown, Texas Christian University, 1965 and 1969, respectively.

(2) Partially communicated in (a) S. D. Brown and J. E. Hodgkins, 22nd Southwest Regional Meeting of the American Chemical Society, Albuquerque, N. Mex., Dec 1966, Abstracts p 60A; (b) J. E. Hodgkins, S. D. Brown, and J. L. Massingill, *Tetrahedron Lett.*, 1321 (1967).

(3) S. D. Brown, J. L. Massingill, Jr., and J. E. Hodgkins, *Phytochemistry*, **7**, 2031 (1968).

(4) S. D. Brown, J. E. Hodgkins, and M. G. Reinecke, unpublished results.

(5) Subsequent to our initial reports,[2] macromerine also was isolated from *Coryphantha runyonii* by L. E. Below, A. Y. Leung, J. L. McLaughlin, and A. G. Paul, *J. Pharm. Sci.*, **57**, 515 (1968).

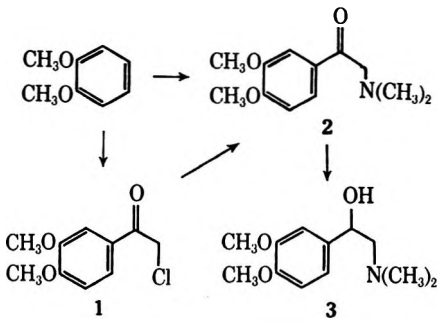
(6) J. C. N. Ma and E. W. Warnhoff, *Can. J. Chem.*, **43**, 1849 (1965).

(3125 cm^{-1}) and the *N*-methyl groups by the occurrence of a base peak in the mass spectrum at *m/e* 58 [$CH_2N(CH_3)_2^+$].[7]

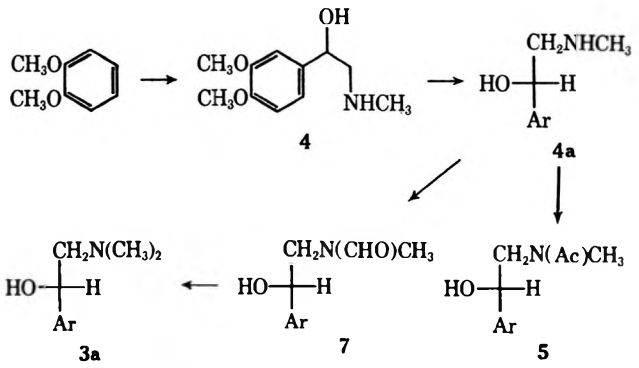
The remainder of the nmr spectrum consists of two coupled sets of double doublets centered at δ 4.60 (1 H) and 2.35 (2 H, partially overlapped by the NMe peak in $DCCl_3$ but separated in D_2O). Since the high field set of peaks moved downfield in acid they were assigned to the CH_2N group. The magnetic nonequivalence of these hydrogens suggests that the remaining hydrogen atom, to which these are coupled, must be on an asymmetric carbon atom and therefore leads to the partial structure $(MeO)_2C_6H_3CHOHCH_2N(CH_3)_2$ for macromerine.

By analogy with the known cactus alkaloids[8] the aromatic ring of macromerine is probably substituted as shown in **3**. The presence of ortho-methoxy groups is substantiated by the peaks at *m/e* 95 and 123 in the mass spectrum,[9] and the 1,2,4 pattern is consistent with the infrared spectrum in the 800–900-cm^{-1} region.[10]

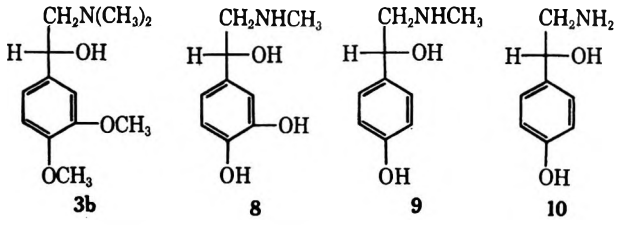
The final proof of structure, however, rests on the two syntheses[11] of (±)-macromerine. Both proceed by reduction of the amino ketone **2**, which is prepared from veratrole by either a Hoesch condensation[12] or by a Friedel–Crafts acylation[13] followed by reaction of the resulting chloro ketone **1** with dimethylamine. The former route is the more convenient and proceeds in higher overall yield (23%).



The structural relationship of macromerine (**3**) to adrenaline (**8**) (the former is the O^3,O^4,N-trimethyl derivative of the latter) prompted an investigation of the configurational relationship of these compounds. The racemic dimethyl ether of adrenaline (**4**) was prepared from veratrole by the same method[12] used to synthesize macromerine. Resolution of **4** *via* the *d*-α-bromocamphor-π-sulfonate salt led to the (+) enantiomer **4a**, which was shown to have the *S* configuration by its conversion to the known[14] (*S*)-(+)-acetamide (**5**). Formylation and reduction[15] of **4a** gave (+)-macromerine (**3a**), the enantiomer of natural (−)-macromerine (**3b**). Since **5** is the enantiomer of the acetamide **6** obtained[14] from adrenaline (**8**), both natural macromerine (**3b**) and natural adrenaline (**8**) must have the *R* configuration. This same relationship also is true[14] for naturally occurring synephrine (**9**)[16] and octopamine (**10**).[16–18]



Ar = 3,4-dimethoxphenyl



Because of the structural similarity of macromerine to adrenaline, mescaline, and other psychotomimetic agents,[19] a study of its physiological and psychopharmacological properties is underway.[1a,2b,20]

Experimental Section

All melting points were taken on a Koefler micro hot stage and are corrected. Microanalyses were performed by Scandinavian Microanalytical Laboratory, Box 25, Herlev, Denmark, or M-H-W Laboratories, P. O. Box 326, Garden City, Mich. 48135. Infrared spectra were taken of KBr discs on a Perkin-Elmer Model 237 instrument. Nmr spectra were recorded on a Varian A-60 spectrometer of $DCCl_3$ solutions with tetramethylsilane as an internal standard, unless otherwise indicated. The uv spectra were measured on a Cary 15 spectrophotometer. Mass spectra were obtained on a Finnegan Model 1015SL instrument at 70 eV. Optical rotations were taken on a Rudolph Model 76 polarimeter.

Extraction of Alkaloids.—The cactus *Coryphantha macromeris* was collected in Big Bend National Park, Brewster County, Texas.[21] The dried (50–55°, *ca.* 10% of the wet weight), powdered plant (500 g) was extracted with 95% EtOH and 0.5% HOAc for 6 days. The extracts were concentrated *in vacuo*, and water and concentrated HCl were added to give an alcohol-free solution containing *ca.* 5% HCl. The aqueous solution was washed with ether, made basic with Na_2CO_3, and extracted with ether in a continuous liquid–liquid extractor. The ether extracts were reextracted with 5% HCl, and the aqueous solutions were made basic (Na_2CO_3) and then extracted once again with ether. The purified ether extracts were dried (Na_2SO_4) and concentrated, leaving 2 g of a dark, viscous oil. Another 2 g of

(7) R. S. Gohlke and F. W. McLafferty, *Anal. Chem.*, **34**, 1281 (1962).
(8) S. Agurell, *Lloydia*, **32**, 206 (1969).
(9) C. S. Barnes and J. L. Occolowitz, *Aust. J. Chem.*, **16**, 219 (1963).
(10) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1958, pp 64–84.
(11) After this work was completed another synthesis was reported by N. B. Chapman, K. Clark, and R. D. Strickland, *Proc. Roy. Soc., Ser. B*, **163**, 116 (1965).
(12) H. D. Moed, M. Asscher, P. J. A. Van Draanen, and H. Niewind, *Recl. Trav. Chim. Pays-Bas*, **71**, 933 (1952).
(13) F. Tutin, *J. Chem. Soc.*, **97**, 2495 (1910).
(14) P. Pratesi, A. La Manna, A. Campiglio, and V. Ghialandi, *ibid.*, 2069 (1958).
(15) F. F. Blicke and C.-J. Lu, *J. Amer. Chem. Soc.*, **74**, 3933 (1952).
(16) T. A. Wheaton and I. Stewart, *Lloydia*, **33**, 244 (1970), and references cited therein.
(17) V. Erspamer, *Nature (London)*, **169**, 375 (1952).
(18) T. Kappe and M. D. Armstrong, *J. Med. Chem.*, **7**, 569 (1964).
(19) A. T. Shulgin, T. Sargent, and C. Naranjo, *Nature (London)*, **221**, 537 (1969).
(20) J. C. Hitt, S. Winokur, and M. G. Reinecke, unpublished results.
(21) We wish to thank Professor Lyman Benson, Pomona College, Claremont, Calif., for aid in classification and the United States Department of the Interior, National Park Service, for permission to harvest the plant in Big Bend National Park, Tex.

crude alkaloids was obtained by continuously extracting the first ether exhausted basic aqueous solution with CH_2Cl_2 for 24 hr.

The crude alkaloid mixture (6.37 g) from several extractions was chromatographed on 264 g of activity grade IV neutral Woelm Al_2O_3 with 400 ml of 1:1 ether–petroleum ether (bp 30–60°) to yield 2.72 g of crystalline macromerine, mp 63–65°. Rechromatography, treatment with charcoal, and recrystallization from ether yielded 2.50 g of analytically pure (−)-macromerine (**3b**): mp 66–67.5°; $[\alpha]^{25}D$ −42.6° (c 0.020, EtOH), −147.0° (c 0.0390, $CHCl_3$); nmr δ 2.25 [s, 7 H, $HCHN(CH_3)_2$], 2.35 [d, 1, J = 5 Hz, $HCHN(CH_3)_2$], 3.88 (s, 3, OCH_3), 3.93 (s, 3, OCH_3), 3.85 (s, 1, shifts with concentration changes and disappears in D_2O, OH), 4.52 and 4.66 [double d, 1, J = 5 Hz, $CHCH_2N(CH_3)_2$], 6.85 (broad s, 2, ArH), 6.95 (broad d, 1, ArH); ir 805, 875, 3125 cm^{-1} (broad); uv max (95% EtOH) 231 mμ (log ε 4.18); mass spectrum *m/e* (rel intensity) 225 (0.02) 208 (0.03), 192 (0.02), 180 (0.02), 167 (0.12), 166 (0.12), 165 (0.15), 164 (0.04), 151 (0.10), 139 (0.57), 123 (0.70), 108 (0.50), 95 (1.0), 81 (0.90), 77 (2.4), 58 (100) (lit.[5] *m/e* 225, 208, 207, 192, 180, 167, 166, 165, 164, 151).

Anal. Calcd for $C_{12}H_{19}NO_3$ (**3b**): C, 63.96; H, 8.52; N, 6.22. Found: C, 63.98; H, 8.56; N, 6.13.

3,4-Dimethoxy-ω-dimethylaminoacetopheneone (2). A.[12]—A stirred mixture of 110 ml of dry nitrobenzene, 68 g (0.51 mol) of $AlCl_3$, 27.2 g (0.23 mol) of dimethylaminoacetonitrole hydrochloride, and 31.2 g (0.23 mol) of veratrole was protected from moisture and held at 20° while dry HCl gas was bubbled through the mixture for 8 hr. The resulting viscous solution was poured into 225 ml of H_2O, boiled for 10 min, and cooled, the organic layer was decanted, and the aqueous solution was cooled to 0°. The crystals which formed were recrystallized from ethanol–2-butanone four times, yielding 22.5 g (39%) of **2** hydrochloride after drying over P_2O_5 *in vacuo*, mp 193–196° dec, ir 1685 cm^{-1} (C=O). Without the vacuum drying, the salt forms a hydrate, melting at 100°, which resolidifies and melts at 193–196°.

Anal. Calcd for $C_{12}H_{18}NClO_3$ (**2a** HCl): C, 55.49; H, 6.94; N, 5.40. Found: C, 55.39; H, 7.04; N, 5.23.

B.—3,4-Dimethoxy-ω-chloroacetopheneone (**1**) (34.6 g), prepared from veratrole by the method of Tutin,[13] was dissolved in 100 ml of absolute EtOH and added to a solution of 72.6 g of dimethylamine in 110 ml of absolute EtOH in a 500-ml boiling flask equipped with a reflux condenser and a $CaCl_2$ drying tube. The solution was stirred for 2 hr at room temperature and 2 hr at 60°, after which it was cooled at room temperature for 24 hr. The dimethylamine hydrochloride was precipitated with anhydrous ether, filtered, and washed with ether, and the combined filtrates were concentrated *in vacuo*. The residual oil was taken up in ether, dried (Na_2SO_4), and the ether removed by distillation *in vacuo*, leaving 26 g of **2** as a thick yellow oil which solidified overnight, mp 48–56°, hydrochloride mp 193–196° dec.

(±)-Macromerine (3).—A solution of 10 g (0.039 mol) of **2** hydrochloride in 50 ml of water containing 1.85 g (0.05 mol) of $NaBH_4$ was stirred for 2 hr and extracted with ether, and the ether was dried (Na_2SO_4) and removed *in vacuo*. The residual oil was recrystallized from dry ether–*n*-hexane (1:1) three times to give 5.1 g (59%) of **3**, mp 47.5–48.5°. The ir (CS_2), nmr, and uv spectra of **3** were identical with those of natural (−)-macromerine. A picrate was prepared, mp 147–148° (lit.[11] 157°).

Anal. Calcd for $C_{18}H_{22}N_4O_{10}$ (**3** picrate): C, 47.55; H, 4.89; N, 12.34. Found: C, 47.49; H, 5.02; N, 12.09.

***N*-Methyl-2-hydroxy-2-(3′,4′-dimethoxyphenyl)ethylamine (Adrenaline Dimethyl Ether) (4).**—To a solution of 20 g (0.08 mol) of *N*-methyl-2-keto-2-(3′,4′-dimethoxyphenyl)-ethylamine[12] in 60 ml of H_2O was slowly added 6.4 g (0.17 mol) of $NaBH_4$. The mixture was stirred for 2 hr and extracted with CH_2Cl_2, and the extracts were dried over Na_2SO_4. After removal of the solvent *in vacuo*, 16 g (82%) of **4** was obtained which after two recrystallizations from EtOAc melted at 107–108.5° (lit.[12] 103–105°).

Resolution of 4.—(−)-α-Bromocamphor-π-sulfonic acid ammonium salt (5.94 g, 0.018 mol) and 3.82 g (0.018 mol) of **4** were mixed in 100 ml of MeOH. The solvent was successively removed and added until the odor of ammonia was not longer present. The resulting glass was dissolved in EtOH, treated with charcoal, and recrystallized from EtOH–EtOAc to a constant melting point of 150.5–151.0° and rotation $[\alpha]^{25}D$ of +84.7° (c 0.034, EtOH).

Anal. Calcd for $C_{21}H_{32}BrNO_7S$ (**4a** bromocamphorsulfonate): C, 48.26; H, 6.13; N, 2.68; Br, 15.33; S, 6.13. Found: C, 48.28; H, 6.04; N, 2.70; Br, 16.15; S, 6.04.

A solution of 5.36 g (0.0099 mol) of the above salt in 100 ml of 1.5 *M* NH_4OH was extracted with ten 20-ml portions of CH_2Cl_2. The CH_2Cl_2 extracts were washed with 20 ml of 1.5 *M* NH_4OH, H_2O, and two 30-ml portions of saturated salt solution and dried over Na_2SO_4. The solvent was removed at reduced pressure, leaving 2.06 g (0.0098 mol) of oil **4a**, $[\alpha]^{28}D$ +23.48° (c 0.0921, EtOH), hydrochloride mp 130–131.

Anal. Calcd for $C_{11}H_{18}NO_3Cl$ (**4a** HCl): C, 53.33; H, 7.27; N, 5.66. Found: C, 53.30; H, 7.43; N, 5.61.

4a Acetamide (5).—Following the procedure of Pratesi, *et al.*,[14] 0.155 g of the resolved amine **4a** was converted to 0.106 g of the acetamide **5** after one recrystallization from benzene: mp 127–128°; $[\alpha]^{25}D$ +70.0° (c 0.00383, $CHCl_3$) [lit.[14] mp 123–124°, $[\alpha]^{18}D$ +77.4 (1.13% w/v in $CHCl_3$)]; nmr δ 2.00 (s, 3, $NCOCH_3$), 2.90 (s, 3, NCH_3), 3.39 (d, 1, J = 5 Hz, HCHN), 3.56 (d, 1, J = 5 Hz, HCHN), 3.87 (s, 6, 2 OCH_3), 4.87 and 4.96 (double d, 1, J = 5 Hz, $HCCH_2N$), 6.69 (broad s, 2, ArH), 6.80 (broad s, 1, ArH).

Anal. Calcd for $C_{13}H_{19}NO_4$ (**5**): C, 61.63; H, 7.58; N, 5.53. Found: C, 61.52; H, 7.77; N, 5.39.

4a Foramamide (7).—To a solution of 1.90 g (9 mmol) of the resolved amine **4a** in 50 ml of freshly distilled, dried (Na_2SO_4) $CHCl_3$ at 0° was added 1.33 g (9 mmol) of Cl_3CCHO freshly distilled from sulfuric acid. The solution was stirred for 5 min at 0° and 5.5 hr at room temperature, after which the $CHCl_3$ was removed at reduced pressure. The residual oil was dried by repeated solution in dry benzene followed by evaporation at reduced pressure. Eventually concentration to *ca.* 20 ml gave 1.37 g (65%) of **7**, which after recrystallization from benzene had mp 88–90°; $[\alpha]^{25}D$ +44.1° (c 0.0229, EtOH); nmr δ 2.88 (s, 3, NCH_3), 3.35 (d, 1, J = 5 Hz, HCHN), 3.52 (d, 1, J = 5 Hz, HCHN), 3.87 (s, 6, 2 OCH_3), 4.68 and 4.82 (double d, 1, J = 5 Hz, $HCCH_2N$), 6.90 (m, 3, ArH), 7.96 (s, 1, NCHO).

Anal. Calcd for $C_{12}H_{17}NO_4$ (**7**): C, 60.23; H, 7.18; N, 5.85. Found: C, 59.96; H, 7.28; N, 5.73.

(+)-Macromerine (3a).—A perforated aluminum cup containing 0.189 g (7.9 mmol) of the formamide **7** was fitted into a 24/40 to 14/20 adapter attached to a 100-ml 14/20 flask charged with 2.98 g of $LiAlH_4$ in 50 ml of dry ether. A 24/40 condenser equipped with a $CaCl_2$ drying tube was fitted on the adapter and the ether was heated under reflux until all the formamide was in solution (32 hr) and then for 12 hr longer. Excess $LiAlH_4$ was destroyed at 0° by the dropwise addition of the calculated amount of water with vigorous stirring. The mixture was filtered, the granular precipitate was washed with $CHCl_3$ (100 ml), the ether and $CHCl_3$ wash were combined and dried (Na_2SO_4), and the solvent was removed at reduced pressure to give 0.096 g of crude **3a** (mp 50–60°). Chromatography on 3 g of Woelm activity IV Al_2O_3 with 5:1 ether–*n*-hexane yielded in the second 50 ml fraction 0.014 g of pure **3a** (glc), mp 59–62°, $[\alpha]^{26}D$ +34.2° (c 0.0354, absolute EtOH). The ir and nmr spectra of synthetic (+)-macromerine (**3a**) and natural (−)-macromerine (**3b**) are identical.

Registry No.—2, 33061-24-4; 2 (HCl), 33061-25-5; (±)-**3**, 33122-27-9; **3a**, 33066-27-2; **3b**, 33066-28-3; **4a** (bromocamphorsulfonate), 33066-29-4; **4a** (HCl), 33066-30-7; **5**, 33066-31-8; **7**, 33066-32-9.

Acknowledgment.—This research was generously supported by research grants from the T. C. U. Research Foundation and The Robert A. Welch Foundation.

Mass Spectrometry in Structural and Stereochemical Problems. CCXV.[1] Behavior of Phenyl-Substituted α,β-Unsaturated Ketones upon Electron Impact. Promotion of Hydrogen Rearrangement Processes[2]

R. J. LIEDTKE,[3a] A. F. GERRARD,[3b] J. DIEKMAN,[3c] AND CARL DJERASSI*

Department of Chemistry, Stanford University, Stanford, California 94305

Received August 4, 1971

This study is concerned with the effect of phenyl substitution upon the mass spectral behavior of α,β-unsaturated ketones as an example of a substance with three potential charge-retaining sites (carbonyl, double bond, aromatic ring). Compounds of the type $C_6H_5(CH_2)_nCH{=}CHCOCH_3$, n = 2–7 (I–VI), are examined. In general, the 70-eV spectra of these compounds are dominated by peaks at *m/e* 91 (tropylium ion) and *m/e* 43 (α cleavage). At nominal 12 eV, however, lower activation energy rearrangement reactions are favored. 7-Phenylhept-3-en-2-one (II) exhibits intense peaks at *m/e* 84 and 130 (M − 58) in its mass spectrum which are notably absent in the spectrum of 3-octen-2-one (VII). The ion of mass 84 arises *via* a specific hydrogen transfer from the C_7 position while the origin of the M − 58 fragment is more complex and involves a double hydrogen atom rearrangment. The M − 58 peak in the spectrum of 6-phenylhex-3-en-2-one (I), on the other hand, is generated by transfer of a C_4 and C_6 hydrogen atom (Schemes I, IV, V). Alkyl radicals are expelled from the molecular ions of compounds II–VI. Elimination of a benzyl radical predominates for compounds in which n = 3–5, while other routes are favored in the higher homologs, n = 6–7. The loss of a water molecule is an important fragmentation pathway especially at low voltage for 9-phenylnon-3-en-2-one (IV) and 10-phenyldec-3-en-2-one (V). The "olefin McLafferty rearrangement" involves site specific hydrogen transfer when the hydrogen migrates from a benzylic position (*e.g.*, 6-phenylhex-2-ene).

Part A

Recent years have seen much effort devoted to understanding the role various functional groups play in directing electron impact induced fragmentation processes.[4] This has not only been essential for the facile application of mass spectrometry to problems of structure elucidation but has, moreover, enabled work to progress in this laboratory dedicated to the application of the principles of artificial intelligence to the interpretation of mass spectra.[5] Naturally occurring molecules, however, often contain an array of functional groups. Thus, it is not only important to appreciate the fragmentation-directing capabilities of isolated functionalities in a molecule; it is of primary significance to determine the extent to which functional centers within a molecule interact with each other after ionization.[6] In considering this problem with respect to a molecule containing functional groups A and B, two questions arise. (1) Are the individual fragmentation pathways associated with A and B retained in the spectrum of the bifunctional compound? (2) Do new decomposition routes not characteristic of either A or B individually appear? In answering, it is important to note the effect of varying the distance separating the A and B centers.

This paper is concerned with the mass spectrometric study of phenyl-substituted α,β-unsaturated ketones. In light of several recent investigations, this topic is particularly relevant. Although subject to little past attention, the mass spectral behavior of aliphatic unsaturated ketones has been the focus of a just completed, comprehensive study by Sheikh, *et al.*[7] In addition, the electron impact induced rearrangements of isomeric 1-phenylheptenes have seen recent intensive scrutiny,[8] and the marked effect that a *nonconjugated* double bond can exert on the well-known fragmentation behavior of carbonyl compounds has just been evaluated.[9]

In the course of this work, then, compounds I–VI

$C_6H_5(CH_2)_nCH{=}CHCOCH_3$

I, n = 2	IV, n = 5
II, n = 3	V, n = 6
III, n = 4	VI, n = 7

were synthesized and their mass spectra were obtained at high and low ionizing energies.[10] High-resolution mass measurements of fragment peaks were performed where necessary. Second-field free transitions were examined with computer assistance and first-field free transitions were observed using the defocusing method.[11] Compounds I–III attracted our main interest and a number of their deuterium labeled analogs were prepared, an effort that proved eminently useful.

Results and Discussion

The 70 and nominal 12 eV mass spectra of 7-phenylhept-3-en-2-one (II) and 8-phenyloct-3-en-2-one (III) are reproduced in Figures 1a,b and 2a,b, respectively. These suffice to demonstrate the typical fragmentation behavior exhibited by the compounds investigated. At 70 eV the principal peaks appear at *m/e* 91 (benzylic fission) and 43 (α cleavage adjacent to the vinylic bond). The spectrum of II exhibits a weak molecular ion even at low ionizing voltage, while that of III shows

(1) For the preceding paper, see P. D. Woodgate, K. K. Mayer, and C. Djerassi, *J. Amer. Chem. Soc.*, in press.

(2) Financial assistance by the National Institutes of Health (Grants Nos. AM 12758 and AM 04257-11) is gratefully acknowledged.

(3) (a) National Institutes of Health Predoctoral Fellow, 1968–1971; (b) Postdoctoral Research Fellow, 1968–1969; (c) Postdoctoral Research Fellow, summer, 1970.

(4) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967.

(5) (a) A. Buchs, A. M. Duffield, G. Schroll, C. Djerassi, A. B. Delfino, G. G. Buchanan, G. L. Sutherland, E. A. Feigenbaum, and J. Lederberg, *J. Amer. Chem. Soc.*, **92**, 6831 (1970); (b) A. Buchs, A. B. Delfino, A. M. Duffield, C. Djerassi, B. G. Buchanan, E. A. Feigenbaum, and J. Lederberg, *Helv. Chim. Acta*, **53**, 1394 (1970).

(6) See for example, (a) M. Sheehan, R. Spangler, and C. Djerassi, *J. Org. Chem.*, in press; (b) J. R. Dias and C. Djerassi, unpublished work; (c) P. J. Wagner, *Org. Mass Spectrom.*, **3**, 1307 (1970); C. Fenselau, A. A. Baum, and D. O. Cowan, *ibid.*, **4**, 229 (1970).

(7) Y. M. Sheikh, A. M. Duffield, and C. Djerassi, *ibid.*, **4**, 273 (1970).

(8) A. F. Gerrard and C. Djerassi, *J. Amer. Chem. Soc.*, **91**, 6808 (1969).

(9) J. R. Dias, Y. M. Sheikh, and C. Djerassi, *ibid.*, submitted for publication.

(10) The behavior of $C_6H_5CH{=}CHCOCH_3$ upon electron impact has been the subject of earlier work: J. Ronayne, D. H. Williams, and J. H. Bowie, *ibid.*, **88**, 4980 (1966).

(11) K. R. Jennings, *J. Chem. Phys.*, **43**, 4176 (1965).

a strong M^+ peak, a feature typical of the higher homologs IV–VI. Loss of water generates a significant M − 18 peak in the 12 eV spectrum (Figure 2b) of III and this process becomes increasingly more important in the spectra of 9-phenylnon-3-en-2-one (V) and 10-phenyldec-3-en-2-one (VI). The dominant fragmentation process at low voltage for II–VI involves elimination of 58 mass units, formally the loss of a molecule of acetone from the molecular ion. Thus, the base peak in the 12 eV spectrum of 7-phenylhept-3-en-2-one (II) is found at *m/e* 130 while that of III appears at *m/e* 144. This rearrangement requires transfer of two hydrogen atoms from the charge-retaining moiety to the ejected neutral fragment. Expulsion of a benzyl radical accounts for the abundant ion of mass 97 in Figure 1b and also the intense *m/e* 111 peak in Figure 2b. The molecular ion of 8-phenyloct-3-en-2-one (III) can also eject a 2-phenylethyl radical which generates a moderate peak at *m/e* 97 (Figure 2b). An intense peak in the 12 eV spectrum (Figure 1b) of 7-phenylhep-3-en-2-one (II) appears at *m/e* 84 and is the first subject to be dealt with in detail.

m/e **84 Peak.**—The observation of an abundant ion of mass 84 (78%, Σ_{40} = 26.6)[12] in the spectrum of II (Figure 1b) is surprising since virtually no *m/e* 84 peak (2%, Σ_{10} = 0.009) is seen in the 12 eV spectrum (Figure 3) of 3-octen-2-one (VII). This observation is, in

$$\mathrm{RCH_2CH_2CH{=}CHC(=O)CH_3}$$

II, R = $PhCH_2$
VII, R = CH_3CH_2

itself, a striking reflection of the ability of a phenyl substituent to enhance a particular fragmentation pathway in concert with the α,β-unsaturated ketone function.

The mass 84 ion possesses the elemental composition C_5H_8O, thus requiring the transfer of one hydrogen atom for its formation. Its increased intensity at low ionizing energy suggests its generation directly from the molecular ion. Although no normal metastable peak can be seen, use of the defocusing method results in the observation of one parent, the molecular ion, for the mass 84 species. Examination of the mass spectra of the deuterium-labeled analogs IIa–f (Table I) clearly

TABLE I

PEAK SHIFTS IN THE MASS SPECTRA OF ISOTOPICALLY LABELED ANALOGS OF 7-PHENYLHEPT-3-EN-2-ONE (II) FOR THE *m/e* 84 ION[a]

		% of *m/e* 84 which appears at[a]			
		84	85	86	87
7,7-d_2	IIa	4	96		
6,6-d_2	IIb	99	1		
5,5-d_2	IIc		1	99	
4-d_1	IId	2	98		
1,1,1-d_3	IIe				100
C_6D_5–	IIf	95	5		

[a] All compounds have been corrected to 100% isotopic purity and the shifts calculated after correcting for natural ^{13}C abundance.

demonstrates that bond fission occurs between carbon atoms 5 and 6 with carbon atoms 1–5 being encompassed by the charge-retaining moiety. Most importantly, *specific transfer* of a C_7 hydrogen to the *m/e* 84 fragment occurs. In the spectrum of 7,7-d_2-7-phenylhept-3-en-2-one (IIa) 96% of the *m/e* 84 peak is shifted to *m/e* 85.

(12) The first number refers to the relative intensity, the second to the per cent total ionization.

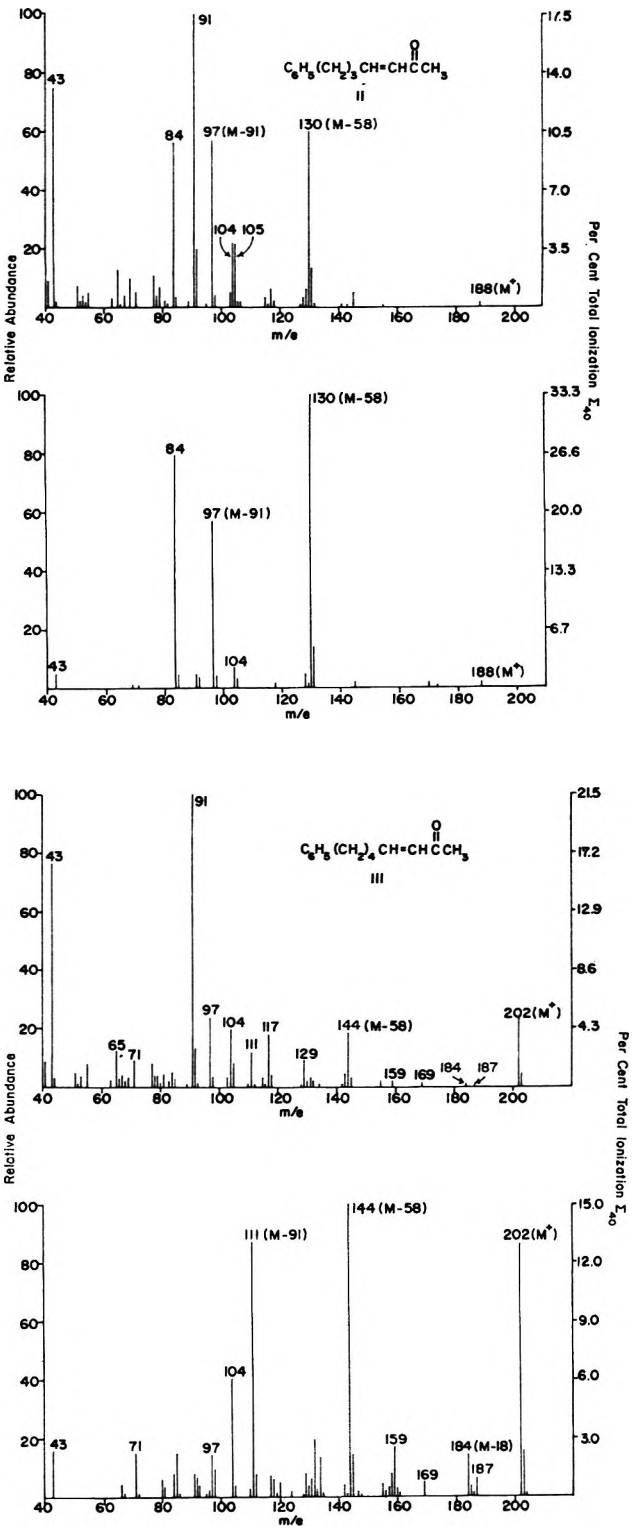
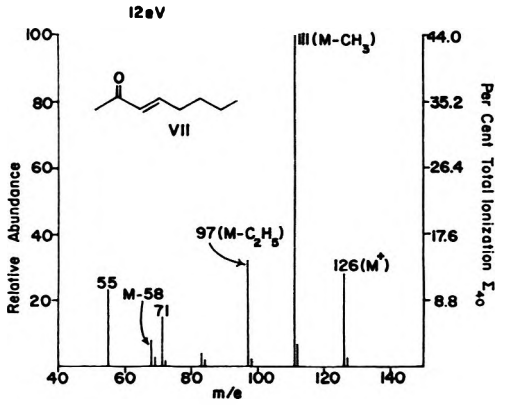


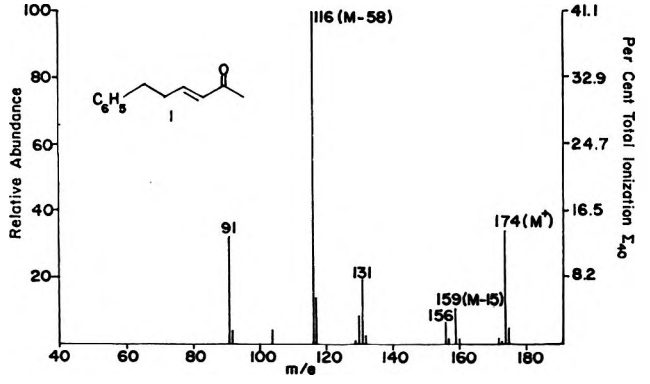
Figure 1a.—Mass spectrum (70 eV) of 7-phenylhept-3-en-2-one (II) (top).

Figure 1b.—Mass spectrum (12 eV) of 7-phenylhept-3-en-2-one (II) (bottom).

Figure 2a.—Mass spectrum (70 eV) of 8-phenyloct-3-en-2-one (III) (top).

Figure 2b.—Mass spectrum (12 eV) fo 8-phenyloct-3-en-2-one (III) (bottom).





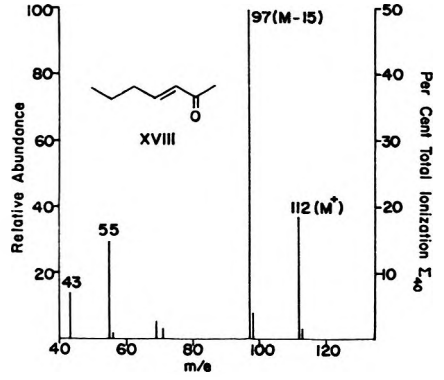


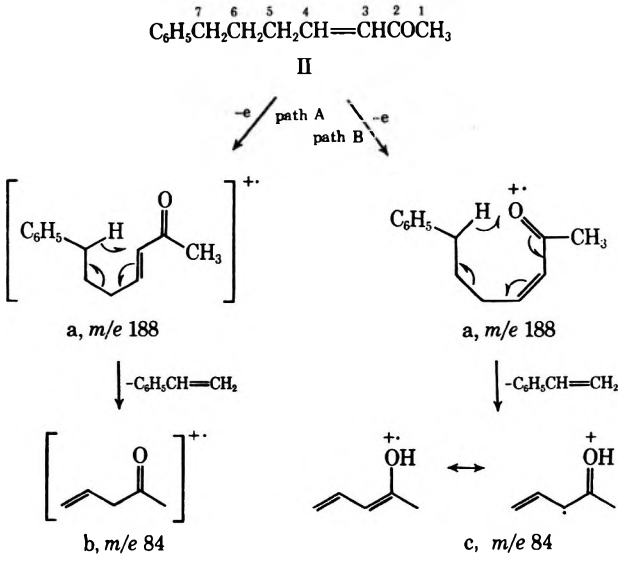
Figure 3.—Mass spectrum (12 eV) of oct-3-en-2-one (VII).
Figure 4.—Mass spectrum (12 eV) of 6-phenylhex-3-en-2-one (I).
Figure 5.—Mass spectrum (12 eV) of hept-3-en-2-one (XVIII).

Although providing evidence regarding the generation of the *m/e* 84 peak, the deuterium labeling results do not allow an unequivocal distinction between two logical pathways which can generate ions of mass 84 with totally different structures. One mode of genesis (Scheme I, path A) involves site-specific transfer of the benzylic hydrogen atom to the C_3 position with elimination of the elements of styrene and the production of a β,γ-unsaturated ketone ion b. The alternate route (path B) invokes transfer of the benzylic hydrogen atom to the ketone oxygen atom through an unusual eight-membered transition state,[13,14] with migration of the double bond to the C_4–C_5 position and the generation of a dienol ion c.

Further investigation reveals that the scope of this

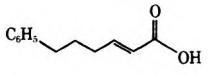
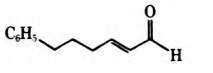
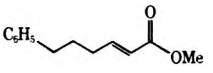
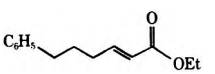
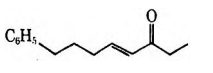
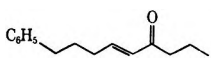
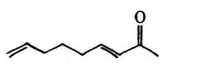
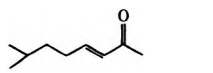
(13) An eight-membered transition state plays the dominant role in the origin of the important $M^+ - CH_3$ ion in heptyl vinyl ether.
(14) M. Katoh and C. Djerassi, *Chem. Commun.*, 1385 (1969).

SCHEME I



rearrangement process is not limited to α,β-unsaturated methyl ketones (Table II). The spectra of the

TABLE II
ABUNDANCES OF IONS RESULTING FROM THE PROCESS DEPICTED IN SCHEME I FOR VARIOUS α,β-UNSATURATED COMPOUNDS

Compd		Mass of ion formed	70 eV: % rel abundance	70 eV: % total ionization, Σ_{40}	12 eV: % rel abundance	12 eV: % total ionization, Σ_{40}
	VIII	86	14	2.5	28	5.9
	IX	70	30	6.5	42	15.1
	X	100	47	8.0	63	14.8
	XI	114	45	6.9	73	20.4
	XII	98	54	12.2	100	40
	XIII	112	43	13.3	100	25
	XIV	84	14	3.1	43	9.2
	XV	84	15	3.7	41	8.2

unsaturated acid VIII, the aldehyde IX, the methyl ester X, and ethyl ester XI all show loss of a styrene molecule to give intense peaks at *m/e* 86, 70, 100, and 114, respectively. Similarly, the process depicted in Scheme I generates the base peak of the 12-eV spectrum of both the ethyl and propyl ketones XII and XIII. All of the above-mentioned compounds have one important feature in common, a benzylicly activated hydrogen atom at C_7. An allylic or tertiary hydrogen atom can also be transferred as shown by the *m/e* 84 peaks in the spectra of XIV and XV, respec-

tively, although these peaks are of only moderate abundance. As noted before, the secondary hydrogen atom at C_7 in 3-octen-2-one (VII) does not migrate.

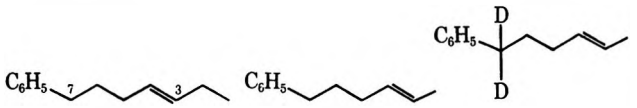
From the above data it is clear that phenyl substitution enables this hydrogen transfer process to compete successfully with other possible fragmentation routes by providing two driving forces. First, benzylic carbon–hydrogen bond dissociation energy is about 10 kcal/mol less than that of a secondary carbon–hydrogen bond.[15] Second, the phenyl group serves to stabilize the neutral olefin fragment formed. Furthermore, it is evident that ring size is of particular importance in the rearrangement process. If the phenyl group is one further position removed from the unsaturated ketone center, as in 8-phenyloct-3-en-2-one (III), only a very weak peak at m/e 84 is observed (Σ_{40} = 1.2, Figure 2b). In the spectrum of *8,8-d_2*-8-phenyloct-3-en-2-one (IIIa), 60% of the small m/e 84 peak shifts to

$RCH_2CH_2CH_2CH{=}CHC(=O)CH_3$

III, R = $C_6H_5CH_2$
IIIa, R = $C_6H_5CD_2$

m/e 85 implying that some 40% C_7 hydrogen atom transfer is occurring. Transfer of a C_8 hydrogen atom through a seven- or nine-membered transition state results not in the expulsion of a neutral olefin but in a diradical species which in the absence of internal hydrogen migration occurs as a phenyl-substituted cyclopropane. Although this path can compete with unfavorable secondary hydrogen atom transfer from C_7, the transition state energy for the process is not sufficiently low to enable favorable competition with alternative fragmentation paths available to ionized III.

m/e 104 Peak.—The 70 eV spectrum (Figure 1a) of 7-phenylhept-3-en-2-one (II) exhibits a moderately intense peak at mass 104. The genesis of this ion could follow the process outlined in Scheme I, the charge in this case being retained by the olefin fragment with ejection of a neutral C_5H_8O moiety. Transfer of the C_7 benzylic hydrogen atom is involved as the m/e 104 peak shifts (>90%) to mass 105 in the spectrum of the *7,7-d_2* labeled analog IIa. It has been observed that the mass spectrum of 7-phenylhept-3-ene (XVI)



XVI XVII XVIIa

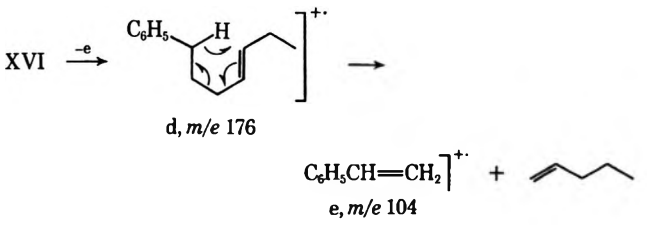
exhibits a base peak at m/e 104 both at high and low ionizing voltages.[8] The generation of this 104 ion could similarly involve specific transfer of a C_7 hydrogen to C_3, the charge remaining with the phenyl-substituted olefin fragment e, C_8H_8 (Scheme II). McLafferty type rearrangements of ionized disubstituted alkenes are known, however, to be preceded by extensive hydrogen randomization and double bond isomerization.[16] Therefore, it is desirable to examine the nature of the process depicted in Scheme II in more detail, since the result could have a bearing on this present study.

6-Phenylhex-2-ene (XVII) and its *6,6-d_2* analog

(15) S. Meyerson and L. C. Leitch, *J. Amer. Chem. Soc.*, **93**, 2244 (1971), and references cited therein.

(16) (a) B. J. Millard and D. F. Shaw, *J. Chem. Soc. B*, 1529 (1966); (b) M. Kraft and G. Spiteller, *Org. Mass Spectrom.*, **2**, 865 (1969); (c) K. K. Mayer and C. Djerassi, *ibid.*, in press.

SCHEME II



XVIIa were conveniently prepared and their mass spectra were scrutinized. The ion of mass 104 accounts for the base peak in the 12 eV spectrum of XVII, while in the spectrum of XVIIa the base peak is quantitatively shifted to m/e 105. Thus, the placement of a phenyl moiety at the γ position relative to the double bond results in a site-specific migration of the benzylic hydrogen atom and the process does occur as illustrated in Scheme II. It might be speculated, then, that the production of the mass 84 species by the ionized unsaturated ketone II is simply a special case of this "olefin McLafferty rearrangement." This argument would require some special charge-stabilizing capacity associated with the ionized β,γ-unsaturated species b, at least in relation to the alternative charge-carrying C_8H_8 fragment. Since authoritative information on this point is lacking, the opposite position could be taken. That is, path B of Scheme I must be operative, since only the dienol ion c could be expected to compete with the mass 104 species (e) in its ability to carry the positive charge. Clearly the method to settle the question would be to determine the actual structure of the mass 84 ion (b or c). Our previous experience with the ion–molecule reactions of other enol and keto ions[17] suggested that ion cyclotron resonance (icr) studies would be an excellent way to approach this task. Unfortunately, however, differentiation between the enone b and the dienol c was not possible by icr. Results of this work are given in part B.

$M^+ - 58$ Ion.—A striking feature of the 12 eV spectrum (Figure 4) of 6-phenylhex-3-en-2-one (I) is the base peak at m/e 116 ($M^+ - 58$), formally corresponding to loss of an acetone molecule from the molecular ion. This takes on added significance when the spectrum in Figure 4 is compared with that (Figure 5) of hept-3-en-2-one (XVIII). The most abun-

$RCH_2CH_2CH{=}CHC(=O)CH_3$

I, R = C_6H_5
XVIII, R = CH_3

dant ion observed in the latter's spectrum has a mass of 97 ($M^+ - 15$) and is the result of the conventional α cleavage.[7] Moreover, no peak at all is seen at $M^+ - 58$ (m/e 54). Thus, replacement of a methyl group with a phenyl moiety (XVIII, R = CH_3, *vs.* I, R = C_6H_5) has resulted in a dramatic change in favored decomposition pathways.[18] Operating the mass spec-

(17) J. Diekman, J. K. MacLeod, C. Djerassi, and J. D. Baldeschwieler, *J. Amer. Chem. Soc.*, **91**, 2069 (1969).

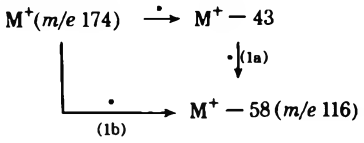
(18) Loss of what formally is a molecule of acetone has been noted previously (ref 7) in the spectra of simple unsaturated methyl ketones but only for i, R > C_4, and in these cases the process is not the most favored fragmentation path.

$CH_3C(=O)CH{=}CHR$

i

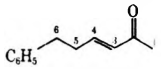
trometer in the defocusing mode, two metastable transitions leading to the mass 116 species are observed (Scheme III) with direct formation from the molecular ion predominating [(1b)/(1a) = 2.3].

SCHEME III



Several deuterium-labeled analogs of 6-phenylhex-3-en-2-one were synthesized and their mass spectra were recorded (Table III) in order to uncover the origin

TABLE III
DEUTERIUM INCORPORATION INTO THE EXPELLED NEUTRAL FRAGMENT DURING FORMATION OF THE M − 58 PEAK IN THE SPECTRUM OF 6-PHENYLHEX-3-EN-2-ONE[a]

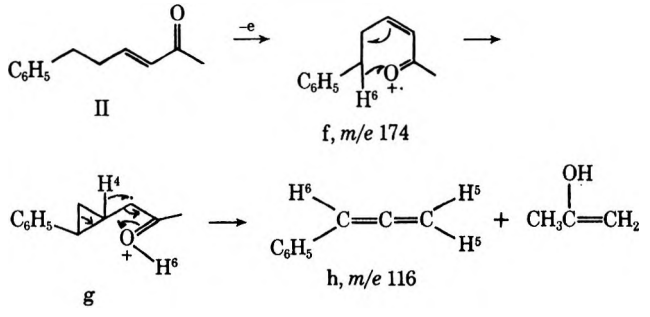


		% M+ − 58	% M+ − 59
6,6-d_2	Ia	13	87
5,5-d_2	Ib	94	6
4-d_1	Ic	6	94

[a] Data obtained at 12 eV. See footnote *a*, Table I.

of the two hydrogen atoms which must be transferred to the ejected neutral acetone molecule in the course of this process. Clearly a C_6 and the C_4 hydrogen atom are implicated. Migration of the C_4 hydrogen atom is remarkable, since fission through the C_3–C_4 olefinic bond must also occur, meaning that a total of three bonds to C_4 are broken. The possible interpretation outlined in Scheme IV is in accord with these labeling results.

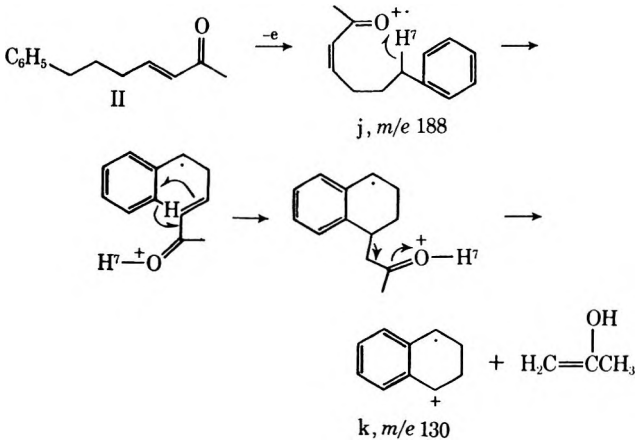
SCHEME IV



Expulsion of C_3H_6O by ionized 6-phenylhex-3-en-2-one (I) is not atypical, as loss of 58 mass units constitutes common behavior of II–VI, especially at low ionizing energy where it accounts for the base peak in the 12 eV spectrum of each compound excepting 11-phenylundec-3-en-2-one (VI), in which *m/e* 104 ion formation is slightly favored. With the several deuterium-labeled analogs of 7-phenylhept-3-en-2-one available, it is again possible to closely examine the M+ − 58 peak producing process (Table IV). As with 6-phenylhex-2-en-2-one a major source of migrating hydrogen is the benzylic C_7 position and two progenitors are found for the M+ − 58 ions formed in the first field free region, the molecular ion (*m/e* 188) and the M+ − 43 ion (*m/e* 145), the relative intensity being 1.6/1.[19] The labeling results of II are more complex than those of I, since only 23% transfer of the C_4 vinylic hydrogen is observed and notably 52%[20] of the M+ − 58 peak shifts to M+ − 59 when the aromatic ring hydrogens are replaced with deuterium.

The labeling results are consistent with prior exchange of hydrogen between *certain* positions (note that IIb and IIf give clean distributions) before rearrangement and/or several differing specific paths. Nevertheless, since the aromatic and benzylic positions are the predominant sources of migrating hydrogen, a process such as that outlined in Scheme V (j → k)

SCHEME V



appears reasonable. The scheme has the advantage of accounting for M+ − 58 ion generation irrespective of the distance between the phenyl and α,β-unsaturated ketone function. The only further stipulation is that the alkyl chain be allowed to coil in such a way as to bring the two groups into proximity, which certainly seems plausible.[6,15] The only higher homolog for which a labeled derivative was available is 8-phenyloct-3-en-2-one (III). In the spectrum of 8,8-d_2-8-phenyloct-3-en-2-one (IIIa) 41% of the M+ − 58 peak is shifted to M+ − 59 and 9% appears at M+ − 60. Thus, the benzylic position continues to be a major source of transferred hydrogen.

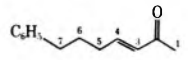
Like the process outlined in Scheme I, this double hydrogen rearrangement is not limited to ionized unsaturated methyl ketones. The α,β-unsaturated aldehydes IX and XIX exhibit intense M+ − 44 peaks in their 12 eV mass spectra while the ethyl and propyl unsaturated ketones of XII and XIII generate abundant M+ − 72 and M+ − 86 ions, respectively (Table V). Furthermore, allylic or tertiary hydrogen centers readily trigger this process (XIV, XV, XXII). On the other hand double hydrogen transfer is not such a favored fragmentation path for the unsaturated esters and acids examined.

(19) In instances in which a value such as this is cited, the number given reflects the behavior of only those ions possessing an amount of excess energy such that they fragment in the first field free region. Thus, the behavior of only a small group of ions is observed. Those higher energy ions fragmenting in the source area which constitute the normal mass spectrum could give a quite different value.

(20) The 52% is a minimum value since correction for deuterium incorporation (71% d_5, 24% d_4, 5% d_3) was made assuming equal distribution of label about the ring positions; furthermore, it is not known whether hydrogen transfer originates from a specific ring position(s).

TABLE IV

DEUTERIUM INCORPORATION INTO THE EXPELLED NEUTRAL FRAGMENT DURING THE FORMATION OF THE M − 58 PEAK IN THE SPECTRUM OF 7-PHENYLHEPT-3-EN-2-ONE (II)[a]

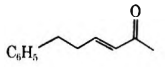
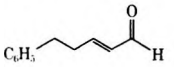
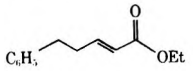
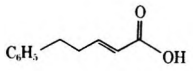
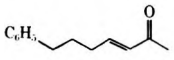
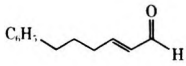
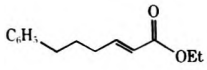
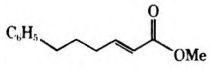
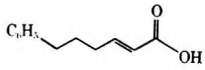
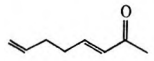
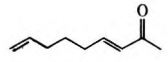
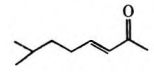
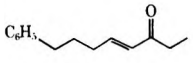
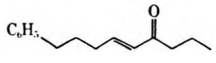


		% M⁺ − 58	% M⁺ − 59	% M⁺ − 60	% M⁺ − 61	% M⁺ − 62	% M⁺ − 63
7,7-d$_2$	IIa	12	77	12			
6,6-d$_2$	IIb	97	3				
5,5-d$_2$	IIc	89	11				
4-d$_1$	IId	77	23				
C_6D_5–	IIf	48	52				
1,1,1-d$_3$	IIe				100		
1,1,1,3,5,5-d$_6$	IIg					10	90

[a] Data obtained at 12 eV. See footnote *a*, Table I.

TABLE V

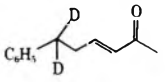
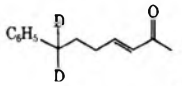
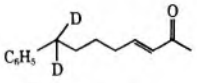
ABUNDANCES OF IONIS FORMED BY DOUBLE HHYDROGEN TRANSFER WITH FISSION THROUGH THE OLEFINIC BOND AFTER IONIZATION OF VARIOUS PHENYL-SUBSTITUTED UNSATURATED CARBONYL COMPOUNDS

Compd		Peak formed by process	70 eV % rel abundance	70 eV % total ionization, Σ_{40}	12 eV % rel abundance	12 eV % total ionization, Σ_{40}
	I	116 (M − 58)	20	11	100	41.1
	XIX	116 (M − 44)	17	10	100	40
	XX	116 (M − 88)	1.3	0.9	10	3.6
	XXI	116 (M − 60)	2.5	1.6	92	19.7
	II	130 (M − 58)	60	10.5	100	33.3
	IX	130 (M − 44)	46	10	100	36
	XI	130 (M − 88)	36	5.5	38	10.5
	X	130 (M − 74)	37	6.3	60	14
	VIII	130 (M − 60)	28	7	100	16.2
	XXII	66 (M − 58)	9	2.4	23	5.8
	XIV	80 (M − 58)	34	7.5	100	21.4
	XV	82 (M − 58)	22	5.5	100	20
	XII	130 (M − 72)	40	9.7	74	29.6
	XIII	130 (M − 86)	35	10.9	82	20.5

m/e **91 Peak.**—As mentioned earlier, the mass 91 ion is a dominant feature of the mass spectra of II–VI at high electron beam energies. Its intensity sharply diminishes at 12 eV (Figure 1a *vs.* Figure 1b), and this behavior is consistent with a high activation energy for this bond cleavage process. Data in Tables VI and VII, however, indicate that the situation is more complex. Table VI lists the shifts of the *m/e* 91 peak in the spectra of analogs Ia, IIa, and IIIa in which the benzylic position has been specifically deuterated. While 96% of the *m/e* 91 peak in the spectrum of *6,6-d*$_2$-6-phenyl-3-en-2-one (IVa) is shifted to *m/e* 93, only 78% shifts to mass 93 in the spectrum of *7,7-d*$_2$-7-phenylhept-3-en-2-one (IIa), 13% being found at *m/e* 92 and 9% remaining at mass 91. Similarly intriguing, only 60% of the *m/e* 91 peak appears at mass 93 in the

TABLE VI

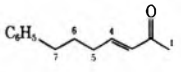
SHIFT OF THE *m/e* 91 PEAK IN THE MASS SPECTRA OF DEUTERIUM-LABELED ANALOGS OF I–III[a]

Compd		% of *m/e* 91 peak which appears at 91	92	93
	Ia	1	3	96
	IIa	9	13	78
	IIIa	18	23	60

[a] Data collected at 70 eV; see footnote *a*, Table I.

TABLE VII

SHIFT OF THE *m/e* 91 PEAK IN THE SPECTRA OF DEUTERIUM-LABELED ANALOGS OF II[a]



		% of peak at *m/e* 91 in the spectrum of II which appears at 91	92	93	94	95	96
C_6D_5	IIf					8	92
7,7-d$_2$	IIa	9	13	78			
6,6-d$_2$	IIb	87	13				
5,5-d$_2$	IIc	78	22				
4-d$_1$	IId	97	3				
1,1,1-d$_3$	IIe	100	0				
1,1,1,5,5,5-d$_6$	IIg	78	22				

[a] See footnote *a*, Table I; data taken at 70 eV and corrected for contribution of *m/e* 92 peak.

spectrum of *8,8-d*$_2$-8-phenyloct-3-en-2-one, 18% actually remaining at *m/e* 91. It is evident that considerable hydrogen exchange is occurring in the last two cases. Shifts of the *m/e* 91 peak in the other available labeled analogs of 7-phenylhept-3-en-2-one (II) are shown in Table VII. The major contributors to the exchange process are the allylic hydrogens at C_5 and those at C_6.[21]

Generation of the *m/e* 91 peak in 6-phenylhex-3-en-2-one (I) is especially facile because the bond cleaved is both benzylic and allylic. This accounts for the relatively low degree of hydrogen exchange. In compounds II and III a slightly higher energy bond must be broken and additionally, more degrees of freedom are available in which to distribute excess excitation energy. Hydrogen exchange, thus, is more evident in the latter two cases. It is also conceivable that low activation rearrangement pathways involving hydrogen exchange could be directly contributing to mass 91 ion formation and concomitantly to the labeling results. The tropylium ion structure l is favored for the *m/e*

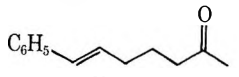
l

91 species[22] and in these examples cleavage may be accompanied to some extent by simultaneous rearrangement to l.

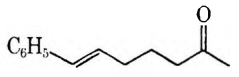
(21) The data are internally consistent; *i.e.*, the sum of deuterium migration from positions C_4, C_5, and C_6 approximately equals that observed when C_7 and the aromatic ring positions are labeled.

(22) I. Howe and F. W. McLafferty, *J. Amer. Chem. Soc.*, **93**, 99 (1971), and references cited therein.

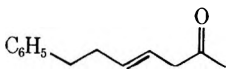
Other $C_{13}H_{16}O$ Double Bond Isomers.—It has been observed that the mass spectra of 1-phenylheptene isomers are qualitatively identical owing to the ease of double bond migration after ionization.[8] Therefore, it is pertinent to compare the mass spectra of phenyl-substituted unsaturated ketone isomers of II in which the double bond is not in conjugation with the carbonyl function (*e.g.*, XXIII–XV). The only abundant ion



XXIII



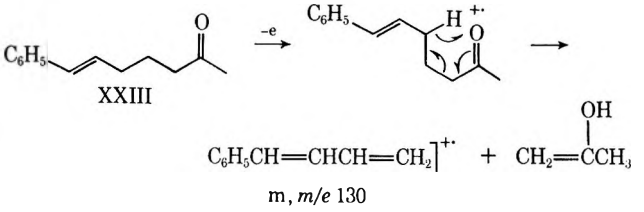
XXIV



XXV

generated by ionized 7-phenylhept-6-en-2-one (XXIII) at 70 eV has mass 130. Minor fragments of mass 43, 91, and 115 are observed. At 12 eV the ion of mass 130 accounts for 85% of the total ion current.[23] While in the case of 7-phenylhept-3-en-2-one (II) a double hydrogen transfer process is required for $M^+ - 58$ ion formation, in this instance a simple McLafferty rearrangement with preferred charge retention by the olefinic species m rather than the carbonyl-containing fragment no doubt accounts for the *m/e* 130 peak (Scheme VI).

SCHEME VI



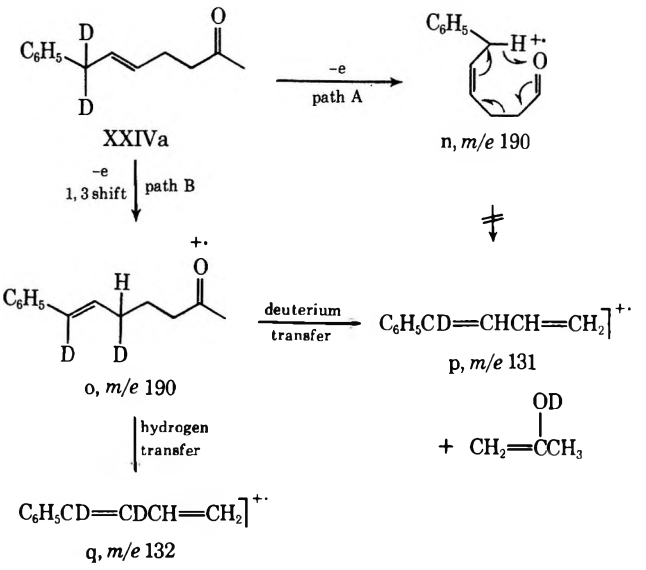
m, *m/e* 130

The spectra of ionized 7-phenylhept-5-en-2-one (XXIV) at 70 and 12 eV are virtually identical with those of XXIII except for the much smaller molecular ion peak in the former. To elucidate the rearrangement pathway involved in the formation of the mass 130 species from ionized XXIV, the spectrum of its *7,7-d*$_2$ labeled analog XXIVa was examined. Direct transfer of a C_7 deuterium atom to the carbonyl oxygen through an eight-membered transition state, n → p (Scheme VII, path A) would require that the 130 peak shift solely to *m/e* 131 in the spectrum of XXIVa. In actual fact, however, 48% of the *m/e* 130 peak appears at *m/e* 131 and 52% at *m/e* 132. This striking result is best accommodated by double bond isomerization (1,3-hydrogen shift) to the C_6–C_7 position after ionization giving o and subsequent transfer of either hydrogen or deuterium from C_5 *via* a six-membered transition state yielding respectively ion q (*m/e* 132) and ion p (*m/e* 131).

The β,γ-unsaturated ketone isomer 7-phenylhept-4-en-2-one (XXV), on the other hand, exhibits a mass spectrum qualitatively similar to that of 7-phenylhept-3-en-2-one (II). The *m/e* 91 and 43 ions account for slightly higher portions of the ion current in the 70 eV spectrum of XXV compared with that of II, and at low

(23) Corrected for ^{13}C isotope contributions. The molecular ion accounts for the remaining 15%.

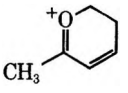
SCHEME VII



ionizing voltage a notable difference is that the *m/e* 97 ion ($M^+ - 91$) rather than *m/e* 130 is base peak. These observations are reasonable, since α cleavage involves allylic rather than vinylic fission and the bond broken in the process of *m/e* 91 and *m/e* 97 generation is both benzylic and allylic in the case of XXV. Migration of the double bond into conjugation with the carbonyl group prior to fragmentation would account for the qualitative similarities of the spectra.

Part B

Expulsion of various phenyl-substituted alkyl radicals from the molecular ions of II–VI is a favored fragmentation behavior (Table VIII). Peaks formed as a result of these processes generally increase in relative intensity at low ionizing energy, indicating that low activation energy rearrangement pathways are likely being followed. Phenyl substitution is not a strict requirement for radical expulsion. The 12-eV spectrum of oct-3-en-2-one (Figure 3) contains a prominent *m/e* 97 ion ($M^+ - C_2H_5$) for which structure r, consistent with labeling results, has been postulated.[7] Preferential formation of this six-membered ring structure is a satisfactory explanation for the predominance of *m/e* 97 ion formation ($M^+ - R\cdot$) in the series of unsaturated ketones VII, XXVII, and XXVIII.



r, *m/e* 97

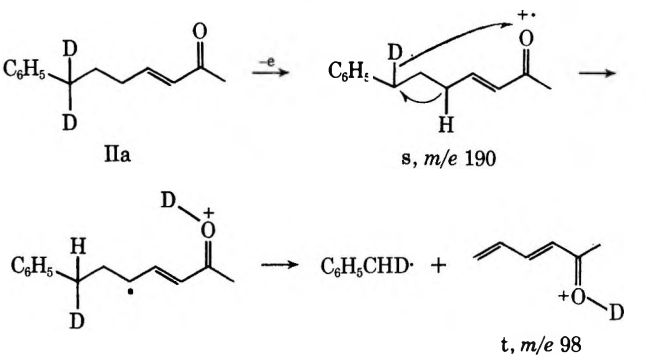
$CH_3COCH{=}CHCH_2CH_2R$

VII R = C_2H_5
XXVII R = C_3H_7
XXVIII R = C_4H_9

Examination of the data presented in Table VIII reveals, however, that the relative stability of the departing radical has an important influence on the most favored ejection modes. Six-membered ring formation would be consistent with the generation of the intense *m/e* 97 peak ($M^+ - 91$) in the spectrum (Figure 1b) of 7-phenylhept-2-en-3-one (II). However, in the spectrum of 8-phenyloct-3-en-2-one (III) and 9-pyenyl-3-en-2-one (IV) loss of the more stable benzyl radical effectively dominates the factor(s) (ring formation is a plausible one) favoring production of the *m/e* 97 species in the aliphatic ketone series. On the other hand, benzyl radical expulsion is not the dominant route followed by ionized 10-phenyldec-3-en-2-one (V) and 11-phenyldodec-3-en-2-one (VI), thus confirming that the interplay of several factors must determine the extent to which the various possible radicals are ejected.

The shifts of the mass 97 peak in the spectra of the labeled analogs of II appear in Table IX. Significant exchange of the C_7 (benzylic), C_5 (allylic), and aromatic ring hydrogen atoms occurs before cleavage. A reciprocal hydrogen transfer process of the type illustrated in Scheme VIII (s → t) offers a plausible ex-

SCHEME VIII



planation for C_7–C_5 hydrogen exchange. As observed for the mass 91 ion, $M^+ - 91$ ion formation by III upon electron impact is accompanied by increased exchange of the benzylic hydrogens relative to II. In the 12 eV spectrum of the *8,8-d*$_2$ analog IIIa only 35% $M^+ - 93$ loss is observed while 48% $M^+ - 92$ and 17% $M^+ - 91$ expulsion is seen.

Further Discussion.—An abundant metastable ion at *m/e* 56.7 is found in the spectrum of II representing the ejection of a methyl radical from the mass 84 ion. Metastable defocusing confirms the mass 84 ion as a parent to the *m/e* 69 species. In the spectrum of *1,1,1-d*$_3$-phenylhept-3-en-2-one (IIe), the *m/e* 84 peak shifts quantitatively to *m/e* 87 while 84% of the *m/e* 69

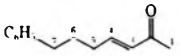
TABLE VIII

PHENYL-SUBSTITUTED ALKYL RADICAL EXPULSION PROCESSES IN THE MASS SPECTRA OF THE PHENYL-SUBSTITUTED KETONES II–VI

	Radical expelled (relative abundance, 12 eV)				
Compd	$PhCH_2\cdot$ (M − 91)	$PhCH_2CH_2\cdot$ (M − 105)	$Ph(CH_2)_2CH_2\cdot$ (M − 119)	$Ph(CH_2)_3CH_2\cdot$ (M − 133)	$Ph(CH_2)_4CH_2\cdot$ (M − 147)
$C_6H_5(CH_2)_3CH{=}CH(C{=}O)CH_3$ II	97[a] (57)[b]				
$C_6H_5(CH_2)_4CH{=}CH(C{=}O)CH_3$ III	111 (87)	97 (14)			
$C_6H_5(CH_2)_5(CH{=}CH(C{=}O)CH_3$ IV	125 (79)	111 (41)	97 (52)		
$C_6H_5(CH_2)_6CH{=}CH(C{=}O)CH_3$ V	139 (18)	125 (52)	111 (9)	97 (19)	
$C_6H_5(CH_2)_7CH{=}CH(C{=}O)CH_3$ VI	153 (3)	139 (2)	125 (20)	111 (6)	97 (15)

[a] Mass of ion formed. [b] Relative abundance.

TABLE IX
SHIFT OF *m/e* 97 PEAK IN THE MASS SPECTRA OF DEUTERIUM-LABELED ANALOGS[a] OF II



		% of *m/e* 97 peak which appears at						
		97	98	99	100	101	102	103
C_6D_5–	IIf	70,[b] 79[c]	30, 21					
7,7-d$_2$	IIa	84, 63	15, 36	1, 1				
6,6-d$_2$	IIb		2, 2	98, 98				
5,5-d$_2$	IIc	1, 4	45, 42	54, 54				
4-d$_1$	IId	0, 0	100, 100					
1,1,1-d$_3$	IIe			1, 1	99, 99			
1,1,1,3,5,5-d$_6$	IIg					1, 3	55, 55	44, 42

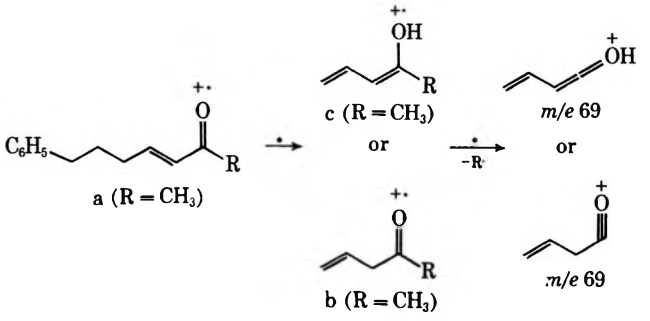
[a] See footnote *a*, Table I. [b] 70 eV. [c] 12 eV.

TABLE X
ABUNDANCE OF *m/e* 104, $M^+ - 104$, AND $M - H_2O$ IONS IN SPECTRA OF II–VI (12 eV)

		m/e 104		$M^+ - 104$		$M^+ - H_2O$	
Compd		% rel abundance	% total ionization, Σ_{40}	% rel abundance	% total ionization, Σ_{40}	% rel abundance	% total ionization, Σ_{40}
$C_6H_5(CH_2)_3CH{=}CH(C{=}O)CH_3$	II	7	2.3	78	26.6	2	0.7
$C_6H_5(CH_2)_4CH{=}CH(C{=}O)CH_3$	III	40	6.0	8	1.2	14	2.1
$C_6H_5(CH_2)_5CH{=}CH(C{=}O)CH_3$	IV	45	5.5	9	1.1	51	6.1
$C_6H_5(CH_2)_6CH{=}CH(C{=}O)CH_3$	V	43	4.9	2	0.2	56	6.4
$C_6H_5(CH_2)_7CH{=}CH(C{=}O)CH_3$	VI	60	12	2	0.4	15	3

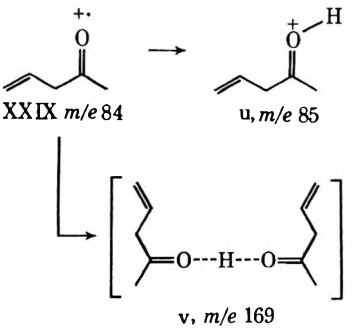
peak remains at mass 69, demonstrating that predominant ejection of the C_1 carbon atom and attached hydrogens is taking place (Scheme IX, R = CH_3). Significant *m/e* 69 peaks are likewise seen in the 70 eV spectra of 8-phenyloct-4-en-3-one (XII, R = C_2H_5) and 9-phenylnon-5-en-4-one (XIII, R = C_3H_7). The appropriate metastable peaks are observed for these latter two cases supporting the pathway outlined in Scheme IX.

SCHEME IX



Phenyl substitution stimulates the loss of H_2O from the molecular ions of compounds III–VI at low ionizing voltage (Table X). In the spectrum of 11-phenylundec-3-en-2-one (VI) the $M^+ - 18$ ion has a 54% relative abundance, the base peak being the molecular ion. Similarly, the mass 104 ion, although of minor importance in the 12 eV spectrum of II (Figure 1b), exhibits a higher degree of prominence in the low voltage spectra of III–VI and the mass 104 ion, in fact, is the most abundant fragment generated by VI upon ionization. Large-membered transition states could be involved on the transfer of the single hydrogen atom that is necessarily part of this latter process. On the other hand, double bond migration to the γ,δ position relative to the benzylic carbon atom followed by hydrogen transfer through a favorable six-membered ring is also possible. In the spectrum of *8,8-d*$_2$-8-phenyloct-3-en-2-one (IIIa) 63% of the *m/e* 104 peak moves to mass 105, 17% to 106, with 20% remaining at *m/e* 104. Thus, the progenitors of the mass 104 species possess sufficient lifetimes for extensive hydrogen exchange to take place, and concomitant double bond migration in these ions would not be surprising. Mass 104 ion generation by various 1-phenylheptene isomers was found to be far from straightforward, and several rearrangement pathways involving extensive 1, 2 and 1, 3 hydrogen shifts were invoked to explain the labeling data.[8]

Ion Cyclotron Resonance Studies.—In order to differentiate between paths A and B (Scheme I), facile and unambiguous generation of the isomeric enone b and dienol c C_5H_6O ions by electron impact followed by a comparison of the ion–molecule reactions of each by ion cyclotron resonance techniques would be necessary. The enone ion b is generated by ionization of pent-4-en-2-one (XXIX) and the ion cyclotron resonance spectrum of XXIX does display a strong molecular ion at mass 84.[24] The two α-cleavage ions, *m/e* 43 (aa) and 69 (bb), result from collision induced[25] or unimolecular decompositions of ionized pent-4-en-2-one. Ion–molecule reactions produce the protonated molecular ion (u, *m/e* 85) and the loosely bound protonated dimer (v, *m/e* 169).[17,22] Surprisingly, none of the condensation reactions found in the ion cyclotron resonance spectra[17,26] of saturated alkanones are ob-



(24) It is reported (E. Stenhagen, S. Abrahamsson and F. W. McLafferty, "Atlas of Mass Spectral Data," Vol. 1, Interscience Publishers, New York, N. Y., 1969, p 124) that this molecular ion of pent-4-en-2-one is very weak at 70 eV, but we observed that this peak carries 24% of the total ion current at 12 eV.

(25) F. Kaplan, *J. Amer. Chem. Soc.*, **90**, 4483 (1968).

(26) F. Kaplan, unpublished work; F. Kaplan, J. L. Beauchamp, J. Diekman, and C. Djerassi, unpublished observations.

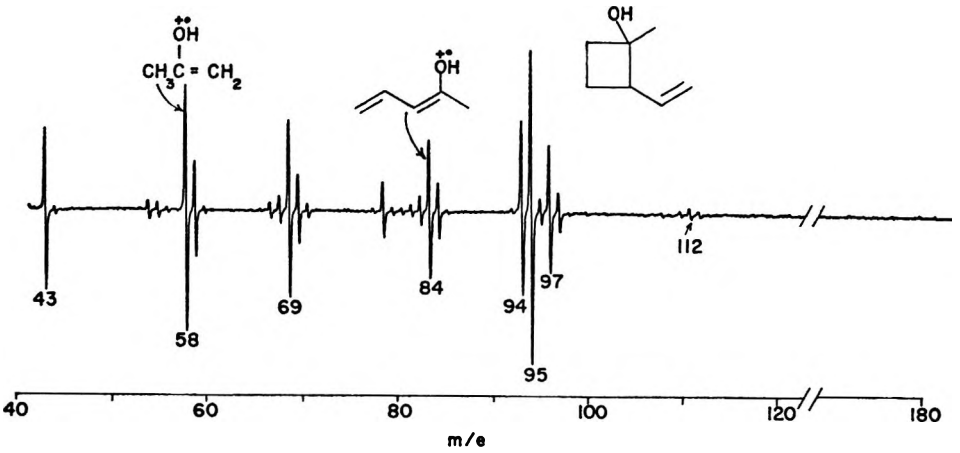
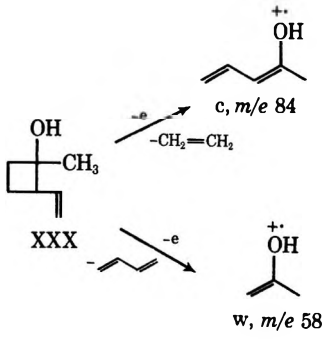


Figure 6.—Ion cyclotron resonance spectrum of pent-4-en-2-one (XXIX), $\omega_1/2\pi$ = 123.0 kcps, 6×10^{-6} Torr, 14 eV

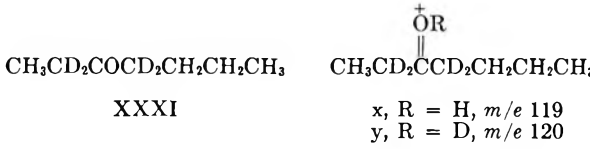
served, thereby eliminating the possibility of utilizing condensation reactions to differentiate between the isomeric mass 84 ions. Such reactions are important in distinguishing between the enol and keto ions of acetone. Emphasis thus focussed on proton transfer reactions for purposes of distinguishing the enone b and dienol c isomers. Pulsed double resonance spectra of the protonated molecular ion u (*m/e* 85) reveal that only the *m/e* 43 acylium ion aa transfers a proton to neutral pent-4-en-2-one. That proton transfer from the enone b (*m/e* 84) ion to neutral ketone does not occur was determined by pulsed double resonance experiments on the protonated molecular ion of 3-heptanone (equimolar mixture with pent-4-en-2-one).

Fragmentation of the molecular ion of 2-vinyl-1-methylcyclobutan-1-ol (XXX) should yield the desired dienol ion c of mass 84. Although the 12 eV mass spectrum (Figure 6) of this compound indicates that the preferred ring fission involves loss of butadiene (XXX → w, Scheme X), the *m/e* 84 peak (XXX → c)

SCHEME X



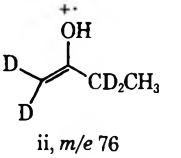
is of significant enough intensity (47%, Σ_{40} = 9.8) to be useful in ion cyclotron resonance experiments. With the intention of studying proton transfer from the dienol ion c to a neutral ketone acceptor, the ion cyclotron resonance spectrum of a mixture of *2,2,4,4-d*$_4$-3-heptanone[27] (XXXI) and 2-vinyl-1-methylcyclobutan-1-ol (XXX) was recorded. As anticipated, the only peaks observed, except for those attributed to the normal unimolecular decomposition of compounds XXX and XXXI, are those associated with the protonated (x, *m/e* 119) and deuterated (y, *m/e* 120) molecular ions of *2,2,4,4-d*$_4$-3-heptanone (XXXI). It was surprising to observe that the dienol species (c) of mass 84 does *not* transfer a proton to the neutral ketone (XXXI). The ion of mass 43 is the only significant proton transfer agent, as its signal pictured in the double resonance spectrum (Figure 7) is only 20% of its actual intensity. As observed in previous studies,[17] the mass 58 acetone enol ion donates a proton; and to a very minor extent the enolic species of mass 76[28] and the α-cleavage ion of mass 59 also donate a proton to the 3-heptanone analog (XXXI). Other work in these laboratories[29] has shown that triethylamine is far superior to aliphatic ketones in abstracting protons from charged species, but ion cyclotron resonance experiments involving a mixture of triethylamine and 2-vinyl-1-methylcyclobutan-1-ol (XXX) indicated again that no proton transfer from the dienol ion c to triethylamine occurs.



Since no characteristic reactions were observed for the C_5H_8O ions of either the dienol (c) or enone (b) structure, no statement is possible concerning the structure of the mass 84 ion generated from 7-phenyl-3-hepten-2-one (II). The inertness of the C_5H_8O ions toward ion–molecule reactions under experimental conditions[17] in which the acetone enol and keto species do indeed react deserves further comment. Proton transfer reactions from the dienol c may be endothermic and thus not detectable. Although the C_3H_6O enol ion readily transfers a proton to neutral species, subtle changes in ion structure can totally alter the reactivity of the ion. The additional conjugated double bond in

(27) A deuterated analog (XXXI) of 3-heptanone was utilized so as to move the protonated molecular ion of 3-heptanone into a region of the spectrum entirely free of other peaks. The protonated molecular ion thus has a mass of 119 and the deuterated molecular ion a mass of 120.

(28) This enolic species is generated from *2,2,4,4-d*$_4$-3-heptanone *via* the McLafferty rearrangement.



ii, *m/e* 76

(29) M. Sheehan and C. Djerassi, unpublished observations.

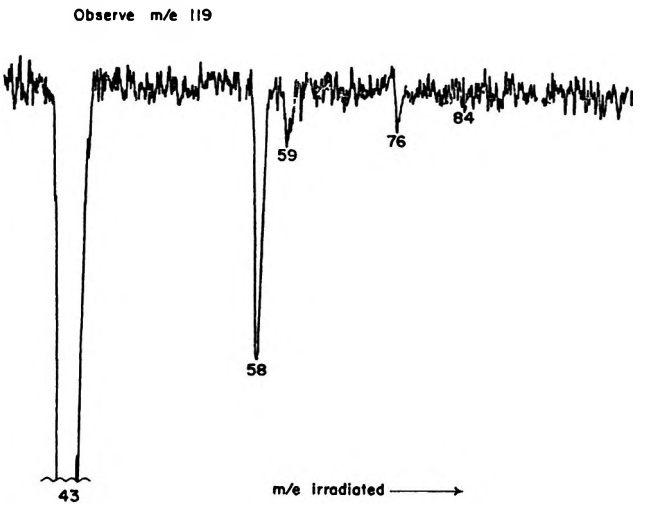
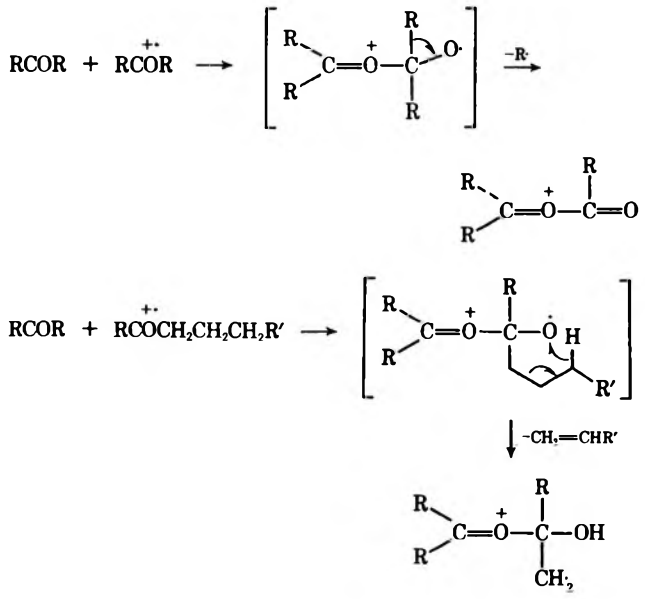


Figure 7.—The pulsed double resonance spectrum of the M + 1 (m/e 119) ion of *2,2,4,4-d*$_4$-3-heptanone (XXXI) in an equimolar mixture of 2-vinyl-1-methylcyclobutan-1-ol (XXX), and *2,2,4,4-d*$_4$-3-heptanone. The species of mass 119 is observed with $\omega_1/2\pi$ = 151.0 kcps, while frequency ω_2 is swept through the mass range 40–115. The recorder has been increased in attenuation to the point where the intensity of the m/e 43 signal is only 20% of its true value. This was done in order to observe any possible minor contributions from the m/e 84 species. The spectrum was recorded at 5×10^{-6} Torr, 0.08 irradiating voltage, and 13 eV ionizing energy.

dienol c may allow delocalization of the positive charge throughout the ion so as to make transfer of a proton an unfavorable process. It is also a possibility that the dienol ion c rearranges to some other structure, perhaps b, which does not participate in proton transfer reactions. That the m/e 84 enone ion b does not take part in the condensation reactions found to be typical of smaller aliphatic keto ions is also surprising, since both the radical eliminated and the product ion formed would appear to be quite stable species (Scheme XI).

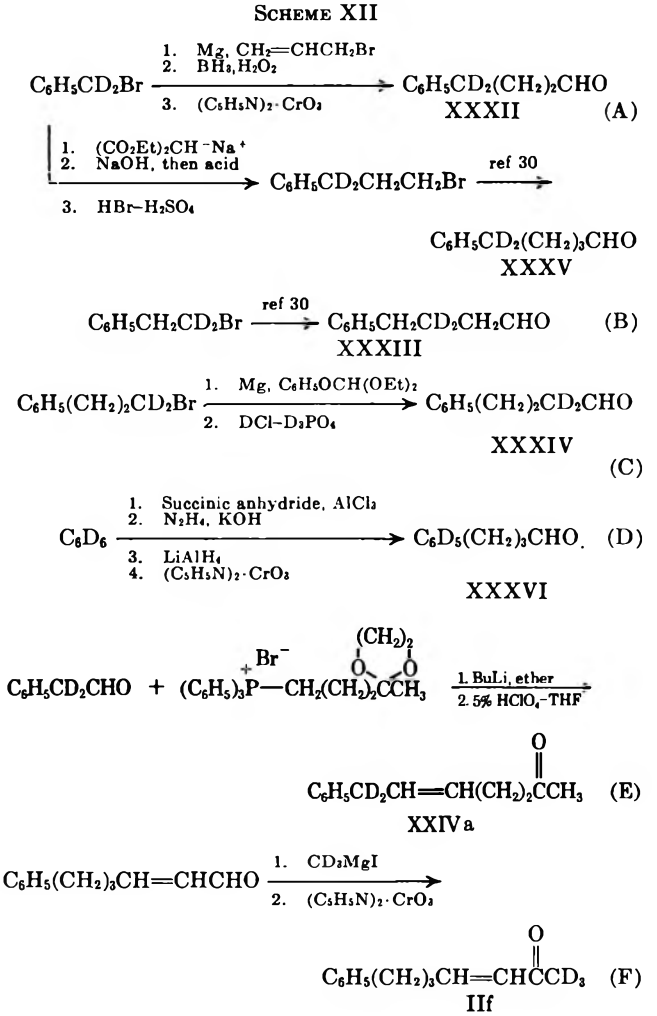
SCHEME XI



The presence of a double bond in the β,γ position of the side chain of b apparently makes the occurrence of these reactions less favorable.

Synthesis of Labeled Compounds.—In general, the deuterium-labeled α,β-unsaturated ketones employed in this study were prepared by the reaction of the appropriate deuterium-labeled aldehyde with the ylide derived from 2-oxopropyltriphenylphosphonium chloride. The aldehydes were synthesized as outlined in Scheme XII (A, B,[30] C,[30] D). Deuterium was first

SCHEME XII



introduced into a suitable phenyl-substituted alcohol by lithium aluminum deuteride reduction of the corresponding acid, followed by alkyl chain homologation of the corresponding labeled alkyl halide. Reaction of α-deuterium labeled aldehydes such as XXXIV with the ylide was complicated by exchange of the deuterium atoms with the active hydrogen of the ylide under a variety of experimental conditions.[31] However, stirring equimolar amounts of Li_2CO_3, the phosphonium salt, and aldehyde XXXIV in 70% THF–H_2O overnight at room temperature effectively avoided this problem.

7,7-d$_2$-7-Phenylhept-5-en-2-one (XXIVa) and *1,1,1-d*$_3$-phenylhept-3-en-2-one (IIf) were made as illustrated in Scheme XII (E and F, respectively).

(30) (a) A. I. Meyers, A. Nabeya, H. Adickes, and I. R. Politzer, *J. Amer. Chem. Soc.*, **91**, 763 (1969); (b) A. I. Meyers, E. M. Smith, and A. F. Jurjevich, *ibid.*, **93**, 2314 (1971), and references cited therein to experimental procedures.

(31) T. B. Malloy, Jr., R. M. Hedges, and F. Fisher, *J. Org. Chem.*, **35**, 4256 (1970).

Experimental Section

Mass spectra were obtained by Mr. R. G. Ross using an AEI MS-9 double-focusing mass spectrometer (heated inlet 150°, ion source temperature 180°) and by Mr. R. Conover on an Atlas CH-4 instrument using an E-4B ion source and direct insertion probe (samples absorbed on charcoal). Spectra of compounds run on both of these instruments were essentially identical. The direct inlet procedure had the advantage of minimizing metal-catalyzed dehydrogenation observed to a slight extent when several of the samples were passed through the heated inlet system of the MS-9. Metastable transitions in the first field-free region were observed with the aid of the defocusing procedure.[11] The Varian V-5900 spectrometer fitted with a dual inlet system was used in the ion cyclotron resonance studies. The spectrometer, the method, and applications of single and double resonance have been described.[32,33] Compounds were submitted for mass spectral measurement only after purification by vapor phase chromatography (6 ft × 0.25 in., 3% OV 25 on Gas-Chrom Q; 6 ft × 0.25 in, 5% Carbowax 20M on Chromosorb W, both columns glass).

Infrared characterization was carried out using a Perkin-Elmer Model 700 spectrophotometer. Nmr spectra were obtained with either a Varian Model T-60 spectrometer or a Varian HA-100 spectrometer (measured by Mr. M. Bramwell) and are recorded in δ values with carbon tetrachloride as solvent and tetramethylsilane as an internal reference standard. The spectral characteristics not explicitly stated of all compounds used in this study were found to be in agreement with the material's assigned structure. The elementary composition of all new compounds was determined by mass spectral molecular weight determination.

α,β-Unsaturated Ketones $C_6H_5(CH_2)_nCH{=}CHCOCH_3$ (n = 2–7) (I–VI).—Compounds I–VI were prepared from the appropriate aldehyde precursor by similar procedures illustrated for II (n = 3). 4-Phenylbutanal was prepared in 80% yield by oxidation of 4-phenylbutanol[34] on a 10-mmol scale using chromium trioxide–pyridine complex made *in situ*.[35] The aldehyde (1.0 g, 6.75 mmol), 2-oxopropyltriphenylphosphonium chloride (2.4 g, 6.75 mmol), and 800 mg of sodium carbonate were stirred with 23 ml of tetrahydrofuran and 7 ml of water at reflux for 15 hr. Ether was added, the layers were separated, and the organic material was washed with brine and dried over magnesium sulfate. Evaporation of the solvent was followed by the addition of hexane and gravity filtration to remove the crystalline triphenylphosphine oxide. The hexane was evaporated and the product was distilled (bulb to bulb, 1 Torr) to give 1.1 g (87%) of 7-phenylhept-3-en-2-one (II). Analysis by vpc showed the presence of two isomers (ratio ~ 90:10) and the major peak was collected: ir λ_{max}^{neat} 1618, 1670, and 1690 cm^{-1}; nmr δ 1.83 (m, 2 H, $CH_2CH_2CH_2$), 2.12 (s, 3 H, $COCH_3$), 2.22 (m, 2 H, CH_2-$CH_2CH{=}$), 2.64 (t, 2 H, $C_6H_5CH_2CH_2$), 5.96 (d, 1 H, J = 16 Hz, $CH{=}CHCO$), 6.65 (d of t, 1 H, $CH_2CH{=}CH$), 7.12 (m, 5 H, C_6H_5). The 16-Hz coupling constant allows assignment of trans double bond geometry.

The other aldehydes used in preparation of III–VI were obtained as follows. 3-Phenylpropanal is commercially available. 5-Phenylpentanal was obtained in moderate yield from 1-bromo-3-phenylpropane using the procedure of Meyers, *et al.*[30] The precursor of IV (n = 5), 6-phenylhexanal, is available by conversion of 4-phenylbutanol to its bromide (hydrobromic acid–sulfuric acid) and then two carbon chain homologation employing the standard diethyl malonate procedure.[36] Reduction of the resulting 6-phenylhexanoic acid to its alcohol and subsequent oxidation[35] gave 6-phenylhexanal.

The synthesis of 7-phenylheptanal was accomplished by first converting 6-phenylhexanol to its bromide. Then, under argon, 643 mg of magnesium (26.4 mmol, 10% excess) was placed in a dry 250-ml flask equipped with magnetic stirrer, reflux condenser, and serum cap. 1-Bromo-6-phenylhexane (500 mg) in 3 ml of dry ether was added. After reaction initiation the remainder of the bromide (5.04 g, 24 mmol total) was added with 75 ml of ether. After heating under reflux for 45 min the mixture was cooled (ice bath) and diethyl phenyl orthoformate[37] (4.24 g, 21.6 mmol) in 10 ml of ether was added. The mixture was refluxed for 1 hr, cooled to room temperature, and poured into 30% ammonium chloride. The organic layer was washed with 5% sodium hydroxide (three times), water, and brine. Distillation gave 3.8 g of the diethyl acetal of 7-phenylheptanal (63% from the bromide).[38] Conversion to the aldehyde was done by stirring the acetal (25°) with 25 ml of 5% hydrochloric acid overnight (argon). Distillation (bulb to bulb, 1 Torr) gave 7-phenylheptanal (2.4 g, 90%).

8-Phenyloctanal was prepared by oxidation[35] of 8-phenyloctan-1-ol, which was made from 1-bromo-4-phenylbutane by successive diethyl malonate homologations and reduction of the resulting 8-phenyloctanoic acid.

***O*-Methyloxime Derivatives.**—Due to the low-intensity molecular ion peak observed for compounds IIa–f it was necessary to find a suitable derivative having an abundant molecular ion and negligible $M^+ - 1$ and $M^+ - 2$ peaks for isotopic analysis. The *O*-methyloxime fulfilled these requirements and in addition was easily prepared. Equimolar amounts of the unsaturated ketone, *N*-methoxyamine hydrochloride, and pyridine were heated for 10 min on a steam bath and allowed to stand overnight. Ether was added and the organic material was washed with water and dried (magnesium sulfate). A sample of the unsaturated *O*-methyloxime was then purified by vpc and submitted for mass spectral analysis at 12 eV.

***7,7-d_2*-7-Phenylhept-3-en-2-one (IIa).**—Reduction of methyl benzoate (11 g, 80 mmol) with lithium aluminum deuteride (2.5 g, 60 mmol) in dry ether and work-up by adding first 2 ml of deuterium oxide followed by 10% sulfuric acid gave after distillation α,α-d_2-benzyl alcohol (7.7 g, 90%). Conversion to the chloride was accomplished by dissolving pyridine (5.5 g, 70 mmol) and the alcohol (7.7 g, 70 mmol) in 50 ml of chloroform. Thionyl chloride (8.82 g, 73.5 mmol) in 25 ml of chloroform was then added dropwise over 30 min (spontaneous reflux). The mixture was stirred at 25° for 3 hr, washed with water, 5% sulfuric acid, 10% sodium bicarbonate, and brine, and dried over magnesium sulfate. Distillation gave α,α-d_2-benzyl chloride (7.4 g, 83%). The chloride (7.4 g) was converted to the Grignard reagent which was coupled with allyl bromide[39] to give *4,4-d_2*-4-phenylbut-1-ene (5.63 g, 74%). Conversion to *4,4-d_2*-phenylbutan-1-ol using diborane and hydrogen peroxide was done in the usual way. Oxidation[35] of the alcohol gave *4,4-d_2*-4-phenylbutanal (XXXII) (2% d_1, 98% d_2), which gave IIa as described above for II. A sample of IIa was converted to its *O*-methyloxime derivative, M^+ 219 (98% d_2), 218 (2% d_1).

***6,6-d_2*-7-Phenylhept-3-en-2-one (IIb).**—Reduction (lithium aluminum deuteride) of methyl phenylacetate gave *1,1-d_2*-2-phenylethanol, which after conversion to its bromide[40] gave according to the procedure of Meyers, *et al.*,[30] *3,3-d_2*-4-phenylbutanal (2% d_1, 98% d_2) which was converted to IIb as above; *O*-methyloxime derivative, M^+ 219 (98% d_2), 218 (2% d_1).

***5,5-d_2*-7-Phenylhept-3-en-2-one (IIc).**—Reduction of methyl 3-phenylpropionate with lithium aluminum deuteride was followed by conversion of the resulting alcohol to its bromide. Treatment of the corresponding Grignard reagent with diethyl phenyl orthoformate gave the diethyl acetal of *2,2-d_2*-4-phenylbutanal. Hydrolysis (5% deuteriochloric acid–deuteriophosphoric acid from deuterium oxide and phosphorus pentachloride) gave *2,2-d_2*-4-phenylbutanal (5% d_1, 95% d_2). Reaction of the aldehyde with the ylide derived from 2-oxopropyltriphenylphosphonium chloride (equimolar amount) in 70% tetrahydrofuran–water at 25° overnight gave IIc: *O*-methyloxime derivative, M^+ 220 (<2% d_2), 219 (93% d_2), 218 (<5% d_1); nmr δ 2.22 ($CH_2CH_2CH{=}$) *absent*, integration of olefinic protons at δ 5.96 and 6.65 gave a ratio of one to one.

***4-d_1*-7-Phenylhept-3-en-2-one (IId).**—Treatment of methyl 4-phenylbutanoate with lithium aluminum deuteride gave *1,1-d_2*-

(32) J. L. Beauchamp, Ph.D. Thesis, Harvard University, Cambridge, Mass., 1967.

(33) J. D. Baldeschwieler, *Science*, **159**, 263 (1968).

(34) Prepared by reduction of 4-phenylbutanoic acid, the synthesis of which is described by E. L. Martin, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 499.

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

(36) (a) R. Adams and R. M. Kamm, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1932, p 250; (b) E. Vliet, C. S. Marvel, and C. M. Hseuh, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 416.

(37) Available from the Aldrich Chemical Co.

(38) The procedure is essentially that of H. Stetter and E. Reske, *Chem. Ber.*, **103**, 643 (1970).

(39) A. Turk and H. Chanan, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 121.

(40) G. A. Wiley, R. L. Hershkowitz, B. M. Rein, and B. C. Chang, *J. Amer. Chem. Soc.*, **86**, 964 (1964).

4-phenylbutan-1-ol, which was oxidized[35] to *1*-d_1-4-phenylbutanal (1% d_0, 99% d_1) and converted to IId, *O*-methyloxime derivative, M^+ 218 (99% d_2), 217 (1% d_1).

1,1,1-d_3-**7-Phenylhept-3-en-2-one** (**IIe**).—4-Phenylbutanal (11.4 g, 77 mmol) was converted to ethyl 6-phenylhex-2-enoate (XI) (10.5 g, 48 mmol) using the ylide derived from triethyl phosphonoacetate and sodium hydride.[41] Reduction of XI (10 g) with aluminum hydride (lithium aluminum hydride and 100% sulfuric acid)[42] yielded 6-phenylhex-2-en-1-ol (6.5 g, 37 mmol). This material was oxidized[35] to 6-phenylhex-2-en-1-al (IX) (4.4 g, 25.5 mmol) which was then added (1.74 g, 10 mmol) to an equimolar amount of d_3-methylmagnesium iodide in the normal manner to give *1,1,1*-d_3-7-phenylhept-3-en-2-ol (1.15 g, 6 mmol). Oxidation[35] of this led to IIe. Ice cold aqueous solutions were employed in the work-up procedure. A sample (10 mg) of IIe was obtained by preparative gas chromatography and converted to its *O*-methyloxime derivative, M^+ 220, (91%, d_3), 219 (9% d_2).

7-(d_5-**Phenyl**)**hept-3-en-2-one** (**IIf**).—d_6-Benzene was converted to 4-(d_5-phenyl)butanoic acid *via* Friedel–Crafts reaction with succinic anhydride[43] and subsequent reduction of the keto acid.[44] Lithium aluminum hydride reduction gave 4-(d_5-phenyl)butan-1-ol and oxidation[35] produced 4-(d_5-phenyl)butanal (5% d_3, 23% d_4, 72% d_5). Conversion to IIf followed as usual; *O*-methyloxime derivative, M^+ 222 (71% d_5), 221 (24% d_4), 220 (5% d_3).

6,6-d_2-**6-Phenylhex-3-en-2-one** (**Ia**) (2% d_1, 98% d_2), *5,5*-d_2-**6-phenylhex-3-en-2-one** (**Ib**) (19% d_1, 75% d_2, 5% d_3), and *4*-d_1-**6-phenylhex-3-en-2-one** (**Ic**) (1% d_0, 99% d_1) were prepared in ways analogous to the syntheses of IIa, IIc, and IId. *8,8*-d_2-**8-phenyloct-3-en-2-one** (**IIIa**) was made by treatment of the Grignard reagent derived from *4,4*-d_2-1-bromo-4-phenylbutane (see above) with diethyl phenyl orthoformate and hydrolysis by the resulting acetal to give *5,5*-d_2-5-phenylpentanal (2% d_1, 98% d_2), also available *via* Scheme XIIA, which was combined with the ylide derived from 2-oxopropyltriphenylphosphonium chloride, *O*-methyloxime derivative of IIIa, M^+ 233 (98% d_2), 232 (2% d_1).

Treatment of 6-phenylhex-2-en-1-al (IX) with ethylmagnesium bromide and propylmagnesium bromide, respectively, followed by oxidation[35] of the resulting unsaturated alcohols gave **8-phenyloct-4-en-3-one** (**XII**) and **9-phenylnon-5-en-4-one** (**XIII**). Hydrolysis of ethyl 6-phenylhex-2-enoate (XI) and ethyl-5-phenylpent-2-enoate (XX) (5% sodium hydroxide) gave **6-phenylhex-2-enoic acid** (**VIII**) and **5-phenylpent-2-enoic acid** (**XXI**). **Ethyl-5-phenylpent-2-enoate** (**XX**) was prepared using the Wadsworth–Emmons procedure, while **5-phenylpent-2-en-1-al** (**XIX**) was obtained under the conditions of Meyers, *et al.*[31] **Methyl 6-phenylhex-2-enoate** (**X**) was made by the reaction of carbomethoxymethylenetriphenylphosphorane with 4-phenylbutanal in refluxing tetrahydrofuran. Vapor phase oxidation over cupric oxide[7] of hex-5-en-1-ol and 4-methylpentan-1-ol gave hex-5-en-1-al and 4-methylpentanal. Reaction of these aldehydes with the ylide derived from 2-oxopropyltriphenylphosphonium chloride gave **nona-3,8-dien-2-one** (**XIV**) and **7-methyloct-3-en-2-one** (**XV**), respectively. Likewise, **octa-3,7-diene-2-one** (**XXII**) was synthesized starting with pent-4-en-1-ol.

6-Phenylhex-2-ene (**XVII**) and *6,6*-d_2-**6-phenylhex-2-ene** (**XVIIa**) were prepared by the reaction of the appropriate aldehyde (see above) with the ylide generated from ethyltriphenylphosphonium bromide by butyllithium in diethyl ether, XVIIa M^+ 162 (98% d_2), 161 (2% d_1).

1,1,1,3,5,5-d_6-**7-Phenylhept-3-en-2-one** (**IIf**) was prepared in low yield by the aldol condensation (5% NaOD, D_2O) of d_6-acetone with *2,2*-d_2-4-phenylbutanal,[45] isotopic purity 9% d_5, 91% d_6.

7-Phenylhept-6-en-2-one (**XXIII**)—Reaction of cyclopropylphenylcarbinol (7.4 g) with a fourfold excess of 48% hydrobromic acid for 10 min at 0° gave after distillation 7.8 g of 1-bromo-4-phenylbut-3-ene. Addition of this bromide to the anion derived by reaction of sodium hydride and methyl acetoacetate in tetrahydrofuran, stirring at room temperature overnight, and heating the crude alkylation product with ethanolic barium hydroxide[46] gave in low yield 7-phenylhept-6-en-2-one (XXIII): ir $\nu_{max}^{CCl_4}$ 1710, 1600, 960 cm^{-1} (s); nmr δ 1.78 (m, 2 H, $CH_2CH_2CH_2$), 2.06 (s, 3 H, $COCH_3$), 2.18 (t, 2 H, CH_2-CH_2CO), 2.40 (t, 2 H, $CHCH_2CH_2$), 6.06 (d of t, 1 H, CH=$CHCH_2$), 6.34 (d, 1 H, J = 16 Hz, C_6H_5CH=CH), 7.20 (m, 5 H, C_6H_5). The coupling constant (J = 16 Hz) and ir band at 960 cm^{-1} indicate trans double bond geometry.

7-Phenylhept-5-en-2-one (**XXIV**) and *7,7*-d_2-**7-phenylhept-5-en-2-one** (**XXIVa**).—Reaction of phenyl acetaldehyde with the ylide generated by the action of butyllithium on the ethylene ketal of 4-oxopentyltriphenylphosphonium bromide[47] in dry ether gave the ethylene ketal of XXIV. Treatment of this ketal with 5% perchloric acid–tetrahydrofuran for 15 min (25°) gave 7-phenylhept-5-en-2-one (XXIV): ir $\lambda_{max}^{CCl_4}$ 1710, 1600, 960 cm^{-1} (w); nmr δ 2.06 (s, 3 H, $COCH_3$), 240 (m, 4 H, HC-CH_2CH_2CO), 3.37 (d, 2 H, J = 6 Hz, $C_6H_5CH_2CH$), 5.5 (m, 2 H, CH=CH), 7.14 (m, 5 H, C_6H_5). Spectral data indicated a mixture of cis and trans isomers. The labeled analog was similarly prepared from α,α-d_2-phenylacetaldehyde and the ylide, M^+ 189 (4.5% d_1), 190 (89% d_2), 191 (6.5% d_3).

7-Phenylhept-4-en-2-one (**XXV**) was prepared by the photolysis of 7-phenylhept-3-en-2-one under the conditions of Yang:[48] ir $\lambda_{max}^{CCl_4}$ 1710 cm^{-1}; nmr δ 1.98 and 2.00 [s, 3 H (sum), $COCH_3$], 2.37 (m, 2 H, CH_2CH_2CH), 2.66 (m, 2 H, $PhCH_2CH_2$), 2.98 (m, 2 H, CH_2CH_2CH), 5.56 (m, 2 H, CH=CH), 7.12 (m, 2 H, C_6H_5). The absorptions quoted indicate the presence of cis and trans β,γ-unsaturated isomers (87%). Additional absorptions show cis α,β-unsaturated isomer present (13%).

Pent-4-en-2-one (**XXIX**).—Oxidation of 860 mg of pent-4-en-2-ol in 70 ml of acetone at 15° with 2.5 ml of Jones reagent according to the conditions of Djerassi, *et al.*,[49] yielded 820 mg of crude pent-4-en-2-one. Vapor phase chromatography gave the pure ketone, ir $\lambda_{max}^{CCl_4}$ 1715 and 1649 cm^{-1}.

2-Vinyl-1-methylcyclobutan-1-ol (**XXX**).—Reaction of the sodium enolate of ethyl acetoacetate with 4-bromobut-1-ene in dry tetrahydrofuran according to the conditions of Ronald[50] yielded 3-carboethoxyhept-6-en-2-one: bp 115–118° (20 Torr); ir λ_{max}^{neat} 1740, 1720, 1650, 915 cm^{-1}. Hydrolysis with sodium hydroxide and decarboxylation in dimethylformamide also according to the conditions of Ronald[50] gave hept-6-en-2-one, which was isolated by distillation: bp 97–98° (110 Torr) [lit.[51] bp 41–43° (10 Torr)]; ir λ_{max}^{neat} 1709, 1640, 920 cm^{-1}. Photolysis of a 10% solution of hept-6-en-2-one in pentane according to the conditions of Yang[52] gave a mixture of products from which pure 2-vinyl-1-methylcyclobutan-1-ol was isolated by preparative vpc. The infrared and nmr spectra were identical with those reported by Yang.[52]

2,2,4,4-d_4-**3-Heptanone** (**XXXI**).—A mixture of 1.5 g of 3-heptanone, 30 ml of deuterium oxide, and 30 ml of glyme was heated under reflux for 48 hr. Sodium chloride was added and the labeled 3-heptanone (XXXI) was extracted with ether. After evaporation of the ether, *2,2,4,4*-d_4-3-heptanone was isolated by preparative vpc, M^+ 116 (3% d_2), 117 (6% d_3), 118 (91% d_4).

Registry No.—I, 33046-41-2; Ia, 33046-42-3; Ib, 33046-43-4; Ic, 33191-92-3; II, 33191-93-4; IIa, 33191-94-5; IIb, 33046-44-5; IIc, 33191-95-6; IId, 33046-64-9; IIe, 33046-65-0; IIf, 33046-66-1; IIg, 33046-67-2; III, 33046-68-3; IIIa, 33046-69-4; IV, 33046-70-7; V, 33046-71-8; VI, 33046-72-9; VII,

(41) W. S. Wadsworth, Jr., and W. D. Emmons, *J. Amer. Chem. Soc.*, **83**, 1733 (1961).

(42) W. M. Yoon and H. C. Brown, *ibid.*, **90**, 2927 (1968).

(43) L. F. Somerville and C. F. Allen, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 81.

(44) Huang-Minlon, *J. Amer. Chem. Soc.*, **68**, 2487 (1946).

(45) See ref 7 and references cited therein.

(46) S. F. Brady, M. A. Ilton, and W. S. Johnson, *J. Amer. Chem. Soc.*, **90**, 2882 (1968).

(47) We express thanks to the Zoecon Corp., Palo Alto, Calif., for a generous sample of this material.

(48) N. C. Yang and M. J. Jorgenson, *Tetrahedro Lett.*, 1203 (1964).

(49) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(50) R. Ronald, Ph.D. Thesis, Stanford University, Stanford, Calif., 1970.

(51) "Dictionary of Organic Compounds," Vol. 3, Oxford University Press, New York, N. Y., 1965.

(52) N. C. Yang, S. P. Elliot, and B. Kim, *J. Amer. Chem. Soc.*, **91**, 7551 (1969); N. C. Yang, A. Morduchowitz and D. H. Yang, *ibid.*, **85**, 1017 (1963). We thank Professor Yang for supplying us with detailed experimental conditions regarding both the photolysis and isolation of XXX.

1669-44-9; VIII, 24271-23-6; IX, 33046-75-2; X, 33046-76-3; XI, 33046-77-4; XII, 33046-78-5; XIII, 33046-79-6; XIV, 33046-80-9; XV, 33046-81-0; XVIIa, 33046-82-1; XVIII, 1119-44-4; XIX, 33046-84-3; XX, 6048-08-4; XXI, 24271-22-5; XXII, 3643-55-8; XXIII, 33046-88-7; XXIV, 33046-89-8; XXIVa, 33046-90-1; XXV, 33046-91-2; XXIX, 13891-87-7; XXX, 33046-93-4.

The Synthesis of the A,B and D,E Rings of Medicagenic Acid[1]

JAMES D. METZGER, MICHAEL W. BAKER, AND ROBERT J. MORRIS*

Department of Chemistry and the Division of Biochemistry, University of Nevada System, Reno, Nevada 89507

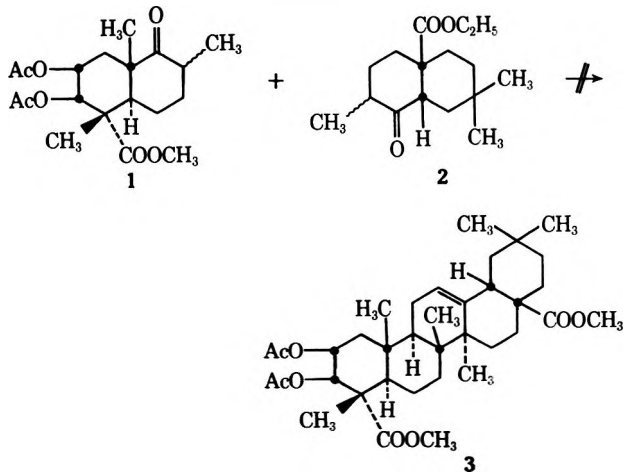
Received July 6, 1971

The synthesis of two decalin derivatives to be used in an AB + DE type synthesis of dimethyl diacetoxymedicagenate (3) has been accomplished. The A,B segment has a final structure of 1β,6,10β-trimethyl-1α-carbomethoxy-2β,3β-diacetoxy-*trans*-5-decalone (1). The D,E portion has a final structure of 10-carbethoxy-2,7,7-trimethyl-*cis*-decal-1-one (2). These compounds represent versatile intermediates which will be used in seeking a total synthesis of the sapogenin molecule through annelation of the two fragments.

Interest in medicagenic acid has developed from several studies including its isolation, purification, physiological activity, and biological role in alfalfa forage.[2,3] As reported in earlier communications,[4,5] medicagenic acid was found to be the aglycone in both alfalfa root and blossom saponins, and a pure root saponin was synthesized from the purified natural acid and β-D-glucose.[6]

Our approach to the synthesis focused on an AB + DE sequence in order to avoid the extremely difficult task of building the molecule by attaching each of the five rings with their variety of substituents in successive order. The first half of the study, reported here, required the creation of two stereospecific decalin precursors possessing suitable reaction sites for coupling. A second investigation will be devoted to an examination of different annelation procedures in order to successfully join these two compounds (Scheme I).

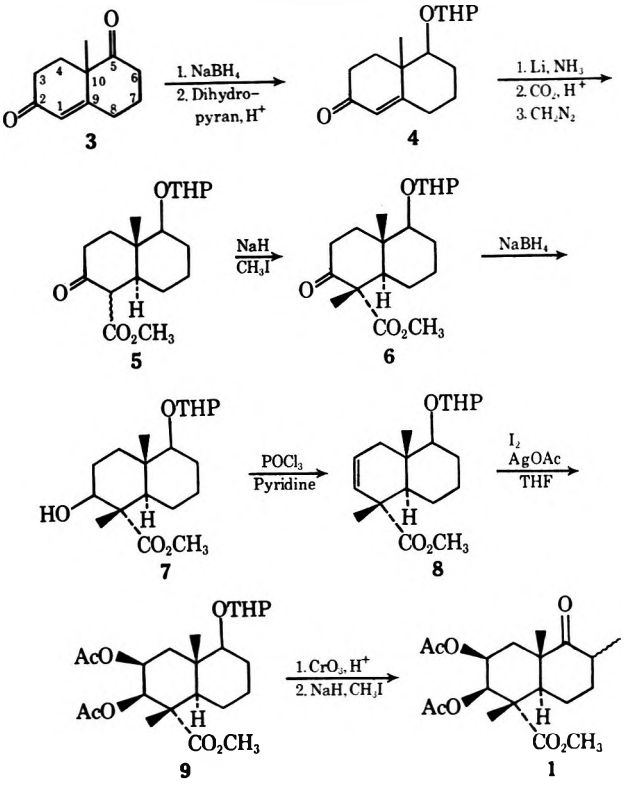
SCHEME I



To allow for flexibility in the synthesis, bicyclic systems were chosen which offer both a high degree of versatility and yet essentially duplicate large portions of the natural molecule. The adaptability of these compounds for the coupling reaction is determined by the variety of reactions which can occur at the ketone groups.

The two compounds will be treated separately, beginning with the synthesis of the A,B ring system (Scheme II). The problems anticipated were essentially threefold: (1) effecting a trans ring juncture; (2) the formation of the correct stereochemistry for the groups at carbon 1; and (3) the introduction of the 2β,3β-diacetoxy group.

SCHEME II



A solution to the first two of these problems was conveniently offered by one series of reactions. Stork

(1) Partial support for this work provided by the University of Nevada, Reno, Agricultural Experiment Station, Journal Series 188 is gratefully acknowledged.

(2) E. D. Walter, G. R. Van Atta, C. R. Thompson, and W. D. Maclay, *J. Amer. Chem. Soc.*, **76**, 2271 (1954).

(3) C. Djerassi, D. B. Thomas, A. L. Livingston, and C. R. Thompson, *ibid.*, **79**, 5292 (1957).

(4) R. J. Morris, W. B. Dye, and P. S. Gisler, *J. Org. Chem.*, **26**, 1241 (1961).

(5) R. J. Morris and E. W. Hussey, *ibid.*, **30**, 166 (1965).

(6) R. J. Morris and D. L. Tankersley, *ibid.*, **28**, 240 (1963).

and his coworkers found that lithium in liquid ammonia specifically reduced 10-methyl-$\Delta^{1(9)}$-octal-2-one and other enones of the same type preferentially to the trans fused compound.[7,8] It should be noted that, in following the general outline of this method, the β-keto acid, resulting from trapping the enolate salt with carbon dioxide, was protected immediately by preparing the methyl ester to avoid rapid decarboxylation. It was also important to introduce the C_1 methyl group in 1,2-dimethoxyethane solvent with methyl iodide as the alkylating agent. Under these conditions, the 1β-methyl compound was prepared almost exclusively over the α epimer.[9] The two epimers were distinguished by an nmr analysis which showed a characteristic chemical shift for the C_1 group.[10] In this manner, **6** was prepared as described by Spencer except that the tetrahydropyranyl ether was not removed.[11,12]

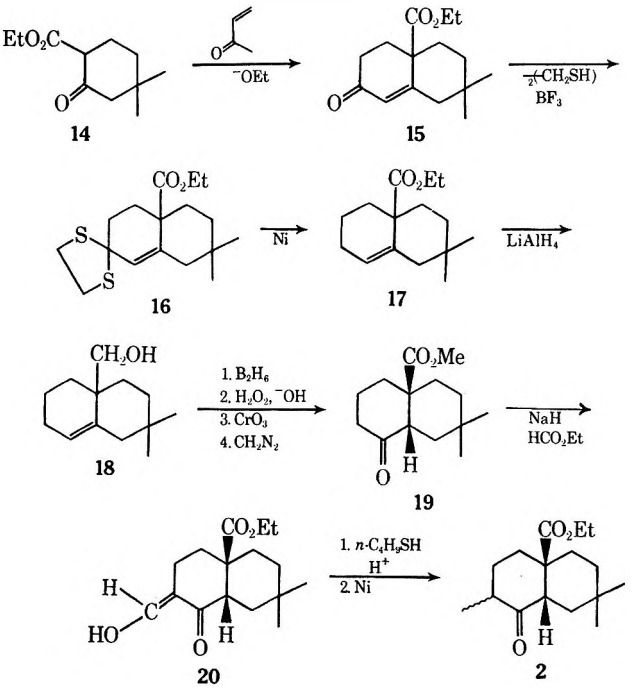
A most difficult problem to solve was the placement of the cis diacetate at carbon atoms 2 and 3. Woodward and colleagues found that iodoacetate would react with olefins to yield cis diacetates, but the conditions of the reaction needed careful control.[13] Although the solvent was not highly critical,[14] it was necessary to maintain 1 equiv of water in the reaction mixture to prepare the cis isomer in good yield. Following Woodward's method, the 2β,3β-diacetoxy group was introduced in the decalin system by the use of the pseudohalogen, iodoacetate.

The final steps of the synthesis were carried out by conventional methods. The tetrahydropyranyloxy group protecting the C_5 position was removed by mild acid hydrolysis and the resultant alcohol was oxidized with the Jones reagent. The C_6 methyl group was introduced using sodium hydride and methyl iodide in dimethoxyethane solution. It was subsequently found in the preparation of **2** that a better α-methylation procedure, resulting in a much cleaner product, employs the use of ethyl formate, followed by butyl mercaptan, with a final reduction by Raney nickel.[15] Work is now in progress to apply this procedure to the A,B ring system reported here.

The remainder of the text will be devoted to the problems associated with the synthesis of the D,E ring system (Scheme III).

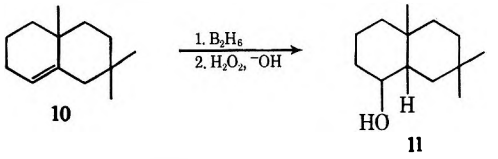
Annelation of **14** with methyl vinyl ketone[16] provided a decalin skeleton upon which three of the five necessary groups had already been positioned. Completion of the sequence consisted of removal of the 2-keto function, introduction of the 1-keto and 2-methyl substituents, and isolation of the cis isomer. It was originally thought that these steps could be accomplished by formation of the thioketal **16** followed by

SCHEME III



desulfurization with Raney nickel,[17] hydroboration of the unsaturated ester,[18] and finally methylation.

Preparation of the thioketal did proceed smoothly and treatment of **16** with Raney nickel in refluxing 95% ethanol for 3 hr provided a single product. Diborane would not react with **17** as expected, even though Sondheimer had reported the hydroxylation of hydrocarbon **10** in good yield.[19] The isomer obtained ex-



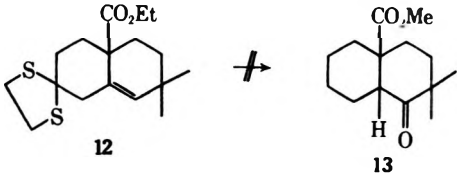
clusively in the formation of **11** was that containing a cis ring juncture. This was attributed to the blocking effect of the C_7 methyls to the approach of the diborane from the α side of the molecule. The carbethoxy group in **17** was suspected to be large enough so that now both sides of the olefin **17** would be blocked. Thus, reduction of the ester with lithium aluminum hydride to provide a group at the 10 position comparable in size to methyl was indicated. In addition, this hydroxymethyl function would not affect or be affected by the hydroxylation sequence. The additional step was found to be very beneficial, for the intermediate **18** proved to be easily sublimed and thus provided a convenient method for collecting very pure material midway through the scheme.

The alcohol did react with diborane. The resulting diol was not isolated but was oxidized with chromic acid–acetone solution to the keto acid. The acid was then treated with diazomethane to give *cis*-**19**. This manner of introducing the 1-keto function thus ensured the isolation of **2** exclusively in only one of its possible isomeric forms and eliminated the alternative, re-

(7) G. Stork and S. D. Darling, *J. Amer. Chem. Soc.*, **82**, 1512 (1960).
(8) G. Stork and J. Tsuji, *ibid.*, **83**, 2783 (1961).
(9) E. Wenkert, A. Afonso, J. Bredenberg, C. Kaneko, and A. Tahara, *ibid.*, **86**, 2038 (1964).
(10) K. L. Williamson, T. Howell, and T. A. Spencer, *ibid.*, **88**, 325 (1966).
(11) T. A. Spencer, T. D. Weaver, R. M. Villarica, R. J. Friary, J. Posler, and M. A. Schwartz, *J. Org. Chem.*, **33**, 712 (1968).
(12) T. A. Spencer, R. J. Friary, W. W. Schmiegel, J. F. Simeone, and D. S. Watt, *ibid.*, **33**, 719 (1968).
(13) R. B. Woodward and F. V. Brutcher, Jr., *J. Amer. Chem. Soc.*, **80**, 209 (1958).
(14) K. B. Wiberg and K. A. Saegebarth, *ibid.*, **79**, 6256 (1957).
(15) R. E. Ireland and J. A. Marshall, *J. Org. Chem.*, **27**, 1615, 1620 (1962).
(16) A. S. Hussey, H. P. Liao, and R. H. Baker, *J. Amer. Chem. Soc.*, **75**, 4727 (1953).
(17) G. R. Pettit and E. E. van Tamelen, *Org. React.*, **12**, 356 (1962).
(18) H. C. Brown and K. A. Keblys, *J. Amer. Chem. Soc.*, **86**, 1795 (1964).
(19) F. Sondheimer and S. Wolfe, *Can. J. Chem.*, **37**, 1870 (1959).

quiring the tedious chromatographic separation of isomers.

Methylation of **19** with methyl iodide under a variety of conditions could not be effected. The possibility that the double bond may have migrated into the opposite ring when the thioketal was formed was considered, although this is usually observed only on preparation of the oxygen-containing analogs.[20] All subsequent reactions would then take place in the alternate ring and lead to **13**, which would not be expected



12 13

to react readily with methyl iodide since two of the three α positions are already methylated. All analytical methods available to us could not distinguish between the two thioketals or between any of the possible pairs of products in subsequent reactions.

However, when the ketone and 2-furfuraldehyde were allowed to stand in an aqueous methanolic solution, an adduct was formed which had a molecular ion peak at *m/e* 316.[21] Such addition could take place only if the ketone possessed two α hydrogens, and, of the two isomers in question, only **19** does. It seemed that, if **19** would condense with 2-furfuraldehyde, it might also react with ethyl formate and so provide an alternative to direct methylation.

Introduction of an *n*-butylthiomethylene group at the 2 position can be effected by treating the hydroxymethylene derivative of the ketone[22] with *n*-butyl mercaptan.[15] Desulfurization with Raney nickel will lead to the overall insertion of methyl. This three-step sequence has been shown to be compatible with an ester group,[23] and by using sodium hydride as the base the cis ring juncture introduced in the hydroxylation of **18** would not be affected.

The reactions proceeded with ease and provided **2** in good yield.

Experimental Section

General.—Infrared spectra were determined with a Perkin-Elmer Infrared Model 257 recording spectrophotometer. Ultraviolet measurements were obtained from a Beckman Model DB-G spectrometer. Nuclear magnetic resonance spectra were determined using a 60-MHz Varian Associates A-60 spectrometer. All nmr chemical shifts are reported in parts per million from the tetramethylsilane trace used as an internal standard (TMS = 0 ppm). Unless otherwise stated, all samples were neat.

The solvents and analytical reagents for chromatographic separation, ir analyses, and nmr determinations were all of CP grade.

Microanalyses were obtained from Chemalytics Inc., Tempe, Ariz.

Experimental Procedure for the A,B Ring Synthesis. 1β,10β-Dimethyl-1α-carbomethoxy-5β-tetrahydropyranyloxy-*trans*-2-decalone (6) was prepared by the method of Spencer:[11,12] ir (KBr) 1747 (ester C=O), 1725 (C=O), and 1028 cm^{-1} (COC); nmr 3.72 (s, 3, OCH_3), 1.38 (s, 3, bridgehead methyl), and 1.12 ppm (s, 3, C_1 methyl).

Anal. Calcd for $C_{19}H_{30}O_5$: C, 66.64; H, 8.70. Found: C, 66.46; H, 8.60.

The intermediate, 10β-methyl-1α-carbomethoxy-5β-tetrahydropyranyloxy-*trans*-2-decalone, was isolated as a mixture of the two tetrahydropyranyloxy ether isomers, mp 126–130°.

1β,10β-Dimethyl-1α-carbomethoxy-5β-tetrahydropyranyloxy-*trans*-2-decalol (7).—A stirred solution of **6** (3.0 g, 0.0089 mol) in 50 ml of 95% ethanol was cooled in an ice bath and treated dropwise with a solution of sodium borohydride (0.15 g, 0.0040 mol) in 25 ml of 95% ethanol over a 10-min period. The cooling bath was removed, and the reaction was stirred for an additional 1 hr at room temperature.

Glacial acetic acid (3 ml) was added to destroy the excess borohydride, and the mixture was evaporated to a viscous red residue. The residue was taken up in 200 ml of dichloromethane, washed with two 50-ml portions of water and one 50-ml portion of saturated NaCl solution, dried (Na_2SO_4), filtered, and evaporated to give 2.9 g of product as a light yellow oil: ir shows absence of the 1725 cm^{-1} peak, broadening of the 1747 cm^{-1} peak due to interaction with the alcohol, and strong absorption of a new peak at 3500 cm^{-1} (OH); nmr 3.90 ppm (s, 1, position varies upon dilution, OH).

1β,10β-Dimethyl-1α-carbomethoxy-5β-tetrahydropyranyloxy-*trans*-Δ^2-octalin (8).—While cooling the reaction flask in an ice bath, a stirred solution of **7** (8.0 g, 0.024 mol) in 100 ml of dry, redistilled pyridine was cautiously treated dropwise with phosphorus oxychloride (7.2 g, 0.047 mol). After addition was completed, the reaction mixture was heated on a steam bath for 1 hr and then cooled to room temperature. The reaction mixture was again treated cautiously with cold water to destroy the excess phosphorus oxychloride and then poured into 300 ml of cold water. The mixture was quickly extracted with four 100-ml portions of ether. The combined ethereal fractions were washed with two 100-ml portions of water, two 75-ml portions of 10% HCl, and two 75-ml portions of saturated NaCl. The ethereal solution was dried (Na_2SO_4), filtered, and evaporated. The product, 2.68 g (34.7%), was isolated as a light yellow oil which would rapidly decolorize a 5% bromine–CCl_4 solution, ir 1665 cm^{-1} (C=C), nmr 6.0 ppm (2, vinyls).

1β,10β-Dimethyl-1α-carbomethoxy-5β-tetrahydropyranyloxy-2β,3β-diacetoxy-*trans*-decalin (9).—To a stirred solution of **8** (2.65 g, 0.00823 mol) in 100 ml of dry, redistilled THF was added silver acetate (3.10 g, 0.0185 mol) and finely powdered iodine (2.18 g, 0.00858 mol). The reaction mixture was protected from light and stirred at room temperature for 30 min. Water (0.2 g, 0.009 mol) was added, and the reaction mixture was refluxed for 4 hr, during which time the color deepened. The silver salts were filtered, and the filtrate was treated with sodium acetate (1.5 g, 0.018 mol) and acetic anhydride (2.55 g, 0.0250 mol).

After 12 hr at room temperature the mixture was treated with 100 ml of a saturated NaCl solution to precipitate any residual silver salts and to hydrolyze excess acetic anhydride. The mixture was extracted with three 100-ml portions of ether. The ether portions were combined, dried (Na_2SO_4), filtered, and evaporated. Chromatography of the residue through alumina (50 g) gave 2.4 g (63%) of **9** as a clear, viscous liquid: ir spectrum shows the disappearance of the band at 1665 cm^{-1} and the appearance of a strong peak at 1238 cm^{-1} [O(C=O)CH_3]; nmr exhibits new absorption at 1.95 and 1.90 ppm [s, 3 each, O(C=O)CH_3] which are identical with the acetate absorption values evident in dimethyl diacetoxymedicagenate.

1β,6,10β-Trimethyl-1α-carbomethoxy-2β,3β-diacetoxy-*trans*-5-decalone (1).—The above compound (**9**) (2.40 g, 0.00544 mol) was dissolved in 100 ml of absolute methanol containing 2 drops of concentrated hydrochloric acid and refluxed for 1 hr. The mixture was concentrated to 50 ml, poured into 100 ml of cold, saturated NaCl solution, and extracted with three 75-ml portions of ether. The ether fractions were combined, dried (Na_2SO_4), filtered, and evaporated to a light yellow solid.

This compound (3.2 g) was dissolved in 50 ml of purified acetone and treated dropwise with Jones reagent (8 *N* chromic acid). The mixture was stirred vigorously for 1 hr at room temperature and then concentrated to 25 ml. The reaction mixture separated into two layers, and the aqueous layer was extracted with two 50-ml portions of ether, dried (Na_2SO_4), filtered, and evaporated to 2.95 g of a light yellow compound.

This residue was dissolved in 100 ml of 1,2-dimethoxyethane and treated with NaH (0.38 g of a 53% dispersion in mineral oil, 0.0083 mol) and 10 drops of dry *tert*-butyl alcohol. After the

(20) C. Djerassi, "Steroid Reactions, An Outline for Organic Chemists," Holden-Day, San Francisco, Calif., 1963, p 22.

(21) The authors are indebted to Dr. G. Doyle Daves of the Oregon Graduate Center for the mass spectral study of **19** and its derivatives.

(22) W. S. Johnson and H. Posvic, *J. Amer. Chem. Soc.*, **69**, 1361 (1947).

(23) G. Büchi, J. A. Carlson, J. E. Powell, Jr., and L.-F. Tietze, *ibid.*, **92**, 2165 (1970).

evolution of gas had ceased, the mixture was stirred and treated with methyl iodide (11.4 g, 0.0803 mol). The reaction mixture was refluxed for 3 hr and then allowed to stir at room temperature for 12 hr. Several drops of water were added, and the reaction mixture was evaporated. This solid was dissolved in 200 ml of ether, washed with 100 ml of water and 50 ml of saturated NaCl solution, dried (Na_2SO_4), filtered, and evaporated to a viscous oily residue.

The resulting product was chromatographed through acid-washed alumina (30 g) and eluted successively with dry hexane, ether, acetone, and absolute methanol. The purified product, 1.82 g, was obtained from the ether fraction: ir 1735 (ester C=O), 1710 (C=O), and 1238 cm^{-1} [O(C=O)CH_3]; nmr 3.62 (s, 3, OCH_3), 2.00 [s, 6, O(C=O)CH_3], and a multiplet from 1.5 to 0.8 ppm corresponding to the different methylene groups. Mass spectral data offers final confirmation of the structure and exact molecular weight of the synthetic A,B ring depicted as compound 1 in Scheme II.

Anal. Calcd for $C_{19}H_{28}O_7$: C, 61.94; H, 7.66. Found: C, 60.84; H, 7.70.

Experimental Procedure for the D,E Ring Synthesis. Materials.—The following compounds, all precursors to **15**, were prepared by methods previously reported.

3-Methyl-Δ^2-cyclohexenone[24] has bp 88–89° (18 mm); $n^{28}D$ 1.4911; 59%.

3,3-Dimethylcyclohexanone[25] has bp 78–80° (28 mm); $n^{26}D$ 1.4451; 63%. Cupric acetate monohydrate (0.02 mol) was substituted in place of cuprous chloride. The Grignard (0.75 mol) was prepared in 500 ml of anhydrous ethyl ether, and 3-methyl-Δ^2-cyclohexenone (0.50 mol) in 200 ml of anhydrous THF was added at −5° in 2.5 hr.

2-Carbethoxy-5,5-dimethylcyclohexanone (**14**)[26] has bp 116–118° (11 mm); $n^{24}D$ 1.4700; 78%.

10-Carbethoxy-7,7-dimethyl-$\Delta^{1(9)}$-octal-2-one (15).—A mixture of 2-carbethoxy-5,5-dimethylcyclohexanone (46.9 g, 0.237 mol) and methyl vinyl ketone (15.1 g, 0.216 mol) was added slowly to a solution of sodium ethoxide (0.222 mol prepared from 5.10 g of freshly cut sodium metal and 250 ml of 95% ethanol). The mixture was stirred for 1 hr at 25°, refluxed for 2 hr, and then allowed to stand at room temperature overnight. An additional 15.0 g of methyl vinyl ketone was added and the mixture was refluxed, with stirring, for 4 hr. Ice (*ca.* 100 g) was cautiously introduced followed by 250 ml of dilute HCl. The product, which separated as an orange-red oil, was extracted with three 100-ml portions of ether. The combined ether extracts were washed with 100 ml of 5% aqueous sodium bicarbonate solution and dried (Na_2SO_4). Distillation with a free flame provided 30.3 g (54.6%) of **15**: bp 146–152° (10 mm); ir 1720 (ester C=O), 1680 (C=O), and 1385 and 1365 cm^{-1} (*gem*-dimethyl); nmr (CCl_4) 5.78 (s, 1, vinyl), 4.21 (q, 2, OCH_2CH_3), 1.28 (t, 3, OCH_2CH_3), and 1.04 and 0.89 ppm (s, 3 each, C_7 methyls); uv max (95% ethanol) 239 nm (ϵ 15,500). The bands in the ir spectrum attributed to the *gem*-dimethyl group are very characteristic and appear in the spectra of all subsequent compounds.

Elution of a small sample (50 mg) from activated alumina (8.2 g) with 75 ml of petroleum ether (bp 60–110°) provided a thick, nearly colorless oil which solidified upon refrigeration.

10-Carbethoxy-7,7-dimethyl-$\Delta^{1(9)}$-octal-2-one Ethylene Dithioketal (16).—A mixture of **15** (5.00 g, 0.0200 mol) and ethanedithiol (3.80 g, 0.0403 mol) was cooled in ice before 2 ml of freshly distilled boron trifluoride etherate was added dropwise with stirring. After 2 hr at 25°, 5 ml of absolute methanol was added, the top layer was decanted, and the lower layer was evaporated to constant weight under a stream of dry air. The viscous crude material weighed 6.1 g (95%) and was used directly in the following step without further purification.

A sample (70 mg) was chromatographed on activated alumina (8.0 g) and eluted with 75 ml of petroleum ether, providing pure **16**, nmr (CCl_4) 3.27 ppm (m, 4, CH_2S).

Anal. Calcd for $C_{17}H_{26}O_2S_2$: C, 62.54; H, 8.03. Found: C, 62.87; H, 7.95.

10-Carbethoxy-7,7-dimethyl-$\Delta^{1(9)}$-octalin (17).—Raney nickel (type W-2) was prepared according to "Organic Syntheses,"[27] washed free of base, and allowed to stand under distilled water for 3 days in order to partially deactivate the metal and avoid contamination of **17** with the fully saturated analog. It was then washed twice with 95% ethanol just prior to use.

To the Raney nickel (*ca.* 50 g) in 250 ml of 95% ethanol was added **16** (10.0 g, 0.0310 mol) in an equal volume of solvent. The solution, which warmed spontaneously, was allowed to stand for 15 min at 25° and then refluxed for 3 hr. The mixture was filtered, the nickel was washed with 100 ml of 95% ethanol, and the organic material was dried (Na_2SO_4). Concentration of the resulting solution gave 6.61 g (90.3%), bp 78–82° (0.5 mm), $n^{22.5}D$ 1.4841, >95% pure by glpc analysis.

10-Hydroxymethyl-7,7-dimethyl-$\Delta^{1(9)}$-octalin (18).—A suspension of $LiAlH_4$ (2.00 g, 0.0526 mol) in 50 ml of dry ether was cooled to 0° before a solution of **17** (2.36 g, 0.0100 mol) in 50 ml of dry ether was added with stirring over a period of 20 min. After stirring for 1 hr at 25° ethyl acetate (5 ml) was added to decompose the excess hydride. This treatment was followed by the addition of 100 ml of dilute HCl and overnight stirring. The clear, colorless mixture was then separated and the aqueous layer was extracted with two 50-ml portions of ether. The ether extracts were washed with 100 ml of a 5% aqueous sodium bicarbonate solution, the mixture was dried (Na_2SO_4), the solvent was evaporated, and the residue was sublimed at 70° (0.3 mm) giving 1.71 g (88.1%) of a solid, white waxy product, mp 59.5–64.0°.

An analytical sample melting at 61–64.5° was prepared by resubliming the alcohol three times at 155° (0.3 mm): ir (KBr) 3350 (broad, OH) and no appreciable absorption between 1700 and 1800 cm^{-1}; nmr (CCl_4) 5.43 (s, 1, vinyl), 3.48 (s, 2, CH_2OH), and 2.60 ppm (s, 1, position varies upon dilution, OH).

Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.42. Found: C, 80.31; H, 11.49.

10-Carbomethoxy-7,7-dimethyl-*cis*-decal-1-one (19).—This preparation was carried out without complete purification of the diol or keto acid intermediates.

A.—To **18** (3.88 g, 0.0200 mol) and $LiAlH_4$ (7.60 g, 0.200 mol) in 40 ml of dry ether was added 10 ml of boron trifluoride etherate with stirring and at 0° over a 0.5-hr period. This mixture was stirred at 0° for 1 hr, then at 25° for 24 hr. Ethyl acetate (10 ml) was added followed by 100 ml of dilute HCl. The clear, colorless mixture was separated and the aqueous layer was extracted with 25 ml of ether. The organic material was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was taken up into an ethanolic sodium hydroxide solution prepared from 10 g of sodium hydroxide, 30 ml of water, and 120 ml of 95% ethanol. When the mixture had cooled to room temperature 25 ml of a 20% hydrogen peroxide solution was added dropwise. After stirring at 25° for 5 hr, 100 ml of water and 100 ml of ether were added, the mixture was separated, and the aqueous layer was extracted with three 50-ml portions of ether. Drying (Na_2SO_4) followed by filtration and evaporation of the solvent yielded a residual oil which weighed 4.30 g, nmr (CCl_4) 4.70 (s, 2, position varies upon dilution, OH), no additional absorption downfield from 4.70 ppm.

B.—The diol was dissolved in 150 ml of acetone. With stirring and cooling, Jones reagent[28] was added dropwise until an orange-red color persisted in the acetone layer. Stirring was continued for 0.5 hr, then isopropyl alcohol was added to destroy the excess reagent. To the resulting mixture 100 ml of water and 100 ml of ether were added, the phases were separated, and the aqueous layer was extracted with two 50-ml portions of ether. The ethereal solution was washed with three 100-ml portions of a 15% aqueous sodium carbonate solution, and the combined washings were acidified with dilute HCl and extracted with three 100-ml portions of ether. After drying (Na_2SO_4), filtration, and evaporation of the solvent, 2.08 g of a light yellow solid was obtained: mp 135–142°; ir (KBr) 1720 (acid C=O), 1680 cm^{-1} (C=O); nmr ($CDCl_3$) 10.0 ppm (s, 1, position varies upon dilution, COOH).

C.—The residue was taken up into 50 ml of ether and sufficient diazomethane[29] in an ethereal solution was added at 0° to assure the persistence of the characteristic yellow color. Acetic acid was introduced to destroy the excess reagent and the solution was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude light yellow product weighed 2.02 g, which represented a 42.4% yield from **18**. A portion of this residue (0.92 g) was chromatographed by absorption on activated alumina (25.0 g)

(24) M. W. Cronyn and G. H. Riesser, *J. Amer. Chem. Soc.*, **75**, 1664 (1953).
(25) G. Büchi, O. Jeger, and L. Ruzicka, *Helv. Chim. Acta*, **31**, 241 (1948).
(26) L. Re and H. Schinz, *ibid.*, **41**, 1695 (1958).
(27) R. Mozingo, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 181.
(28) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).
(29) Th. J. de Boer and H. J. Backer, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 250.

and eluted with 200 ml of dry benzene. Evaporation of the solvent gave 0.47 g of product.

An analytical sample was obtained by rechromatographing the above material on acid-washed alumina (38.0 g). Elution with 100 ml of dry hexane provided pure **19**: ir shows no absorptions above 3000 cm^{-1}; nmr (CCl_4) 3.69 ppm (s, 3, OCH_3).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.35. Found: C, 70.63; H, 9.48.

10-Carbethoxy-7,7-dimethyl-2-hydroxymethylene-*cis*-decal-1-one (20).—To a cold suspension of NaH (0.45 g of a 53% dispersion in mineral oil, 0.010 mol) in 4 ml of dry benzene was added dropwise, over a 10-min period, **19** (0.50 g, 0.0021 mol) and ethyl formate (0.75 g, 0.010 mol, distilled from P_2O_5) in 2 ml of dry benzene. After an initial induction period the reaction began spontaneously at room temperature with a rapid evolution of gas and was complete in 12 hr. Additional ethyl formate (15.0 g, 0.203 mol) was added to ensure the complete conversion to the ethyl ester. After stirring for a total of 24 hr at room temperature, 5 ml of water was added followed by 50 ml of ether. The organic material was extracted with three 25-ml portions of a 2% aqueous sodium hydroxide solution. The aqueous mixture was acidified with dilute HCl and extracted with three 25-ml portions of ether. Drying (Na_2SO_4) and evaporation of the solvent provided 0.37 g of a thick orange-red oil which was used directly in the following step without further purification: nmr (CCl_4) 8.52 (s, CHO), 7.40 ppm (s, vinyl). These two resonance peaks vary in intensity but not in position upon dilution. The integrated area of the two peaks is $^1/_{24}$ of the total resonance signal, equivalent to one proton.

Evaporation of the original ethereal solution led to the recovery of 0.12 g of **19**.

2-*n*-Butylthiomethylene-10-carbethoxy-7,7-dimethyl-*cis*-decal-1-one.—The hydroxymethylene derivative (**20**) prepared as above (0.37 g, 0.0010 mol) and *n*-butyl mercaptan (4.50 g, 0.0500 mol) were refluxed for 6 hr in 30 ml of dry benzene to which had been added 0.1 g of *p*-toluenesulfonic acid. The solution was washed with two 10-ml portions of a 2% sodium hydroxide solution and dried (Na_2SO_4), and the solvent was evaporated under dry air to yield 0.57 g of product: ir 1670 (C=O), 1550 cm^{-1} (C=C); nmr (CCl_4) 7.35 ppm (s, 1, vinyl).

10-Carbethoxy-2,7,7-trimethyl-*cis*-decal-1-one (2).—The unpurified thio compound was dissolved in 25 ml of 95% ethanol. Raney nickel (type W-2, *ca.* 1.0 g) was added, and the suspension was refluxed for 3 hr. Filtration and evaporation of the solvent under dry air yielded 0.28 g of **2**. This represents a 73% yield for the last three steps based on unrecovered **19**: ir and nmr are both very similar to those of **19**, but with nmr integration indicating the presence of three additional methyl protons.

An analytical sample was obtained by absorption of a portion of the material (0.13 g) on acid-washed alumina (5.0 g). Successive 30-ml portions of the following solvents were then run through the column: hexane, benzene, 30% ether–70% benzene, 30% ether–70% benzene, absolute methanol. The purest material was recovered upon evaporation of the first ether–benzene fraction. The sample weighed 0.0213 g.

Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 71.84; H, 9.75.

Registry No.—**1**, 33122-28-0; **2**, 33065-73-5; **6**, 33065-74-6; **7**, 33065-75-7; **8**, 33065-76-8; **9**, 33065-77-9; **15**, 33122-29-1; **16**, 33065-78-0; **17**, 33065-79-1; **18**, 33065-80-4; **18** (keto acid), 33065-81-5; **19**, 33069-12-4; **20**, 33069-13-5; 10β-methyl-1α-carbomethoxy-5β-tetrahydropyranyloxy-*trans*-2-decalone, 7381-72-8; 10β-methyl-1α-carbomethoxy-5α-tetrahydropyranyloxy-*trans*-2-decalone, 33069-15-7; 2-*n*-butylthiomethylene-10-carbethoxy-7,7-dimethyl-*cis*-decal-1-one, 33069-16-8.

Notes

Oxidation of Penicillin and Dihydrocephalosporin Derivatives with Ozone

D. O. SPRY

The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46206

Received July 28, 1971

A recent publication revealed that ozone under certain conditions is an ideal reagent for converting penicillins into mixtures of *R* and *S* sulfoxides.[1] This communication details the reactions of ozone with various penicillin and cephalosporin derivatives. The results of the oxidation of various penicillin derivatives with ozone are shown in Table I. The determination of the *S* and *R* sulfoxide isomers was accomplished by a study of the nmr chemical shifts.[2,3]

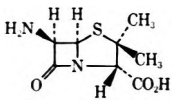
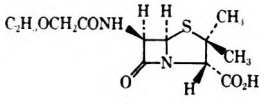
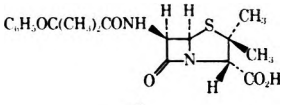
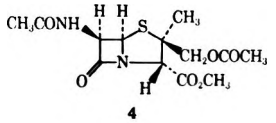
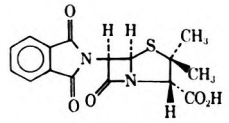
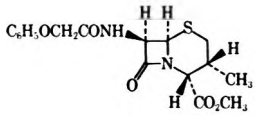
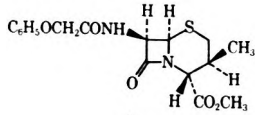
Of particular interest is the high-yielding conversion of 6-aminopenicillanic acid (6-APA) (**1**) into analytically pure, noncrystalline 6-APA sulfoxide having an *S*/*R* ratio of approximately 4/1 as determined from the products formed by acylation with phenoxyacetyl chloride.

Essery, *et al.*, have previously reported the synthesis of 6-APA sulfoxide in 8% yield by oxidation of 6-APA with sodium metaperiodate;[4] the stereochemistry from the latter synthesis, however, has been shown to be *S*, as is the case when various penicillins are oxidized with sodium metaperiodate.[2,5]

Further examination of Table I indicates that the various penicillin compounds exhibit a steric effect on the approach of the ozone molecule which consequently affects the stereochemistry of the resulting sulfoxide. Thus the sulfoxides of the nucleus (**1**) exhibit an *S*/*R* ratio of 4/1 as compared to those of compound **2** with a 1/1 ratio and to the 2-β-acyloxymethyl compound **4** with an *S*/*R* ratio of 1/2. Oxidation of the bulky β-phthalimidopenicillanic acid (**5**) resulted in only the *R* sulfoxide. However, this could possibly result from an *S* to *R* conversion *via* the olefin sulfenic acid, with the driving force being the release of strain between the

(1) D. O. Spry, *J. Amer. Chem. Soc.*, **92**, 5006 (1970).
(2) R. D. G. Copper, P. V. Demarco, J. C. Cheng, and N. D. Jones, *ibid.*, **91**, 1408 (1969).
(3) R. D. G. Cooper, P. V. Demarco, and D. O. Spry, *ibid.*, **91**, 1528 (1969).
(4) J. M. Essery, K. DaDabo, W. J. Gottstein, A. Hallstrand, and L. C. Cheney, *J. Org. Chem.*, **30**, 4388 (1965).
(5) D. H. R. Barton, F. Comer, and P. G. Sammes, *J. Amer. Chem. Soc.*, **91**, 1529 (1969).

TABLE I
OXIDATION OF PENICILLIN AND DIHYDRODEACETOXYCEPHALOSPORIN DERIVATIVES WITH OZONE

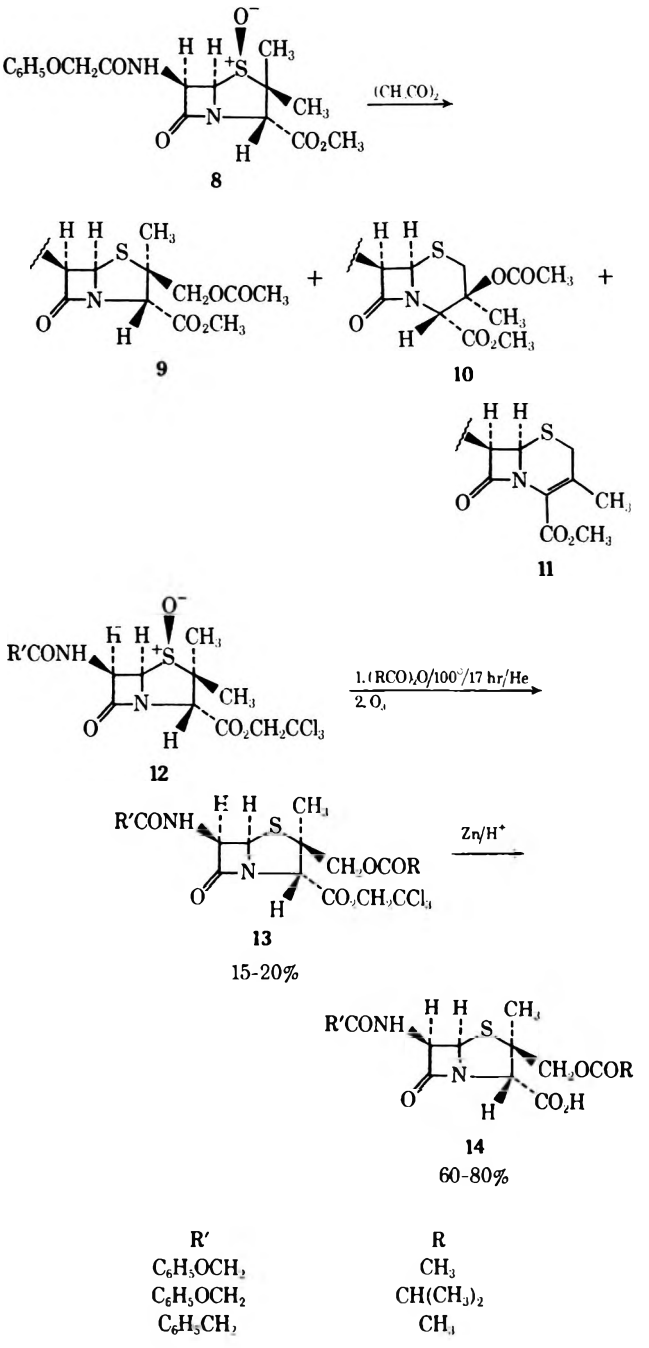
Derivative	Solvent	Yield of sulfoxide, %	S/R ratio
 1	H_2O	>95	4/1
 2	H_2O–acetone	>95	1/1
 3	H_2O–acetone	>95	1.4/1.0
 4	H_2O–acetone	70	1/2
 5	H_2O–acetone	>95	only R
 6	H_2O–acetone	91	1/7
 7	H_2O–acetone	>95	1/24

two bulky β groups.[1,6] Attempts to prepare the cis-β compound by acylation of 6-APA β-sulfoxide with *N*-carboethoxyphthalimide gave 6-epiphthalimido β-sulfoxide due to base-catalyzed epimerization of 6-β-phthalimidopenicillanic acid β-sulfoxide.[3]

Oxidation of the penicillin sulfoxide to sulfone did not occur under these conditions even with a large excess of ozone. Although monosulfides are generally oxidized to sulfones by excess ozone,[7] Bernard has reported that the case of such ozone oxidations is a function of the electron density on sulfur and that sterically hindered sulfoxides, for example, diphenyl sulfoxide, are resistant to further oxidation by ozone.[8]

Treatment of 3-cephems,[9] for example, 7-aminodeacetoxycephalosporanic acid (7-ADCA) or 7-aminocephalosporanic acid (7-ACA), under these conditions failed to give the corresponding sulfoxides, as a result of the double bond being more reactive toward ozone than the sulfide.[8] Hydrogenation of the double bond, however, followed by ozonization of the dihydrodeacetoxycephalosporins, for example, compounds **6** and **7**, led to mixtures of the *S* and *R* sulfoxides with a predominance of the *R* isomer (see Table I).

Further use of ozone in penicillin–cephalosporin chemistry is illustrated by the isolation of pure 2-β-acyloxymethylpenicillin derivatives. Morin, *et al.*, in their elegant conversion of the penam to the cephem system, described the rearrangement of the penicillin sulfoxide **8** in refluxing acetic anhydride to give **9**, **10**, and **11**.[10] Separation of the rearrangement products



R′	R
$C_6H_5OCH_2$	CH_3
$C_6H_5OCH_2$	$CH(CH_3)_2$
$C_6H_5CH_2$	CH_3

could be accomplished by silica gel chromatography; however, basic hydrolysis of the 2-substituted penicillin methyl ester **9** to the salt led to extensive degradation.

(6) Since submission of this manuscript we have found that the ozonization of 2-α-trideuteriomethyl phthalimidopenicillin sulfide methyl ester leads predominately to the α-sulfoxide-α-trideuteriomethyl compound.
(7) H. Bohme and H. Fischer, *Chem. Ber.*, **76**, 1310 (1942).
(8) D. Barnard, *J. Chem. Soc.*, 4547 (1957).
(9) R. B. Morin, B. G. Jackson, E. FHynn, and R. W. Roeske, *J. Amer. Chem. Soc.*, **84**, 3400 (1962).
(10) R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *ibid.*, **91**, 1401 (1969).

Utilizing other ester groups, for example, the trichloroethyl or *p*-nitrobenzyl, in most cases resulted in inseparable mixtures. However, rearrangement of the penicillin sulfoxides **12** under milder conditions, followed by partial ozonization of the reaction mixture, resulted in selective oxidation of the cephem and dihydrocephem compounds. Subsequent silica gel chromatography gave pure **13**, thus providing a route to the various 2-β-acyloxymethylpenicillin derivatives (**14**).

Experimental Section

The ozone oxidations were run using a Welsbach model T-23 ozonizer with an output of 1.18 mm O_3/min or 3.4 g/hr. No attempt was made to monitor the uptake of ozone, excess ozone being employed, and in general on completion of the reaction the solvent was evaporated to give the oxidized product.

6-Aminopenicillanic Acid Sulfoxide.—Into a cooled (5°) slurry of 6-APA (2.16 g, 1.0 mmol) in 200 ml of water was bubbled ozone for 3.0 hr, complete solution being obtained after 2.5 hr. Lyophilization of the aqueous solution gave 2.26 g (98%) of pale yellow sulfoxide: ir (mull) 1790 (β-lactam) and 1025, 1007 cm^{-1} (S→O).

Anal. Calcd for $C_8H_{12}N_2O_4S$: C, 41.38; H, 5.21; N, 12.07. Found: C, 41.10; H, 5.34; N, 12.27.

Phenoxyacetamidopenicillanic Acid Sulfoxide.—Into a cooled (0–5°) solution of phenoxyacetamidopenicillanic acid (3.50 g, 0.01 mol) in 100 ml of 1/1 acetone–water was bubbled ozone for 2.5 hr. Evaporation of acetone from the slurry gave, after filtration, 1.80 g (49.18%) of crystalline β-sulfoxide: ir ($CHCl_3$) 1800 (β-lactam) and 1020, 1035, 1065, 1080 cm^{-1} (S→O); nmr (DMSO-d_6) δ 1.22 (s, 3, α-Me), 1.62 (s, 3, β-Me), 4.45 (s, 1, H_3), 5.47 (d, 1, J = 4 Hz, H_5), 5.95 (q, 1, J = 4, 9 Hz, H_6).

Anal. Calcd for $C_{16}H_{18}N_2O_6S$: C, 52.46; H, 4.95; N, 7.65. Found: C, 52.30; H, 5.02; N, 7.64.

Lyophilization of the aqueous solution gave 1.87 g (51.09%) of noncrystalline α-sulfoxide: ir ($CHCl_3$) 1796 (β-lactam) and 1040, 1065, 1080 cm^{-1} (S→O); nmr (DMSO-d_6) δ 1.25 (s, 3, α-Me), 1.62 (s, 3, β-Me), 4.35 (s, 1, H_3), 4.77 (d, 1, J = 4 Hz, H_5), 5.50 (q, 1, J = 4, 9 Hz, H_6).

Anal. Calcd for $C_{16}H_{18}N_2O_6S$: C, 52.46; H, 4.95; N, 7.65. Found: C, 52.25; H, 5.02; N, 7.48.

Registry No.—**1**, 551-16-6; **1** (*R* sulfoxide), 33069-17-9; **1** (*S* sulfoxide), 33069-18-0; **2**, 87-08-1; **2** (*R* sulfoxide), 33069-20-4; **2** (*S* sulfoxide), 33069-21-5; **3**, 4780-24-9; **4**, 33122-31-5; **5**, 20425-27-8; **6**, 32178-92-0; **7**, 33069-25-9.

Synthesis of 2′,3′-*O*-Isopropylidene-5′-keto-8,5′-cycloadenosine, a Novel Cyclonucleoside[1]

PETER J. HARPER AND ALEXANDER HAMPTON*

The Institute for Cancer Research, Fox Chase, Philadelphia, Pennsylvania 19111

Received August 16, 1971

Cyclonucleosides differ from simple nucleosides in that a nonanomeric carbon of the ribose moiety is linked to the purine or pyrimidine ring. They are useful synthetic intermediates[2-5] and have been valuable as reference compounds in ORD[4,6-9] and CD[10] studies of the disposition of the sugar and base moieties around the glycosidic linkage of nucleosides in aqueous solution.

In cyclonucleosides described hitherto a nonanomeric ribose carbon is bonded either directly to a purine nitrogen or indirectly to a purine or pyrimidine carbon *via* an oxygen, sulfur, or nitrogen. The cyclonucleoside described in this communication is possibly unique in that it contains a bond from a ribose carbon to a purine carbon, although a photolysis product of coenzyme B_{12} has been tentatively identified as 5′-deoxy-8,5′-cycloadenosine.[11] The present cyclonucleoside contains a keto function at the 5′ carbon and reduction to the corresponding secondary alcohol furnishes a 2′,3′-*O*-isopropylidene derivative of the first cyclonucleoside in which all three ribofuranose hydroxyls are retained.

Treatment of 2′,3′-*O*-isopropylidene adenosine 5′-carboxylic acid (**1**)[12] with methyllithium in tetrahydrofuran yielded a complex mixture of products under a variety of reaction conditions. From this, a pale yellow component which fluoresced in ultraviolet light was isolated in *ca.* 5% yield and obtained crystalline and homogeneous. The product was identified as 2′,3′-*O*-isopropylidene-5′-keto-8,5′-cycloadenosine (**3**) on the basis of evidence presented below. Elemental analysis and the pmr spectrum showed that the crystals contained 0.5 mol of tetrahydrofuran. In the mass spectrum the most prominent peak (relative intensity 53) with *m/e* higher than adenine corresponded to the molecular ion of nonsolvated **3**. In accord with the cyclic structure of **3**, the amount of molecular ion relative to adenine ion was *ca.* 50-fold greater than in the case of noncyclic adenine nucleosides.[13,14]

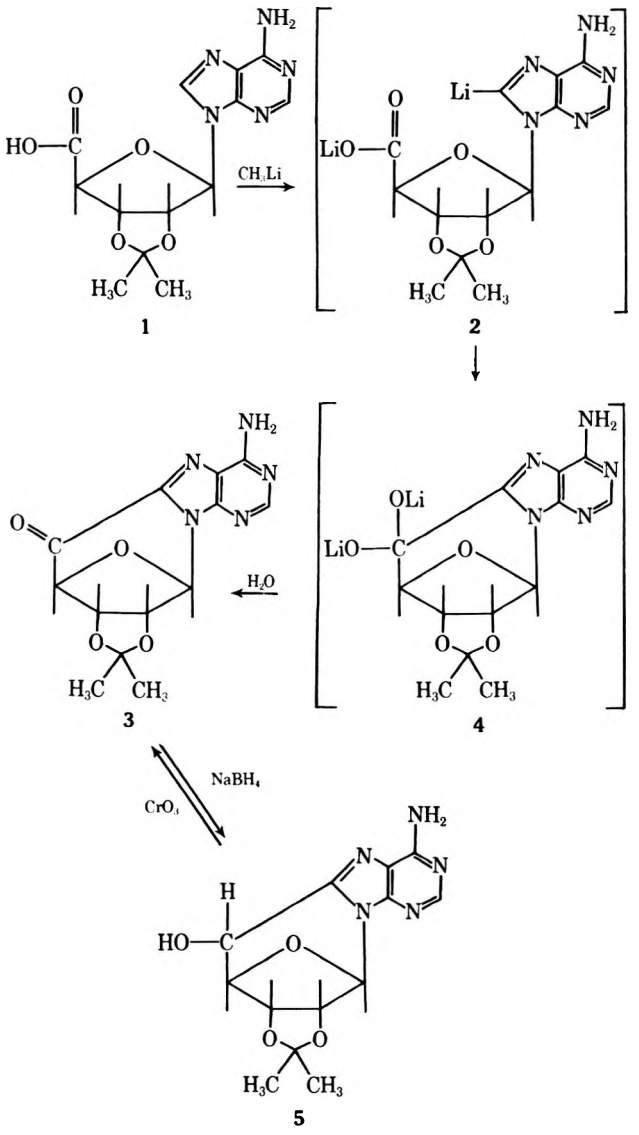
Retention of an adenine ring system in **3** was indicated by uv and ir spectra, by pmr signals assignable to the 6-amino group and to either H-2 or H-8 (but not to both), and by the substantial mass spectral peak of *m/e* 135 corresponding to adenine.

The presence of a keto group in **3** was shown by the formation of an oxime, and by an ir absorption at 1720 cm^{-1} which disappeared upon reduction of **3** with sodium borohydride; furthermore, oxidation of the reduction product **5** with chromic acid regenerated **3**. The product of reduction of **3** showed nmr signals corresponding to the single 5′ proton and one exchangeable proton expected in the secondary alcohol **5**. In addition, large shifts of H-2′, H-3′, and H-4′ signals suggested the removal of the diamagnetically anisotropic

(1) This work was supported by U. S. P. H. S. Grant CA-11196, American Cancer Society Grant T-490, an award from the Pennsylvania Science and Engineering Fund, grants to The Institute for Cancer Research, U. S. P. H. S. Grants CA-06927 and RR-05539 from the National Institutes of Health, and an appropriation from the Commonwealth of Pennsylvania.

(2) J. J. Fox and I. Wempen, *Advan. Carbohyd. Chem.*, **14**, 283 (1959).
(3) A. M. Michelson, "The Chemistry of Nucleosides and Nucleotides, Academic Press, New York, N. Y., 1963, p 15.
(4) M. Ikehara, *Accounts Chem. Res.*, **2**, 47 (1969).
(5) J. Nagyvary, *Biochemistry*, **5**, 1316 (1966), and references cited therein.
(6) T. R. Emerson, R. J. Swan, and T. L. V. Ulbricht, *ibid.*, **6**, 843 (1967).
(7) A. Hampton and A. W. Nichol, *J. Org. Chem.*, **32**, 1688 (1967).
(8) D. W. Miles, R. K. Robins, and H. Eyring, *Proc. Nat. Acad. Sci. U. S.*, **57**, 1138 (1967).
(9) M. Ikehara, M. Kaneko, K. Muneyama, and H. Tanaka, *Tetrahedron Lett.*, 3977 (1967).
(10) D. W. Miles, M. J. Robins, R. K. Robins, M. W. Winkley, and H. Eyring, *J. Amer. Chem. Soc.*, **91**, 831 (1969).
(11) H. P. C. Hogenkamp, *J. Biol. Chem.*, **238**, 477 (1963).
(12) P. J. Harper and A. Hampton, *J. Org. Chem.*, **35**, 1688 (1970).
(13) K. Biemann and J. A. McCloskey, *J. Amer. Chem. Soc.*, **84**, 2005 (1962).
(14) S. J. Shaw, D. M. Desiderio, K. Tsuboyama, and J. A. McCloskey, *ibid.*, **92**, 2510 (1970).

carbonyl group upon conversion of **3** to **5**. The spectrum of **5** showed poorly resolved absorptions for H-4′ and H-5′, as expected, since the product is almost certainly a mixture of stereoisomers at C-5′.



The direct link of the carbonyl group of **3** to the purine ring was indicated by the appearance of an additional absorption peak at 337 nm attendant upon conversion of **1** to **3**. This corresponds to the excitation absorption for the blue fluorescence of **3** and suggests conjugation of another chromophore with the purine ring. In confirmation of this, the borohydride reduction product of **3** lacked both the blue fluorescence and the 337-nm absorption maximum. On the other hand, the oxime of **3** retained the blue fluorescence.

With Corey–Pauling–Koltun space-filling molecular models the 8–5′ bond of **3** could be readily assembled whereas a 2–5′ bond was not possible. Furthermore, the single pmr signal from the purine ring of **3** did not exchange with D_2O under conditions in which H-8 of adenosine did exchange; it is known that H-8 of adenosine exchanges with tritium far more rapidly than does H-2.[15] In addition, the absorption maximum of **5** (264 nm at pH 11 and 268 nm at pH 1) is similar to that of 8-methyladenine (266 nm at pH 11 and 269 nm at pH 1)[16] but different from that of 2-methyladenine (271 nm at pH 11 and 265.5 nm at pH 1).[17]

Conversion of **1** to **3** probably proceeds *via* lithium 2′,3′-*O*-isopropylidene-8-lithioadenosine 5′-carboxylate (**2**). Nucleophilic attack of C-8 on the carbonyl carbon would then give a dilithio intermediate **4** of the type considered to mediate the conversion of carboxylic acids to ketones with organolithium reagents.[18]

Experimental Section

Melting points (uncorrected) were determined by the capillary method. Ultraviolet spectra were obtained in buffered aqueous solutions with a Cary Model 15 spectrophotometer and infrared spectra with a Perkin-Elmer 137 spectrophotometer. The pmr spectra were run with Varian XL-100-15 and Jeolco MH60 instruments. Thin layer chromatograms were run on Merck F-254 silica gel plates in (A) methanol–chloroform (1:9), (B) ethanol–ethyl acetate (1:9), and (C) acetone–diethyl ether (1:4). Elemental analyses were by the Spang Microanalytical Laboratories, Ann Arbor, Mich.

2′,3′-*O*-Isopropylidene-5′-keto-8,5′-cycloadenosine (3).—2′,3′-*O*-isopropylidene adenosine 5′-carboxylic acid[12] (3.2 g, 10^{-2} mol) was suspended in dry THF (100 ml), and methyllithium (30 ml of a 1 *M* solution in ether) was added over 2 hr. The suspension was stirred overnight and ammonium chloride (200 ml of a 20% aqueous solution) was added. The upper layer was removed, washed with saturated sodium bicarbonate (two 100-ml portions), dried (Na_2SO_4), and evaporated to dryness. The residue (0.85 g) was chromatographed on silica (Merck, 85 g) using a linear gradient of chloroform to 20% methanol–chloroform in 1 l. Fractions containing **3** were yellow and exhibited a strong blue fluorescence when irradiated at 360 nm. Removal of volatiles and crystallization of the residue from methanol gave **3** (0.075 g) as flat yellow plates, mp 232–234°, homogeneous upon tlc in systems A, B, and C (R_f 0.78, 0.40, and 0.35, respectively): ir (Nujol mull) 3200, 3100 (NH_2), 1720 (C=O), 1648, 1582 cm^{-1} (C=C, C=N); uv max (pH 2.5) 263 nm (ϵ 19,100), (pH 7.0) 337 (4800) and 267 (16,000), (pH 11.5) 337 (4500) and 267 (16,000); nmr ($CDCl_3$, 100 MHz) δ 8.75 (s, 1, H-2), 8.45 (broad, 2, NH_2), 6.97 (s, 1, H-1′), 5.47 (d of d, 2, J = 5 Hz, H-2′ and -3′), 5.42 (s, 1, H-4′), 3.72 (m, ~2, THF of crystallization), 1.95 and 1.72 (s, 3, isopropylidene methyls), 1.62 (m, ~2, THF of crystallization); mass spectrum (70 eV) *m/e* (rel intensity) 303 (53), 288 (20), 274 (17), 246 (20), 218 (20), 188 (50), 135 (22), 57 (100).

Anal. Calcd for $C_{13}H_{13}N_5O_4 \cdot 0.5C_4H_8O$: C, 53.42; H, 5.06; N, 20.66. Found (for material dried at 78°): C, 53.79; H, 5.02; N, 20.86.

The yield of **3** was essentially constant among reactions run for the optimum periods of time at temperatures between −40 and 50°. Substitution of dioxane or ether for THF at room temperature reduced the yield by *ca.* 50%.

A solution of compound **3** in methanol was treated with hydroxylamine hydrochloride (2 mg) and sodium acetate (5 mg). After 16 hr a single product was observed on tlc with R_f 0.55 (system A) and an intense dark blue fluorescence at 360 nm.

2′,3′-*O*-Isopropylidene-8,5′-cycloadenosine (5).—Compound **3** (75 mg) was dissolved in methanol (20 ml), and 0.1 *M* aqueous sodium borohydride (2.5 ml) was added. After 5 min, tlc in system A showed complete conversion to material of R_f 0.5 which no longer fluoresced. The material was purified by preparative tlc on silica gel in chloroform–methanol (8:1) and crystallized from methanol. The purified material showed uv max (pH 1) 268 nm (ϵ 13,900), (pH 11), 264 (14,500); the ir spectrum (KBr disc) showed absorption at 3300, 3200, 1651, 1585, 1085, and 1040 cm^{-1} but no carbonyl absorption near 1700 cm^{-1}; nmr (DMSO-d_6, 60 MHz) δ 8.62 (s, 1, H-2), 7.70 (broad, 2, exchanges with D_2O, NH_2), 6.56 (s, 1, H-1′), 5.46 (d, 1, J = 6 Hz, H-2′), 4.98 (d, 1, J = 6 Hz, H-3′), 4.32 (broad, 1, H-4′), 3.74 (broad, 2, exchanges 1 H with D_2O, H-5′ and OH), 1.77 (s, 3, CH_3), 1.58 (broad, 3, CH_3).

(15) K. R. Shelton and J. M. Clark, *Biochemistry*, **6**, 2735 (1967).

(16) T. R. Wood and R. K. Robbins, *J. Org. Chem.*, **23**, 1457 (1958).

(17) C. J. Baddiley, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 318 (1944).

(18) M. Jorgenson, *Org. React.*, **18**, 1 (1970).

Anal. Calcd for $C_{13}H_{15}N_5O_4$: C, 51.14; H, 5.00; N, 22.61. Found [sample dried to constant weight at 100° (0.1 mm) over P_2O_5]: C, 50.80; H, 5.09; N, 22.78.

A portion of the material was dissolved in acetone and treated with Jones reagent[19] until an orange color persisted for 2 min. Tlc of this material in systems A, B, and C showed it to be identical with **3** in R_f and fluorescence color, and the ultraviolet absorption characteristics at acid, neutral, and alkaline pH values were likewise indistinguishable from those of **3**.

Registry No.—**3**, 33066-26-1; **5**, 33189-80-9.

Acknowledgment.—The authors are pleased to thank Dr. M. J. Mitchell, University of Pennsylvania, for determination of the mass spectrum.

(19) A. Bowers, T. G. Halsell, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

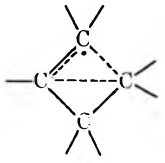
Stereochemistry of the Reduction of Homobenzyl Halides[1]

BRUCE B. JARVIS,* JOSEPH B. YOUNT, III,[2] AND TONG-HUA YANG[2]

Department of Chemistry, University of Maryland, College Park, Maryland 20742

Received August 31, 1971

The existence of homoallylic participation in carbonium ion chemistry is well established.[3] The search for analogous participation in free-radical reactions has proven fruitless.[4] The chemical reactivities[5] and physical properties[6] of these radicals are also consistent only with that of equilibrating radicals rather than a single delocalized species such as **1**.

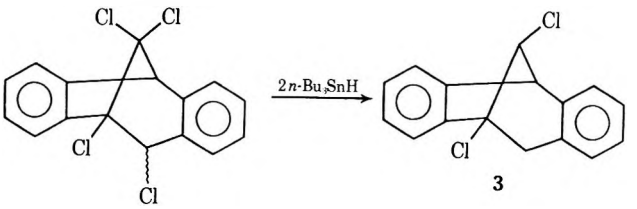


1

Results and Discussion

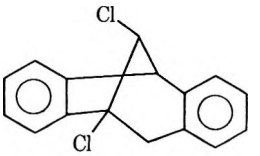
Our interest in this problem arose from the observation that treatment of the tetrachlorides **2**[7] with 2 equiv of tributyltin hydride gave only the dichloride **3** with no observable amount of the epimer **4** formed.

Subsequently it was shown that under these conditions the trichloride **5** reacts with tributyltin hydride to give only **3**; no **4** is formed.[1] The structural assignment for **3** is based on elemental analysis and the proton magnetic resonance (pmr) spectrum of **3**: a pair of



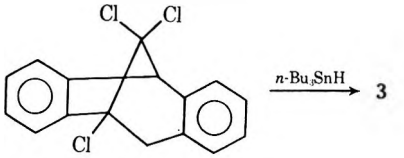
2a, *exo*-Cl
b, *endo*-Cl

3

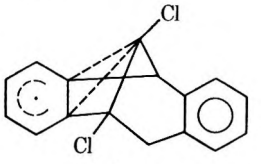


4

doublets (1 H each) at τ 5.97 and 5.33 (J_{18} = 2.5 Hz), a pair of doublets (1 H each) at τ 6.95 and 6.33 ($J_{\text{gem-4}}$ = 17 Hz), and aromatic protons (8 H) at τ 2.5–3.0. The value of the coupling constant J_{18} is consistent only with structure **3**.[8] Since it is the ring anti to the C-4 position that has the highest capability for delocalization of a charge or unpaired electron at C-8,[9] the nonclassical radical intermediate (if one were to exist) should be represented by **6**. The dichloride **4**



5



6

should be the product formed[10] from such an intermediate.

Just what effect the C-5 and C-8 chlorine atoms in **5** have on the stereochemical course of this reaction was not clear. It would be preferable to deal with a radical intermediate that lacked any complicating substituents. For this purpose, the two alkyl bromides **7** and **8** were prepared as shown in Scheme I.

The starting dibromides **9**[13] and **10**[14] have been reported previously. The conversion of **10** to the acetate **11** is analogous to the acetolysis of the corresponding trans dichloride.[15] Treatment of the bromides **7**

(1) For a preliminary communication of a portion of this work, see B. B. Jarvis and J. B. Yount, III, *Chem. Commun.*, 1405 (1969).

(2) Taken in part from the M.S. Theses of J. B. Y., 1970, and T-H. Y., 1970.

(3) B. Capon, *Quart. Rev., Chem. Soc.*, **18**, 45 (1964).

(4) (a) D. I. Davies and S. J. Cristol in "Advances in Free Radical Chemistry," Vol. I, G. H. Williams, Ed., Logas Press, London, 1965; (b) D. I. Davies in "Essays on Free-Radical Chemistry," Special Publication 24 of the Chemical Society, Burlington House, London, 1970, p 201.

(5) (a) G. A. Russell and G. W. Holland, *J. Amer. Chem. Soc.*, **91**, 3968 (1969); (b) S. J. Cristol and A. L. Noreen, *ibid.*, **91**, 3969 (1969).

(6) (a) R. W. Fessenden and R. H. Shuler, *J. Chem. Phys.*, **39**, 2180 (1963); (b) P. Bakuzis, J. K. Kochi, and P. J. Krusic, *J. Amer. Chem. Soc.* **92**, 1434 (1970).

(7) B. B. Jarvis and J. B. Yount, III, *J. Org. Chem.*, **35**, 2088 (1970).

(8) (a) S. J. Cristol, J. R. Mohig, and D. E. Plorde, *ibid.*, **30**, 1956 (1965); (b) A. R. Katrikzky and B. Vallis, *Chem. Ind. (London)*, 2025 (1964).

(9) (a) S. J. Cristol, J. R. Mohig, F. P. Parungo, D. E. Plorde, and K. Schwarzenbach, *J. Amer. Chem. Soc.*, **85**, 2675 (1963); (b) G. W. Klumpp, G. Ellen, and F. Bickelhaupt, *Recl. Trav. Chim. Pays-Bas*, **88**, 474 (1969).

(10) This assumes that the three-membered ring is opened with inversion. Previous workers who have postulated the existence of bridged radicals (bromine and sulfur atom bridging)[11] have observed products consistent with opening of the ring with inversion. However, serious doubts exist as to whether there is such a phenomenon as free radical bridging involving bromine atoms.[12]

(11) For example, see W. Thaler, *J. Amer. Chem. Soc.*, **85**, 2607 (1963).

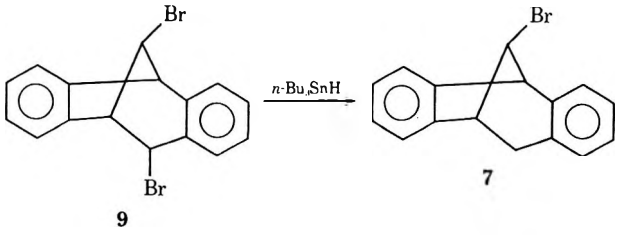
(12) D. D. Tanner, D. Darwish, M. W. Mosher, and N. J. Bunce, *ibid.*, **91**, 7398 (1969).

(13) I. G. Ninulescu, M. Avram, Gh. D. Mateescu, and C. D. Nenitzescu, *Chem. Ind. (London)*, 2023 (1964).

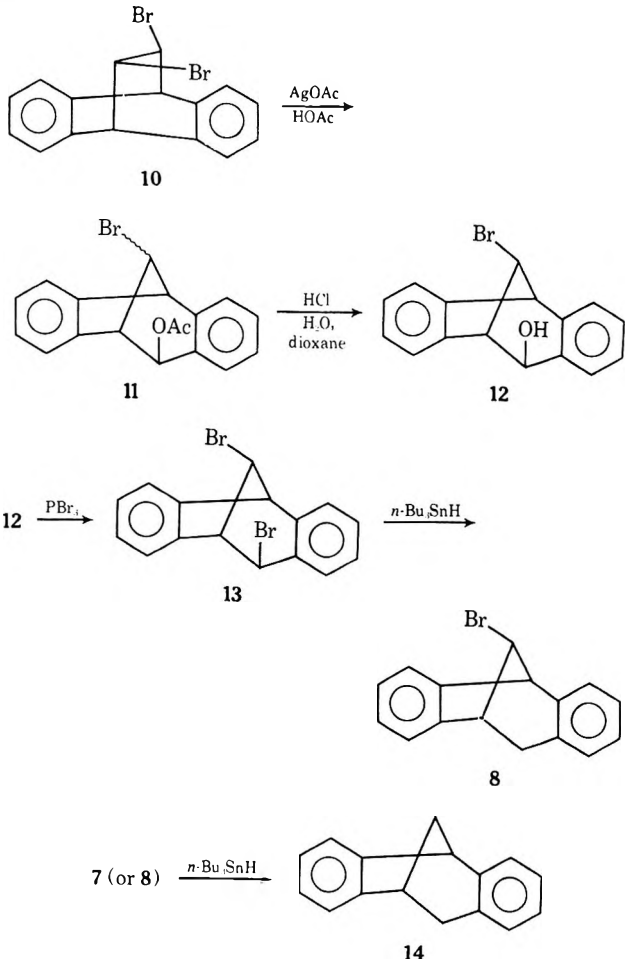
(14) B. B. Jarvis, J. P. Govoni, and P. J. Zell, *J. Amer. Chem. Soc.*, **93**, 913 (1971).

(15) S. J. Cristol, F. P. Parungo, and D. E. Plorde, *ibid.*, **87**, 2870 (1965).

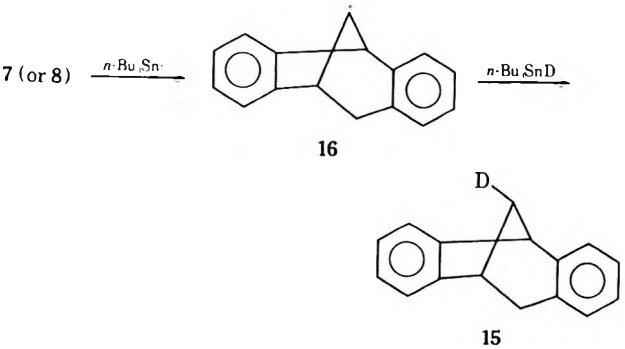
SCHEME I



and **8** with tributyltin hydride gave the known[15] hydrocarbon **14**.

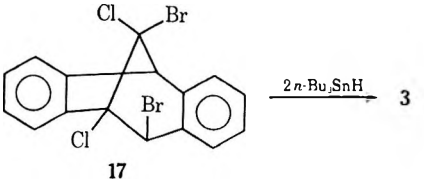


With tributyltin deuteride, **7** and **8** react to give the same deuterated hydrocarbon **15** in which the deuterium atom is in the C-8 anti position. The position of the deuterium atom in **15** is evident from the pmr spectrum. The benzhydryl proton at C-1 appears as a slightly broadened singlet, indicating that it is coupled only to the syn proton at C-8.[8] This result is entirely consistent with that observed in the reduction of **5**; the stereochemistry of the chain transfer to the radical **16** appears to be unaffected by the presence of chlorine atoms at C-5 and C-8.



It is interesting to note that, although **16** reacts with tributyltin hydride (deuteride) in a highly stereoselective manner from the anti side, the difference in reactivity between **7** and **8** is only a factor of two. This figure was obtained by allowing **7** and **8** in separate reaction vessels to react with a stock solution of tributyltin hydride (deuteride) and benzoyl peroxide in benzene. In this manner it was shown that *anti*-**8** reacts *ca.* twice as readily as *syn*-**7** with both tributyltin hydride and tributyltin deuteride. However, the overall reaction rate is much faster with the tributyltin hydride than with the tributyltin deuteride (see Experimental Section). The difference in the selectivity between the abstraction step ($\geq Sn\cdot + BrC\leq \rightarrow \geq Sn\text{-}Br + \cdot C\leq$) and the chain transfer step ($\geq SnH + \cdot C\leq \rightarrow \geq Sn\cdot + HC\leq$) depends upon where the transition state lies along the reaction coordinate. The difference in bond energies between the tin–bromine and carbon–bromine bonds is small (*ca.* 3 kcal/mol),[16] whereas there is a large difference (*ca.* 38 kcal/mol)[16] in the bond energies between the strong carbon–hydrogen bond and the much weaker tin–hydrogen bond. The transition state for chain transfer from tributyltin hydride (or deuteride) to the radical **16** must come very early[17] compared with the transition state in the bromine atom abstraction step. However, it is the latter step (halogen atom abstraction) that is the rate-determining step (in part; initiation–termination are also involved),[18] whereas the former step (chain transfer to radical **16**) is the product-determining step. Clearly, differences in rates between reagents reacting from the anti direction *vs.* syn direction in the dibenzobicyclo[3.2.1]octadiene system depend rather strongly upon the position of the transition state along the reaction coordinate.

We also have tested which is a more important factor in the tributyltin hydride reactions in this system: bromine *vs.* chlorine atom abstraction or anti *vs.* syn reactivity. Treatment of tetrahalide **17** with 2 equiv



of tributyltin hydride gives only dichloride **3**. Clearly, in this reaction the increase in reactivity of a bromine atom over the chlorine atom[19] overrides any rate enhancement of an anti halogen atom over a syn halogen atom.

Chromium(II) chloride in aqueous dimethylformamide (DMF) also reacts with the trichloride **5** to give only **3**. Arguments have been presented elsewhere[1,20]

(16) E. Ebsworth, "Organometallic Compounds of Group IV Elements," Vol. I, A. G. MacDiarmid, Ed., Marcel Dekker, New York, N. Y., 1965, p 46.
(17) G. S. Hammond, *J. Amer. Chem. Soc.*, **77**, 334 (1955).
(18) K. U. Ingold and D. J. Carlsson, *ibid.*, **90**, 7049 (1968).
(19) H. G. Kuivila, *Accounts Chem. Res.*, **1**, 299 (1968).
(20) B. B. Jarvis and J. P. Govoni, *J. Org. Chem.*, in press.

which suggest that the reactions at the C-8 position in this system are governed by steric control; *i.e.*, reagents have a more open approach from the anti side than from the syn direction. The data presented here support this conclusion.

Experimental Section[21]

Solvolysis of Trans Dibromide 10 in Acetic Acid.—Five grams (13.7 mmol) of 10[14] was dissolved in 60 ml of acetic acid which contained 2.32 g of silver acetate. The mixture was placed under reflux for 1.5 hr. This was poured into 50 ml of water and extracted with ether. The ether layer was washed with saturated sodium carbonate solution. The ether was dried over magnesium sulfate and the solvent was removed by rotary evaporation. The oil, after treatment with charcoal, was crystallized from carbon tetrachloride–Skellysolve B to give 3.6 g (78%) of product 11, mp 138–140°.

The pmr spectrum of 11 shows three singlets at τ 4.90 (1 H), 5.73 (1 H), and 7.85 (3 H), a pair of doublets (1 H each) at 4.00 and 6.17 (J_{45} = 2.5 Hz), and a multiplet (8 H) at 2.3–3.0.

Anal. Calcd for $C_{18}H_{15}BrO_2$: C, 62.95; H, 4.37. Found: C, 62.77; H, 4.51.

Acid Hydrolysis of Acetate 11.—One gram (2.91 mmol) of the exo acetate 11 was dissolved in 50 ml of dioxane and treated with 16 ml of 3 *M* hydrochloric acid. The reaction mixture was held at reflux for 2.5 hr, after which it was poured into 200 ml of water. This was extracted with two 50-ml portions of ether, and the ether extracts were washed with saturated sodium carbonate solution. The ether was dried over magnesium sulfate and rotary evaporated. Recrystallization of the residue from Skellysolve B gave 0.65 g (74%) of alcohol 12, mp 154.5–155.5°.

The pmr spectrum of 12 shows three singlets (1 H each) at τ 4.91, 5.81, and 7.42 (–OH), a pair of doublets (1 H each) at 5.23 and 6.23 (J_{45} = 2.5 Hz), and a multiplet (8 H) at 2.4–3.0.

Anal. Calcd for $C_{16}H_{13}BrO$: C, 63.81; H, 4.02. Found: C, 63.88; H, 4.31.

Reaction of Phosphorus Tribromide with *anti*-8-Bromo-4-*exo*-hydroxydibenzobicyclo[3.2.1]octadiene (12).—To a solution of 1.0 g (3.32 mmol) of 12 dissolved in 20 ml of dry methylene chloride (distilled from phosphorus pentoxide) was added 3 ml of phosphorus tribromide in 2 ml of dry methylene chloride and the mixture was held at reflux for 14 hr. This was treated with saturated sodium carbonate solution until no more carbon dioxide was generated. The resulting solution was extracted with two 100-ml portions of ether, and the ether extracts were combined and dried over magnesium sulfate. After treatment with charcoal, an oily material was obtained which on recrystallization from methylene chloride–Skellysolve B gave 0.93 g (77%) of the dibromide 13, mp 141.5–143°.

The pmr spectrum of 13 shows two singlets (1 H each) at τ 4.65 and 5.78, a pair of doublets (1 H each) at 4.58 and 5.90 (J_{45} = 2.5 Hz), and a multiplet (8 H) at 2.4–3.0.

Anal. Calcd for $C_{16}H_{12}Br_2$: C, 52.75; H, 3.33. Found: C, 52.50; H, 3.56.

Hydrogenolysis of 9.—One gram (2.75 mmol) of 9,[13] 0.815 g (2.8 mmol) of tri-*n*-butyltin hydride, and 50 mg of benzoyl peroxide were dissolved in 18 ml of dry benzene and held at reflux for 3 hr. The reaction mixture was concentrated and put on a column packed with 50 g of silica gel in Skellysolve B The column was first eluted with Skellysolve B to remove the tributyltin bromide. Eluent of 2% benzene in Skellysolve B gave more tributyltin bromide, followed by small amount of the hydrocarbon 14. Elution with 5% benzene in Skellysolve B gave desired syn bromide 7. Several recrystallizations from 95% ethanol gave 0.5 g (64%) of the syn bromide 7, mp 129.5–130.5°.

The pmr spectrum of 7 shows a doublet (1 H) at τ 6.05, a doublet of doublets (1 H) at 7.33 ($J_{endo\text{-}45}$ = 3.0, $J_{gem\text{-}4}$ = 18.5 Hz), a doublet of doublets that appears a a triplet (1 H) at 5.21 ($J_{18} \cong J_{58}$ = 4.5 Hz), a multiplet (2 H) at 6.34–6.76, and a multiplet (8 H) at 2.6–3.2.

Anal. Calcd for $C_{16}H_{13}Br$: C, 67.38; H, 4.59. Found: C, 67.44; H, 4.66.

Reduction of 8-*anti*-4-*endo*-Dibromobenzobicyclo[3.2.1]octadiene (13) by Tri-*n*-butyltin Hydride.—A mixture of 2.0 g (5.66 mmol) of 13, 1.7 g (5.7 mmol) of tributyltin hydride, and 100 mg of benzoyl peroxide in 25 ml of dry benzene was allowed to reflux for 3 hr under nitrogen. The solvent was removed, the resulting mixture was put on a column packed with 100 g of silica gel in Skellysolve B, and the column was eluted with 2% benzene in Skellysolve B to elute the tin bromide. On elution with 5% benzene, a trace amount of the completely reduced hydrocarbon 14 was obtained, followed by the expected anti bromide 8. Five recrystallizations from 95% ethanol gave 1.12 g (71%) of 8, mp 140–141°.

The pmr spectrum of 8 shows two singlets (1 H each) at τ 5.33 and 5.93, three doublet of doublets (1 H each) at 6.30 ($J_{exo\text{-}45}$ = 5, $J_{endo\text{-}45}$ = 1.8 Hz), 6.63 ($J_{gem\text{-}4}$ = 16.5 Hz), and 7.20, and a multiplet (8 H) at 2.7–3.2.

Anal. Calcd for $C_{16}H_{13}Br$: C, 67.38; H. 4.59. Found: C, 67.28; H, 4.50.

Synthesis of the Tetrahalide 17.—To a solution of 0.63 g (2.28 mmol) of 7,8-dichlorodibenzobicyclo[2.2.2]octatriene[7] in 20 ml of nitromethane was added 2.0 g of bromine, and the vessel was stoppered. The solution was stirred for 3 hr at room temperature after which it was shaken with a mixture of 30 ml of ether and 30 ml of saturated sodium thiosulfate. The ether layer was dried over anhydrous $MgSO_4$ and evaporated to dryness. Crystallization of the oil from ethanol gave 500 mg of 17, mp 150–151°. A pmr spectrum of the mother liquor showed the presence of a small amount of the endo epimer of 17 (H-4 located at τ 4.03), but no attempt was made to isolate the material.

A pmr spectrum of 17 shows two singlets at τ 4.33 and 5.35 and a multiplet (8 H) at 2.3–2.9.

Anal. Calcd for $C_{16}H_{10}Br_2Cl_2$: C, 44.38; H, 2.30. Found: C, 44.42; H, 2.38.

Tri-*n*-butyltin Hydride Reductions.—Reductions of the halides 2,[7] 5,[7] 7,[7] 8, and 17 were run in the following manner. Solutions of the halides (0.05 *M*), tri-*n*-butyltin hydride[22] (0.06 or 0.12 *M* if two halogen atoms were to be removed), and benzoyl peroxide (0.001 *M*) in dry benzene under nitrogen were held at reflux for *ca.* 12 hr. The solutions were concentrated and chromatographed over 25 g of silica gel packed in Skellysolve B. The tin compounds were eluted with 2% benzene in Skellysolve B and the desired products were eluted with 5% benzene in Skellysolve B. Products were analyzed by pmr and ir spectroscopy. The reductions all occurred in a highly stereospecific manner to give only one of the possible two epimers in each case. The yields were 70–90%.

Reduction of the Monobromides 7 and 8 with Tributyltin Hydride.—The reductions of the syn and anti bromides 7 and 8 were carried out in separate reaction flasks. Two 25-ml three-neck flasks were each equipped with a condenser and a nitrogen inlet. Equal amounts of 7 and 8 (50 mg, 0.17 mmol) were placed in the separate flasks. A stock solution was prepared which consisted of 0.2042 g (0.70 mmol) of tributyltin hydride, 30 mg of dibenzyl (internal standard), and 20 mg of benzoyl peroxide in 20 ml of dry benzene; 10 ml of this solution was injected with a syringe into each flask under nitrogen. The two flasks were immersed into a common oil bath maintained at 50°. At each time interval, a 1-ml aliquot was taken from each flask and quenched with 100 μl of 1,2-dibromoethane. Each fraction was concentrated and injected into a gas chromotograph. The column used was a 5-ft stainless steel column packed with 20% SE-30 on Chromosorb W (column temperature 185°, carrier gas helium, flow rate 130 ml/min). The amounts of the starting bromides and the reduced hydrocarbon were measured by a disc integrator in the recorder.

Preparation of *anti*-8-Deuteriodibenzobicyclo[3.2.1]octadiene (15).—Two hundred milligrams (0.70 mmol) of 7 and 200 mg (0.70 mmol) of 8 were placed in separate sealed tubes. A stock solution was prepared which consisted of 1.024 g (3.5 mmol) of tri-*n*-butyltin deuteride[23] and 150 mg of benzoyl peroxide in 12 ml of dry benzene. Under a nitrogen atmosphere 5 ml of this solution was injected with a syringe into the tube containing 7 and 5 ml into the tube which contained 8. The two tubes were

(21) Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Proton magnetic resonance spectra were run in carbon tetrachloride solutions (unless otherwise noted) and measured with a Varian A-60D spectrometer with tetramethylsilane (τ 10.00) as the internal standard. *J* values are "observed" ones. Ir spectra were taken on a Perkin-Elmer 337 infrared spectrometer in 0.5-mm matched cells with carbon tetrachloride as the solvent. Microanalyses were performed by Dr. F. K. Kasler, University of Maryland.

(22) H. G. Kuivila and O. F. Beumel, Jr., *J. Amer. Chem. Soc.*, **83**, 1246 (1961).

(23) L. W. Menapace and H. G. Kuivila, *ibid.*, **86**, 3047 (1964).

heated at 100° in a common oil bath overnight. The reactions were found to be complete after 10 hr (incomplete after 2 hr). Each reaction mixture was evaporated down to a small volume and worked up as usual. The product, **15**, from both reactions was shown to be identical by pmr and ir data.

The relative rates of reaction were determined in the same manner as that described for the hydride reduction. Compound **8** reacts *ca.* twice as fast as **7**.

Chromium(II) Chloride Reduction of 5,8,8-Trichlorodibenzobicyclo[3.2.1]octadiene (5).—To a 10-ml flask, flushed with nitrogen gas, was added 0.60 g (1.94 mmol) of **5** and 5 ml of DMF. The flask was capped immediately with a rubber septum. Nitrogen gas was bubbled through the solution of **5** for 30 min. Six milliliters (12 mmol) of Fisher chromium(II) chloride solution (*ca.* 2 *M*) was injected (*via* syringe) into the solution of **5**, and a dark green color immediately appeared. The reaction solution was diluted with 20 ml of water and extracted twice with 40-ml portions of ether. The combined ether layers were washed with 40 ml of water and dried over anhydrous magnesium sulfate, and the ether was removed by rotary evaporation. A pmr spectrum indicated complete conversion of starting material to **3**. The oil was chromatographed over 10 g of alumina and the fractions were crystallized from carbon tetrachloride to give 400 mg (76% yield) of **3**, mp 119–120°.[7]

Registry No.—**3**, 27995-02-4; **7**, 33065-89-3; **8**, 33065-90-6; **11**, 33065-91-7; **12**, 33065-92-8; **13**, 33065-93-9; **17**, 33065-94-0.

Acknowledgment.—Financial support from the donors of the Petroleum Research Fund of the American Chemical Society (Grant No. 1050-G1) and the National Science Foundation (No. GP-9599) is gratefully acknowledged.

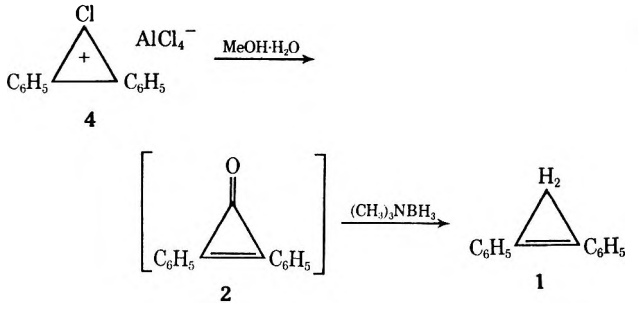
The Reduction of 2,3-Diphenylcyclopropenone and Tropone with Amine–Boranes

W. C. PERKINS* AND D. H. WADSWORTH

Research Laboratories, Eastman Kodak Company, Rochester, New York 14650

Received July 22, 1971

As a possible route to 1,2-diphenylcyclopropene (**1**), the reduction of 2,3-diphenylcyclopropenone (**2**) appeared attractive. Breslow and coworkers[1,2] have



shown, however, that $LiAlH_4$ or catalytic reduction of **2** gives dibenzyl ketone, presumably through a diphenylcyclopropanone intermediate. Tropone (**3**), a similar ketone, on reduction with $LiAlH_4$ gives some cycloheptatriene, but also 3,4-cycloheptadienol and 3,5-cycloheptadienone.[3]

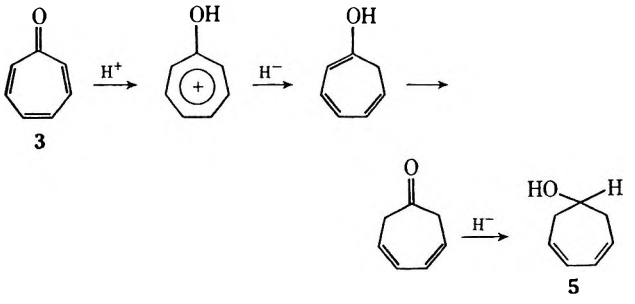
We have found that treatment of 1,2-diphenyl-3-chlorocyclopropenium aluminum chloridate (**4**)[4] in a $MeOH \cdot H_2O$ solution (probable *in situ* formation of **2**) with trimethylamine–borane furnishes **1** in 63% yield. Although isolated **2**, when treated with amine–borane, fails to react, **1** is produced in 90% yield upon subsequent treatment of the reduction medium with anhydrous HCl.

It appears, therefore, that the species being reduced in each case is a Lewis acid complex of ketone **2**. Since **3** also forms a molecular complex with HCl,[5] its reduction in an acidic medium with amine–borane might be expected to produce cycloheptatriene.

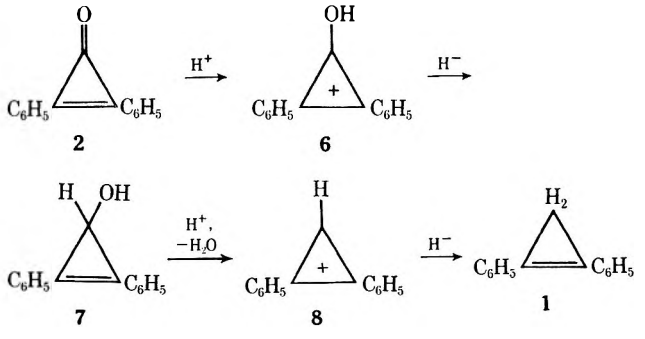
Treatment of **3** with dimethylamine–borane and anhydrous HCl under the reaction conditions, however, gave 3,5-cycloheptadienol (**5**) (the product of a 1,8 conjugate addition)[5,6] as the sole nonvolatile product in 71% yield.

A possible reason for this difference in the observed products from reduction of these vinylogous ketones is summarized in Schemes I and II.

SCHEME I



SCHEME II



Scheme II illustrates a reduction route which involves dehydration of an intermediate to form a cyclopropenium ion (**8**) that is easily reduced by amine–borane in the acidic medium.[7]

The difference between the reduction of **2** and **3** (Schemes I and II) probably lies in the tendency of the cyclopropenyl intermediate **7** to dehydrate, whereas

(1) D. N. Kursanov, M. E. Volpin, and Yu. D. Koreshkov, *Zh. Obshch. Khim.*, **30**, 3877 (1960).

(2) R. Breslow, T. Eicher, A. Krebs, R. A. Peterson, and J. Posner, *J. Amer. Chem. Soc.*, **87**, 1320 (1965).

(3) A. P. TerBorg and H. Kloosterziel; *Recl. Trav. Chim. Pays-Bas*, **82**, 1189 (1963).

(4) S. Tobey and R. West, *J. Amer. Chem. Soc.*, **86**, 4215 (1964).

(5) Yu. G. Borod'ko and Ya. K. Syrkin, *Dokl. Akad. Nauk SSSR*, **136**, 223 (1961).

(6) O. L. Chapman, D. J. Pasto, and A. A. Griswold, *J. Amer. Chem. Soc.*, **84**, 1213 (1962).

(7) W. C. Perkins and D. H. Wadsworth, submitted for publication in *Int. J. Methods Syn. Org. Chem.*

the corresponding intermediate enol of the tropone reduction (formed from a 1,8 conjugate addition of the reducing agent[6]) tends to ketonize and further reduce.

Amine–boranes are quite stable at low pH and become very effective reducing agents for carbonyl groups in the presence of Lewis acids.[8] However, in the presence of anhydrous HCl, trimethylamine–borane and perhaps dimethylamine–borane react to form trimethylamine–chloroborane. Since both trimethylamine–borane and its chlorinated analog will reduce 2 in the presence of HCl but neither will accomplish the reduction in the absence of acid, the actual reducing agent in our system is not known.

It is interesting that tropone is reduced only with dimethylamine–borane–HCl and does not react with trimethylamine–borane–HCl. This seems to indicate a difference in reduction potential between the two amine–boranes in acidic media.

By successive addition of one-half molar amounts of methanolic HCl it was found that complete reduction of 2 required between one and two molar amounts of HCl. Uv analysis immediately after HCl addition indicated complete reduction.

Prolonged treatment with excess anhydrous HCl (as described in the Experimental Section) tended to decompose product at 0°. However, reduction times up to 1 hr with two molar amounts of methanolic HCl at 0° appeared to have no ill effects on the yield of **1**.

Experimental Section

Reduction of 2,3-Diphenylcyclopropenone (2). Method A. *In Situ* Formation and Reduction of 2.—To a solution of 1,2-diphenyl-3-chlorocyclopropenium aluminum chloridate (4, 0.03 mol) in 50 ml of methanol (2% H_2O) at 0° was added 2.10 g of trimethylamine–borane (0.03 mol) in 5 ml of $(CH_2Cl)_2$. The solution was stirred at 0° for 15 min and the solvent was evaporated *in vacuo* at 10°. The residue was suspended in petroleum ether and extracted with ice water. The organic layer was decolorized and cooled on Dry Ice to deposit impurities. The supernatant petroleum ether (bp 35–60°) was then decanted and removed *in vacuo* at 10° to give 3.6 g of **1** (63% yield) melting at 44–47°: nmr ($CDCl_3$) τ 8.48 (1, sharp s) and 2.1–3.0 (5, m); mass spectrum *m/e* (rel intensity) 192 (M^+, 100) and 191 (95); ir (KBr) 1820 cm^{-1}; uv (MeOH) λ_{max} (log ϵ) 228 (3.99), 234 (3.94), 308 (4.14), 318 (4.19), and 336 nm (4.09).[9]

Reduction of Isolated 2. Method B.—To a solution of 1.5 g (0.0073 mol) of 2 in 20 ml of methanol at 0° was added 1.1 g (0.0146 mol) of trimethylamine–borane in 5 ml of $(CH_2Cl)_2$. This solution was acidified with anhydrous HCl over a 2-min period and stirred at 0° for 15 min, and the solvent was evaporated *in vacuo* at 10°. The resulting residue was suspended in petroleum ether and extracted with ice water. The organic layer was decolorized with carbon and stripped *in vacuo* at 10° to give 1.3 g of **1** (91% yield) melting at 44–47° (spectral data identical with above).

Reduction of Isolated 2. Method C.—To a solution of 1.32 g (0.0054 mol) of 2 in 20 ml of methanol at 0° was added 1.1 g (0.0146 mol) of trimethylamine–borane in 5 ml of methanol. This solution was successively acidified with one-half molar equivalents of methanolic HCl (5% solution). After addition of 0.115 g of HCl (0.0032 mol), uv analysis showed partial conversion to **1**. Subsequent additions of one-half molar amounts of methanolic HCl caused immediate increases in the concentration of **1**. Upon addition of a total of 2 molar equiv (0.46 g) of HCl, uv analysis indicated complete disappearance of 2 and **1** as the only evident product. The reaction mixture was allowed to stir for 1 hr at 0° and the solvent was evaporated *in vacuo* at 10°. The resulting residue was suspended in petroleum ether and extracted with ice water. The organic layer was stripped *in vacuo* at 10° to give 1.07 g of **1** (89% yield) melting at 44–49°.

Reduction of Tropone 3.—To a solution of 1.0 g (0.0096 mol) of **3** in 10 ml of CH_2Cl_2 was added 1.0 g (0.0137 mol) of dimethylamine–borane. After treatment with anhydrous HCl over a 2-min period, the solution was stirred at room temperature for 10 min, then extracted with water. The organic layer was separated, dried over molecular sieves, and evaporated *in vacuo* to furnish 0.75 g (71%) of 3,5-cycloheptadienol (**5**). Spectral data (nmr, uv) are consistent with those of Chapman, *et al.*[6]

Registry No.—**1**, 24168-52-3; **2**, 886-38-4; **3**, 539-80-0.

(8) W. M. Jones, *J. Amer. Chem. Soc.*, **82**, 2528 (1960).

(9) D. T. Longone and D. M. Stehouwer, *Tetrahedron Lett.*, **No. 13**, 1017 (1970).

Asymmetric Reduction of Ketones with (+)-Tris[(*S*)-2-methylbutyl]aluminum Etherate

RICHARD A. KRETCHMER[1]

Department of Chemistry, Illinois Institute of Technology, Chicago, Illinois 60616

Received August 4, 1971

Hydrogen transfer from chiral reducing agents to achiral ketones has been extensively studied in an effort to understand the mechanistic details of asymmetric reduction and in order to develop synthetically useful preparations of optically active secondary carbinols. Reducing agents which have been examined include diisopinocamphenylborane and chiral Grignard reagents, metal alkoxides, and metal hydride complexes.[2] Unfortunately, these reducing agents produce optically active by-products which are often difficult to remove from the desired product. In addition, asymmetric Grignard reductions suffer from the fact that product yield is frequently very low as a result of competing addition and enolization reactions.

In view of the stereospecificity, ease of product isolation, and high yield of product on reduction of ketones with triisobutylaluminum,[3] we have examined the utility of (+)-tris[(*S*)-2-methylbutyl]aluminum etherate as an asymmetric reducing agent. The results of reaction with a series of achiral ketones are indicated in Table I. In each case, the resulting secondary carbinol was obtained easily and in excellent yield with an optical purity similar to that obtained upon reduction of the corresponding ketone with the Grignard reagent derived from (+)-(*S*)-1-chloro-2-methylbutane.[4] The convenience of the experimental procedure and the availability of (+)-tris[(*S*)-2-methylbutyl]aluminum etherate combine to make this an attractive preparation of optically active secondary carbinols.

The preferred transition state, **1**, postulated for the corresponding asymmetric Grignard reduction of ke-

(1) Illinois Institute of Technology Faculty Research Fellow.

(2) For a review, see J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Englewood Cliffs, N. J., 1971, pp 160–218.

(3) (a) H. Haubenstock and E. B. Davidson, *J. Org. Chem.*, **28**, 2772 (1963); (b) K. Ziegler, K. Schneider, and J. Schneider, *Justus Liebigs Ann. Chem.*, **623**, 9 (1959); (c) K. Ziegler in "Organometallic Chemistry," H. Zeiss, Ed., Reinhold, New York, N. Y., 1960, pp 236–238.

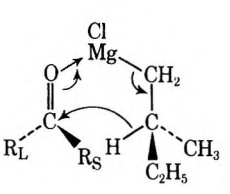
(4) (a) R. MacLeod, F. J. Welch, and H. S. Mosher, *J. Amer. Chem. Soc.*, **82**, 876 (1960); (b) W. M. Foley, F. J. Welch, E. M. La Combe, and H. S. Mosher, *ibid.*, **81**, 2779 (1959).

TABLE I
ASYMMETRIC REDUCTION OF KETONES BY (+)-TRIS[(S)-2-METHYLBUTYL]ALUMINUM ETHERATE IN BENZENE SOLUTION

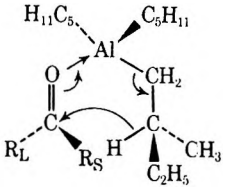
Ketone	Product	Isolated yield, %	$[\alpha]^{25}D$	Configuration	Optical purity, %
Acetophenone	Methylphenylcarbinol	83	−3.38[a]	S[b]	8[c]
Isobutyrophenone	Isopropylphenylcarbinol	93	−14.10[d]	S[e]	30[f]
n-Butyrophenone	*n*-Propylphenylcarbinol	97	−3.39[g]	S[e]	7[h]
3,3-Dimethyl-2-butanone	*tert*-Butylmethylcarbinol	*i*	−0.64[j]	R[k]	13[l]

[a] Determined for the neat liquid. [b] K. Mislow, *J. Amer. Chem. Soc.*, **73**, 3954 (1951). [c] R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, 99, 45 (1911). [d] Determined in ether solution, *c* 23.76. [e] R. MacLeod, F. J. Welch and H. S. Mosher, *J. Amer. Chem. Soc.*, **82**, 876 (1960). [f] P. A. Levene and L. A. Mikeska, *J. Biol. Chem.*, **70**, 355 (1926). [g] Determined in benzene solution, *c* 11.34. [h] J. Kenyon and S. M. Partridge, *J. Chem. Soc.*, 128 (1936). [i] Product isolated by preparative gas chromatography on a 15 ft × 0.25 in. column packed with 10% silicone QF-1 on Chromosorb P; purity >99% by gas chromatography. [j] Determined in absolute ethanol, *c* 7.11. [k] J. Jacobus, Z. Majerski, K. Mislow, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **91**, 1998 (1969). [l] R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **105**, 1115 (1914).

tones, positions the larger carbonyl substituent, R_L, opposite the methyl group of the Grignard reagent while the smaller carbonyl substituent, R_S, is opposite the ethyl group.[2] A similar transition state, **2**, would



1



2

be anticipated to control the product stereochemistry in the asymmetric reduction of ketones with (+)-tris-[(*S*)-2-methylbutyl]aluminum etherate.[3a] This model does, in fact, correctly predict the absolute configuration of the predominant enantiomer resulting from reduction of each alkyl phenyl ketone examined. Surprisingly, however, it fails to predict the absolute configuration of the principal enantiomer resulting from reduction of 3,3-dimethyl-2-butanone. Since only one of the three alkyl groups of a trialkylaluminum reagent is utilized in the reduction of ketones,[3b] it appears that the asymmetry of the two alkyl groups not participating in hydride transfer is capable of exerting a controlling influence on the stereochemistry of this reduction.

Experimental Section[5]

(+)-Tris[(*S*)-2-methylbutyl]aluminum Etherate.—Conversion of 34.006 g (0.319 mol) of (+)-(*S*)-1-chloro-2-methylbutane, $[\alpha]^{25}D$ +1.58° (neat), 95% optical purity,[6] to the Grignard reagent followed by reaction with 9.883 g (0.074 mol) of anhydrous aluminum chloride according to the procedure of Pino, *et al.*,[7] afforded 13.882 g (60%) of (+)-tris[(*S*)-2-methylbutyl]-aluminum etherate: bp 111.0–115.0° (3 mm) [lit.[7] bp 87–89° (0.6 mm)]; $[\alpha]^{25}D$ +22.04° (*c* 16.78, hexane).

Reduction of Acetophenone.—The following preparation is representative of the general procedure. Under an atmosphere of dry nitrogen, 1.191 g (10 mmol) of acetophenone was added by syringe to a solution of 3.192 g (10 mmol) of (+)-tris[(*S*)-2-methylbutyl]aluminum etherate in 30 ml of benzene. An immediate orange coloration developed which faded within 30 sec. The solution was heated at reflux under nitrogen for 2 hr. After cooling to room temperature, the resulting mixture was decomposed with 25 ml of 3 *M* HCl and diluted with an additional 30 ml of benzene. The benzene layer was separated, washed with 25 ml of water, and dried over anhydrous $MgSO_4$. Removal of solvent *in vacuo* followed by distillation afforded 1.008 g (83%) of methylphenylcarbinol: bp 77.0–78.0° (4.5 mm); $[\alpha]^{25}D$ −3.38° (neat); >99% pure by gas chromatography on a 15 ft × 0.25 in. column packed with 10% silicone QF-1 on Chromosorb P.

Registry No.—(+)-Tris[(*S*)-2-methylbutyl]aluminum etherate, 18902-57-3; acetophenone, 98-86-2; isobutylophenone, 611-70-1; *n*-butyrophenone, 495-40-9; 3,3-dimethyl-2-butanone, 75-97-8; methylphenylcarbinol, 1445-91-6.

Acknowledgment.—Financial support by The Petroleum Research Fund of The American Chemical Society is gratefully acknowledged.

(5) Optical rotations were measured with an O. C. Rudolph and Sons, Inc., Model 200 photoelectric polarimeter equipped with a Model 340 oscillating polarizer.

(6) F. C. Whitmore and J. H. Olewine, *J. Amer. Chem. Soc.*, **60**, 2570 (1938).

(7) P. Pino, L. Lardicci, and G. P. Lorenzi, *Ann. Chim. (Rome)*, **48**, 1426 (1958).

Ring Expansion of 1-Azirines to Azepines *via* Cycloaddition

V. NAIR

Department of Chemistry, The University of Iowa, Iowa City, Iowa 52240

Received August 11, 1971

The chemistry of heterotropilidenes has received considerable impetus in recent years due in large part to the elegant synthetic contributions of Paquette and coworkers.[1] In the course of our work on the chemistry of 1-azirines,[2-5] we examined some symmetry-allowed thermal $[\pi^4 + \pi^2]$ cycloadditions of the rigid C=N double bond with dienes. We discovered, as reported briefly earlier,[6] that cyclopentadienones reacted readily with 1-azirines (**1**) to furnish in good yields azatropilidenes.

When 2-phenyl-1-azirine (**1a**) was treated with 2,5-dimethyl-3,4-diphenylcyclopentadienone in benzene at reflux temperatures for 4 days, a relatively stable, pale yellow, crystalline compound was isolated in 65% yield. Mass spectral data and elemental analysis were consistent with the molecular formula $C_{28}H_{23}N$. The in-

(1) L. A. Paquette in "Nonbenzenoid Aromatics," Vol. I, J. P. Snyder, Ed., Academic Press, New York, N. Y., 1969.

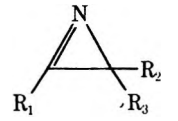
(2) V. Nair, *J. Org. Chem.*, **33**, 2121 (1968).

(3) G. Smolinsky and C. A. Pryde, *ibid.*, **33**, 2411 (1968).

(4) N. J. Leonard and B. Zwanenburg, *J. Amer. Chem. Soc.*, **89**, 4456 (1967).

(5) A. Hassner and F. W. Folwler, *ibid.*, **90**, 2869 (1968).

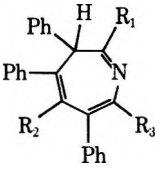
(6) A preliminary report of our results was announced in the 15th Annual Report of the Petroleum Research Fund, 1970. After this manuscript was submitted for publication, a communication on the cycloaddition of azirines to cyclopentadieneones by D. J. Anderson and A. Hassner appeared in *J. Amer. Chem. Soc.*, **93**, 4339 (1971).



1a, R_1 = Ph; R_2 = H; R_3 = H
b, R_1 = Ph; R_2 = CH_3; R_3 = H
c, R_1 = Ph; R_2 = Ph; R_3 = H

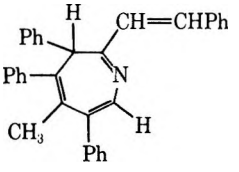
frared spectrum showed no carbonyl or NH absorption. The ultraviolet spectrum in CH_2Cl_2 exhibited absorption maxima at 302 nm (log ϵ 4.03), 270 (4.21), and 235 (4.58). The nmr spectrum ($CDCl_3$) at room temperature showed singlets at δ 1.77 (3 H) and 2.27 (3 H), 5.28 (1 H) and 6.94 (1 H), and a complex multiplet between 7.05 and 7.36 (15 H). The singlet at δ 2.27 disappeared within 20 min at 80° on D_2O exchange.[7] It could not be hydrogenated easily.[8] Attempted cycloadditions with tetracyanoethylene and 1,3-diphenylisobenzofuran were unsuccessful.

The data presented above together with the mechanistic rationalization suggested below led to the 3*H*-azepine (**2a**) as a plausible structure.



2a, R_1 = R_2 = CH_3; R_3 = H
b, R_1 = R_2 = Ph; R_3 = H
c, R_1 = R_2 = R_3 = CH_3
d, R_1 = R_2 = Ph; R_3 = CH_3
e, R_1 = R_2 = CH_3; R_1 = Ph
f, R_1 = R_2 = R_3 = Ph

The protons responsible for the rapid deuterium exchange are those of the 2-methyl group. Thus, when the compound was heated with benzaldehyde in the presence of pyrrolidine, a smooth condensation to the 2-styryl derivative (**3**) occurred.

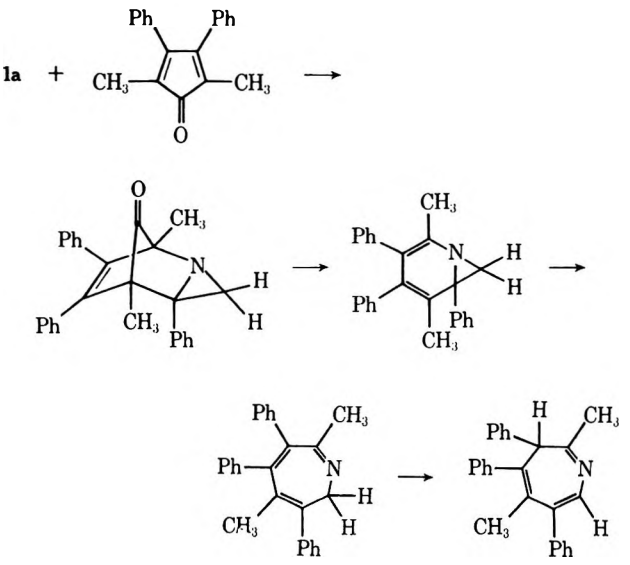


3

The generality of this transformation was established by preparation of compounds **2c** and **2e** from azirines **1b** and **1c** and 2,5-dimethyl-3,4-diphenylcyclopentadienone, and **2b**, **2d**, and **2f** from 2,3,4,5-tetraphenylcyclopentadienone and azirines **1a**, **1b**, and **1c**.

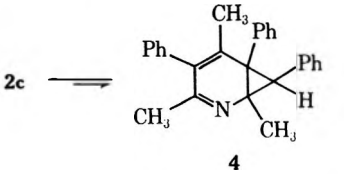
A possible mechanism for the formation of the azepine (Scheme I) assumes a normal Diels–Alder cycloaddition to furnish a strained adduct which undergoes a cheletropic fragmentation[9,10] to give an azanorcaradiene. The symmetry-allowed electrocyclic rearrangement of the azanorcaradiene to its valence tautomer, the azacycloheptatriene (or 2*H*-azepine)[11] is followed by a 1,5-suprafacial sigmatropic shift of the 2 hydrogen to give apparently the thermodynamically more stable 3*H*-azepine.

SCHEME I



Several interesting aspects of the chemistry of these azepines need explanation. Their inability to react with dienophiles or as dienophiles in the Diels–Alder fashion is the result of considerable steric crowding from the spatially large phenyl and methyl substituents. The ultraviolet and nmr spectra reflect not only differences arising from substituents but also any changes in preferred geometry resulting from the crowding.

Of particular interest in our informative D_2O exchange experiments was the observation that the azepine **2c** underwent deuterium exchange not only at the 2-methyl group (20 min at 80°) but also at the 7-methyl group, although the latter exchange was very slow (24 hr at 80°). In contrast, azepine **2d** did not show any tendency to exhibit this behavior at the 7-methyl group. One possible explanation for this is that **2c** undergoes this exchange *via* its valence tautomer **4**, which may be present in very small amounts in equilibrium with the azacycloheptatriene **2c**. This valence tautomerism may not be possible in **2d** because of steric crowding.



4

Initial variable-temperature nmr studies (−100 to 130°) suggest that these azepines (**2a–f**) exist predominantly in one conformation at room temperature and that the energy of activation for the flipping process is high.[12] Of the two conformations **5** and **6** (for **2a**), it would be reasonable to suggest that the preferred

(7) (a) L. A. Paquette, *J. Org. Chem.*, **28**, 3590 (1963); (b) T. J. van Bergen and R. M. Kellog, *ibid.*, **36**, 978 (1971).

(8) Prolonged hydrogenation in the presence of Pt gave a very complex mixture of products which could not be easily handled.

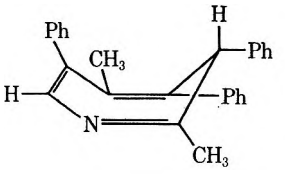
(9) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969).

(10) M. A. Battiste, *Chem. Ind. (London)*, 550 (1961).

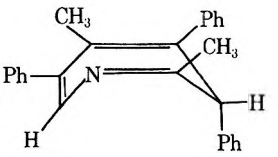
(11) G. Maier, *Angew. Chem., Int. Ed. Engl.*, **6**, 402 (1967).

(12) A. Mannschreck, G. Rissmann, F. Vögtle, and D. Wild, *Chem. Ber.*, **100**, 335 (1967).

conformation would be **5**, where the bulky phenyl group at C-3 occupies the equatorial position.



5



6

Experimental Section

2,5-Dimethyl-3,4,6-triphenyl-3*H*-azepine (2a).—A solution of 468 mg (4 mmol) of 2-phenyl-1-azirine (**1a**)[5] in 10 ml of benzene was treated with a solution of 520 mg (2 mmol) of 2,5-dimethyl-3,4-diphenylcyclopentadienone[13] in 10 ml of benzene.[14] The reaction mixture was heated under reflux for 4 days and then separated by preparative layer chromatography using silica gel PF_{254} with 50% benzene–pentane as the developing solvent. The azepine **2a** crystallized slowly from pentane to give 458 mg of pale yellow plates (65% yield based on the cyclopentadienone): mp 133–134°; uv $\lambda_{max}^{CH_2Cl_2}$ 235 nm (log ϵ 4.58), 270 (4.21), and 302 sh (4.03); nmr $\delta_{TMS}^{CDCl_3}$ 1.77 (s, 3 H), 2.27 (s, 3 H), 5.28 (s, 1 H), 6.94 (s, 1 H), 7.05–7.36 (m, 15 H).

Anal. Calcd for $C_{26}H_{23}N$: C, 88.59; H, 7.43; N, 3.97. Found: C, 88.21; H, 7.05; N, 3.93.

5-Methyl-3,4,6-triphenyl-2-styryl-3*H*-azepine (3) was formed when a solution of the azepine **2c** (100 mg) in benzene (10 ml) was heated under reflux for 4 days with an excess of a mixture of benzaldehyde and pyrrolidine. The solvent and excess reagents were removed under reduced pressure and the residue was chromatographed on preparative plates using silica gel PF_{254}. The styryl derivative **3** crystallized slowly from pentane to give 44 mg of bright yellow rods (36%): mp 161–163°; uv $\lambda_{max}^{CH_2Cl_2}$ end absorption, 283 nm (log ϵ 4.51), 315 (4.26), and 375 (4.16); nmr $\delta_{TMS}^{CDCl_3}$ 1.77 (s, 3 H), 5.81 (s, 1 H), 6.93 (d, 1 H), 7.17–7.38 (m, 22 H).

Anal. Calcd for $C_{33}H_{27}N$: C, 90.57; H, 6.22; N, 3.20. Found: C, 90.74; H, 5.92; N, 3.35.

2,3,4,5,6-Pentaphenyl-3*H*-azepine (2b) was prepared by reaction of 2-phenyl-1-azirine (**1a**) and tetraphenylcyclopentadienone in refluxing mesitylene. The azepine **2b** crystallized from benzene–hexane as yellow plates (90%): mp 217–218°; uv $\lambda_{max}^{CH_2Cl_2}$ 235 nm (log ϵ 4.46), 270 (4.52), and 325 (3.99); nmr $\delta_{TMS}^{CDCl_3}$ 6.45 (s, 1 H), 6.79–7.83 (m, 26 H).

Anal. Calcd for $C_{36}H_{27}N$: C, 91.30; H, 5.74; N, 2.96. Found: C, 90.23; H, 5.21; N, 3.00.

2,5,7-Trimethyl-3,4,6-triphenyl-3*H*-azepine (2c) was prepared from 3-methyl-2-phenyl-1-azirine (**1b**)[2] and 2,5-dimethyl-3,4-diphenylcyclopentadienone. The azepine **2c** crystallized from benzene–pentane as pale yellow plates (69%): mp 182–183°; uv $\lambda_{max}^{CH_2Cl_2}$ 233 nm (log ϵ 4.24), 270 (4.18), and 305 sh (4.03); nmr $\delta_{TMS}^{CDCl_3}$ 1.51 (s, 3 H), 1.57 (s, 3 H), 2.18 (s, 3 H), 5.16 (s, 1 H), 6.74–7.39 (m, 15 H).

Anal. Calcd for $C_{27}H_{25}N$: C, 89.21; H, 6.93; N. 3.85. Found: C, 88.90; H, 6.96; N, 3.79.

7-Methyl-2,3,4,5,6-pentaphenyl-3*H*-azepine (2d) was prepared from 3-methyl-2-phenyl-1-azirine (**1b**) and tetraphenylcyclopentadienone in 84% yield as pale yellow rods: mp 208°; uv $\lambda_{max}^{CH_2Cl_2}$ 235 nm (log ϵ 4.48), 270 (4.54), 350 (3.89); nmr $\delta_{TMS}^{CDCl_3}$ 1.80 (s, 3 H), 6.28 (s, 1 H), 6.83–7.83 (m, 25 H).

Anal. Calcd for $C_{37}H_{29}N$: C, 91.14; H, 6.00; N, 2.86. Found: C, 91.85; H, 6.47; N, 2.45.

A minor product of this reaction (<5% yield) was a very pale yellow crystalline compound, mp 198–201°, which had the molecular formula $C_{37}H_{29}N$ (microchemical analysis and mass spectrometry) and the following spectral characteristics: uv $\lambda_{max}^{CH_2Cl_2}$ 232 nm (log ϵ 4.49), 270 sh (4.33), 292 (4.38), and 325 (4.23); nmr $\delta_{TMS}^{CDCl_3}$ 2.20 (s, 3 H), 5.61 (s, 1 H), 6.68–7.33 (m, 25 H).[15]

Anal. Calcd for $C_{37}H_{29}N$: C, 91.14; H, 6.00; N, 2.86. Found: C, 91.14; H, 5.79; N, 2.94.

2,5-Dimethyl-3,4,6,7-tetraphenyl-3*H*-azepine (2e) was prepared from 2,3-diphenyl-1-azirine (**1c**)[5] and 2,5-dimethyl-3,4-diphenylcyclopentadienone in 58% yield as pale yellow plates: mp 186–188°; uv $\lambda_{max}^{CH_2Cl_2}$ 242 nm (log ϵ 4.16), 270 (4.22), and 312 (4.11); nmr $\delta_{TMS}^{CDCl_3}$ 1.63 (s, 3 H), 2.26 (s, 3 H), 5.27 (s, 1 H), 6.40–7.38 (m, 20 H).

Anal. Calcd for $C_{32}H_{27}N$: C, 90.31; H, 6.40; N, 3.29. Found: C, 90.16; H, 6.90; N, 3.15.

2,3,4,5,6,7-Hexaphenyl-3*H*-azepine (2f) was prepared from 2,3-diphenyl-1-azirine (**1c**) and tetraphenylcyclopentadienone in 91% yield as pale yellow plates: mp 227°; uv $\lambda_{max}^{CH_2Cl_2}$ 243 nm (log ϵ 4.42), 270 (4.53), and 350 (4.12); nmr $\delta_{TMS}^{CDCl_3}$ 6.40 (s, 1 H), 6.74–7.86 (m, 30 H).

Anal. Calcd for $C_{42}H_{31}N$: C, 91.76; H, 5.68; N, 2.56. Found: C, 91.78; H, 5.65; N, 2.82.

Registry No.—**2a**, 33070-60-9; **2b**, 33070-61-0; **2c**, 33070-62-1; **2d**, 33070-63-2; **2d**, 4*H*-azepine isomer, 33070-64-3; **2e**, 33070-65-4; **2f**, 33070-66-5; **3**, 33070-67-6.

Acknowledgment.—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society (Grant No. 1871-G1), for partial support of this research.

(13) (a) F. W. Graw, *J. Chem. Soc.*, **95**, 2131 (1909); (b) C. F. H. Allen and J. A. Van Allan, *J. Amer. Chem. Soc.*, **64**, 1260 (1942).

(14) A twofold excess of the azirine was used in all runs because of the instability of the azirines at elevated temperatures.

(15) This compound is tentatively assigned the 4*H*-azepine isomer of **2d** on analytical and spectral evidence. Further support for this structure came from D_2O exchange studies, which indicated rapid exchange of the methyl group.

THE ORGANIC CHEMISTRY OF PALLADIUM

by PETER M. MAITLIS, Department of Chemistry, McMaster Univ., Hamilton, Ontario, Canada.

..."Both volumes of this book are well written and can be highly recommended to research workers and students interested in organotransition metal chemistry." RICHARD F. HECK, Visiting Professor of Chemistry, Univ. of Delaware in *Industrial Bookshelf*

"...The Author is to be congratulated for producing what will undoubtedly be a major work in organometallic chemistry for the nineteen seventies." ALAN DAVISON, Massachusetts Institute of Technology, in Journal of *Organometallic Chemistry*

VOLUME 1/**METAL COMPLEXES**

CONTENTS:

Preface.
The Inorganic Chemistry Compared to That of the Neighboring Elements.
Compounds with Palladium-Carbon Sigma Bonds and Palladium Hydrides.
Monoolefin and Acetylene Complexes.
Diene Complexes.
π-Allylic Complexes.
Cyclopentadienyl and Benzene Complexes.
Glossary. Bibliography. Author Index—Subject Index.

*1971, 324 pp., $19.00/Set price $16.00**

VOLUME 2/**CATALYTIC REACTIONS**

CONTENTS:

Preface.
Formation and Cleavage of Carbon-Carbon Bonds.
The Formation of Carbon-Oxygen Bonds.
The Formation and Cleavage of Carbon-Hydrogen Bonds.
The Formation of Bonds between Carbon and Halogen, Nitrogen, Sulfur, or Silicon.
Heterogeneous Reactions.
Glossary. Bibliography. Author Index–Subject Index.

*1971, 234 pp., $16.00/Set price $13.50**

***If you order both volumes now, you will receive Volumes I and II at a special discount price of $29.50.**

INTERPRETATION OF MASS SPECTRA OF ORGANIC COMPOUNDS

by MYNARD C. HAMMING, Senior Research Scientist, Continental Oil Company, Ponca City, Okla., **and NORMAN G. FOSTER,** Department of Chemistry, Texas Woman's Univ., Denton, Texas

CONTENTS: Introduction. A Summary of Instrumentation. The Mass Spectrum. The Sample-Its Character and Handling. Fragmentation Reactions-Key to Interpretation of Mass Spectra. Proceeding with an Interpretation. The Rectangular Array and Interpretation Maps. Computerizing Mass Spectral Data. Correlations Applied to Interpretations. GENERAL BIBLIOGRAPHY AND COMPREHENSIVE REFERENCES: Appendix 1: Structure-Correlation References. Appendix 2: Interpretation Maps. Appendix 3: Current Catalogs and Compilations of Mass Spectral Data. Appendix 4: Tables of Isotopic Abundances. Computer Program.

1972, about 600 pp., in preparation

CARBON-13 NMR SPECTROSCOPY

by J. B. STOTHERS, Department of Chemistry, Univ. of Western Ontario, London, Ontario, Canada

CONTENTS: Introduction. EXPERIMENTAL METHODS: Measurements of ^{13}C Parameters. CARBON-13 SHIELDINGS: Hydrocarbon Shieldings. Theory of ^{13}C Shieldings in Hydrocarbons. Substituted Hydrocarbons. Organometallic and Ionic Species. Heterocyclic Systems. Functional Groups. CARBON-13 COUPLING CONSTANTS: General and Theoretical Considerations. A Survey of ^{13}C Spin-Spin Couplings. APPLICATIONS OF ^{13}C NMR: Structural and Stereochemical Applications.

1972, about 520 pp., in preparation

CARBENE CHEMISTRY, 2nd Edition

edited by WOLFGANG KIRMSE, Ruhr-Universitat Bochum, Abteilung für Chemie, West Germany

Provides a comprehensive and up-to-date account of a rapidly expanding field of organic chemistry. It contains a complete survey of carbene-producing reactions, their mechanisms, and their applications in synthesis. Chapters specializing in theoretical aspects of carbene chemistry are also included. The first four chapters review the many reactions known to transfer a formally divalent carbon fragment from one molecule to another. Part 2 (6 chapters) treats the multitude of product-forming reactions of carbenes (carbenoids) with various substrates.

1971, 622 pp., $25.00

THE ENZYMES, Third Edition

edited by PAUL D. BOYER, Dept. of Chemistry and Molecular Biology Inst., Univ. of California, Los Angeles, Calif.

VOLUME 5

HYDROLYSIS: Sulfate Esters, Carboxyl Esters, Glycosides-HYDRATION

CONTENTS:

A. B. ROY, The Hydrolysis of Sulfate Esters.
R. G. NICHOLLS and A. B. ROY, Arylsulfatases.
KLAUS KRISCH, Carboxylic Ester Hydrolases.
DONALD J. HANAHAN, Phospholipases.
HARRY C. FROEDE and IRWIN B. WILSON, Acetylcholinesterase.
JOHN A. THOMA, JOSEPH E. SPRADLIN, and STEPHEN DYGERT, Plant and Animal Amylases.
E. Y. C. LEE and W. J. WHELAN, Glycogen and Starch Debranching Enzymes.
TOSHIO TAKAGI, HIROKO TODA, and TOSHIZO ISEMURA, Bacterial and Mold Amylases.
D. R. WHITAKER, Cellulases.
J. OLIVER LAMPEN, Yeast and *Neurospora* Invertases.
KARL MEYER, Hyaluronidases.
ALFRED GOTTSCHALK and A. S. BHARGAVA, Neuraminidases.
AKIRA TSUGITA, Phage Lysozyme and Other Lytic Enzymes.
JENNY PICKWORTH GLUSKER, Aconitase.
KONRAD BLOCH, β-Hydroxydecanoyl Thioester Dehydrase.
L. GLASER and H. ZARKOWSKY, Dehydration in Nucleotide-Linked Deoxysugar Synthesis.
ROBERT H. ABELES, Dehydrations Requiring Vitamin B_{12} Coenzyme.
FINN WOLD, Enolase.
ROBERT L. HILL and JOHN W. TEIPEL, Fumarase and Crotonase.
W. A. WOOD, 6-Phosphogluconic and Related Dehydrases.
S. LINDSKOG, L. E. HENDERSON, K. K. KANNAN, A. LILJAS, P. O. NYMAN, and B. STRANDBERG, Carbonic Anhydrase.
Author Index-Subject Index.

*January 1972, 752 pp., $31.50/Subscription price $26.75**

VOLUME 6

CARBOXYLATION AND DECARBOXYLATION (NONOXIDATIVE) ISOMERIZATION

TENTATIVE CONTENTS:

MICHAEL C. SCRUTTON and MURRAY R. YOUNG, Pyruvate Carboxylase.
ALFRED W. ALBERTS and P. ROY VAGELOS, Acyl CoA Carboxylases.
HARLAND G. WOOD, Transcarboxylase.
MERTON F. UTTER and HAROLD M. KOLENBRANDER, Formation of Oxalacetate by CO_2 Fixation on Phosphoenolpyruvate.
MARVIN I. SIEGEL, M. DANIEL LANE, and MARCIA WISHNICK, Ribulose 1,5-Diphosphate Carboxylase.
BOB B. BUCHANAN, Ferredoxin-Linked Carboxylation Reactions.
ELIZABETH A. BOEKER and ESMOND E. SNELL, Amino Acid Decarboxylases.
IRWIN FRIDOVICH, Acetoacetate Decarboxylase.
ERNST A. NOLTMANN, Aldose-Ketose Isomerases.
LUIS GLASER, Epimerases.
STANLEY SELTZER, *Cis-Trans* Isomerization.
W. J. RAY, Jr., and E. J. PECK, Jr., Phosphomutases.
ELIJAH ADAMS, Amino Acid Racemases and Epimerases.
H. A. BARKER, Coenzyme B_{12}-Dependent Mutases Causing Carbon Chain Rearrangements.
THRESSA C. STADTMAN, B_{12} Coenzyme Dependent Amino Group Migrations.
P. W. HOLLOWAY, Isopentenyl Pyrophosphate Isomerase.
JORAM HELLER, Isomerizations in the Visual Cycle.
PAUL TALALAY and ANN M. BENSON, Ketosteroid Isomerase
Author Index–Subject Index.

March 1972, about 575 pp., in preparation

ORD AND CD IN CHEMISTRY AND BIOCHEMISTRY

An Introduction

by PIERRE CRABBÉ, Syntex, S. A., Universidad Nacional Autonoma de Mexico and Universidad Iberoamericana, Mexico, D. F., Mexico

This monograph provides a basic introduction to Optical Rotatory Dispersion(ORD) and Circular Dichroism(CD) and their applications to structural and stereochemical problems. After a brief history and review of the elementary principles of stereochemistry, the book discusses the phenomena of optical activity and definitions and units commonly used in ORD and CD, with pertinent references to theoretical considerations and instrumentation. Other chapters deal with the various octant, quadrant, and sector rules (with examples): the influence of the nature of the solvent, the effect of temperature on ORD and CD curves; the optical properties of polymers; and organometallic and inorganic derivatives. The book also discusses in detail the rapidly developing Magnetic Optical Rotatory Dispersion(MORD) and Magnetic Cellular Dichroism(MCD) techniques.

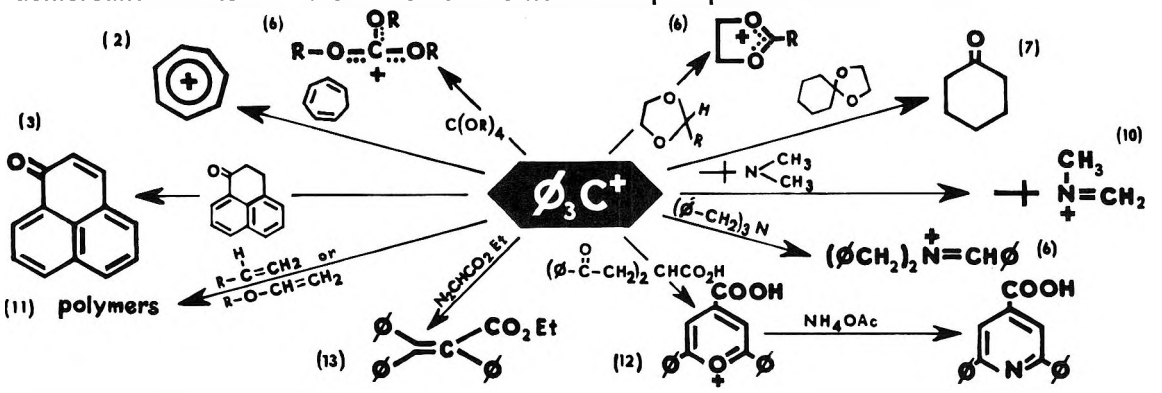
1972, 212 pp., $7.95

ACADEMIC PRESS NEW YORK AND LONDON
111 FIFTH AVENUE, NEW YORK, N. Y. 10003

TRIPHENYLCARBENIUM (TRITYL) SALTS

$\phi_3C^+BF_4^-$ $\phi_3C^+SbCl_6^-$ $\phi_3C^+PF_6^-$

Triphenylcarbenium salts are powerful reagents for hydride abstraction[1] and the most frequently used salt is the tetrafluoroborate which is safer than the perchlorate. The hexachloroantimonate and the more soluble hexafluorophosphate are now also available.



Tropylium ion[2] is readily generated from cycloheptadiene. In some cases the use of trityl salts to effect **dehydrogenations**[3,4] can be superior to NBS or chloranil, e.g. perinaphthanone to perinaphthenone. Alcohols have been oxidized[5] to ketones by trityl salts which can also abstract hydride ion from acetals[6] and ketals.[7] The **regeneration of ketones** from ethylene ketals which is rapid at room temperature was elegantly applied in the synthesis of tetracycline.[8] This method is especially applicable when other acid-sensitive groups are present. **tert**-Methylamines can be converted to **methylene immonium salts.** [9,10] Thus dimethyl-**t**-butylamine, diisopropylmethylamine and dimethylmesitylamine give such salts in high yield to which acetophenone adds to yield Mannich products. Tribenzylamine is easily **debenzylated**[6] through the benzylidene immonium salt which is quantitatively cleaved to benzaldehyde. Trityl salts have been used as cationic polymerization catalysts[11] and in the synthesis[12] of **pyrylium salts.** Ethyl diazoacetate adds[13] to trityl cations with rearrangement to acrylates. However, trityl cation with diphenyldiazomethane acts only as a dimerization catalyst to give tetraphenylethylene.

Phenylcarbenium ion salts other than the trityl salts also abstract hydride ions. Tropylium ion was obtained with diphenylcarbenium hexachloroantimonate[14] and the dichlorophenylcarbenium ion $[C_6H_5CCl_2]^+$ and chlorodiphenylcarbenium ion $[(C_6H_5)_2CCl]^+$ have been described.[15,16] These new carbenium ion salts offer numerous, yet unexplored possibilities in synthetic chemistry.

(1) C. D. Nenitzescu in "Carbonium Ions" Eds., G. A. Olah and P.V.R. Schleyer, Wiley-Interscience Publishers, 1970, Vol. 2, p. 484.
(2) H. J. Dauben Jr., F. A. Gadecki, K. M. Harmon and D. L. Pearson, **J. Amer. Chem. Soc., 79,** 4557 (1957).
(3) W. Bonthrone and D. H. Reid, **J. Chem. Soc.,** 2773 (1959).
(4) H. Brinzbach, D. Seip, L. Knothe and W. Faisst, **Ann., 698,** 34 (1966).
(5) P. D. Bartlett and J. D. McCollum, **J. Amer. Chem. Soc., 78,** 1441 (1956).
(6) H. Meerwein, V. Henerick, H. Morschel and K. Wunderlich, **Ann., 635,** 1 (1960).
(7) D. H. R. Barton, P. D. Magnus, G. Smith and D. Zurr, **Chem. Comm.,** 861 (1971)
(8) D. H. R. Barton, D. L. J. Clive, P. D. Magnus and G. Smith, **J. Chem. Soc.** (C), 1971, 2193.
(9) R. Damico and C. D. Broaddus, **J. Org. Chem., 31,** 1607 (1966).
(10) H. Volz and H. H. Kiltz, **Tetrahedron Letters,** 1917 (1970).
(11) C. E. H. Bawn, C. Fitzsimmons and A. Ledtwidth, **Proc. Chem. Soc.,** 391 (1964).
(12) M. Siemiatycki and R. Fugnitto, **Bull. soc. chim. France,** 538 (1961).
(13) H. W. Whitlock, Jr., **J. Amer. Chem. Soc., 84,** 2807 (1962).
(14) H. Volz, **Angew. Chem., 75,** 921 (1963).
(15) G. A. Olah and M. B. Comisarow, **J. Amer. Chem. Soc., 91,** 2955 (1969).
(16) G. A. Olah and J. J. Svoboda, **Synthesis,** in press.

The following ion salts are specially prepared for Aldrich by Cationics, Inc.

16,455-0	Triphenylcarbenium (trityl) hexachloroantimonate	25g. $12.50; 50g. $20.
16,456-9	Triphenylcarbenium (trityl) hexafluorophosphate	25g. $12.50; 50g. $20.
16,457-7	Triphenylcarbenium (trityl) tetrafluoroborate	25g. $12.50; 50g. $20.
16,458-5	Dichlorophenylcarbenium hexachloroantimonate	10g. $15; 25g. $25.
16,459-3	Chlorodiphenylcarbenium hexachloroantimonate	10g. $17.50
16,460-7	Tropylium hexachloroantimonate	10g. $10; 25g. $20.
16,461-5	Tropylium hexafluorophosphate	10g. $10; 25g. $20.
16,462-3	Tropylium tetrafluoroborate	10g. $10; 25g. $20.
16,463-1	Pentachloroallyl hexachloroantimonate	10g. $12.50; 25g. $20.
16,465-8	Trimethyloxonium hexachloroantimonate	10g. $15; 25g. $30.
16,466-6	Trimethyloxonium hexafluorophosphate	10g. $15; 25g. $30.
16,467-4	Triethyloxonium hexachloroantimonate	25g. $17.50; 50g. $30.
16,468-2	Triethyloxonium hexafluorophosphate	25g. $17.50; 50g. $30.
16,469-0	Methyloxocarbenium (acetyl) hexachloroantimonate	10g. $15.
16,470-4	Benzoyl chloride-antimony pentachloride complex (benzoyl hexachloroantimonate)	10g. $15.
16,471-2	Phenyloxocarbenium (benzoyl) hexafluoroantimonate	10g. $15.