VOLUME 36 FEBRUARY 12, 1971 NUMBER 3 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 Easton, Pa.

Production Staff: Manager, Editorial Production, CHARLES R. BERTSCH; Production Editor, EILEEN SEGAL; Assistant Editor, FERN S. JACKSON; Editorial Assistant, DEBORAH K. MILLER

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

The American Chemical Society and the Editors of *The Journal of Organic Chemistry* assume no responsibility for the statements and opinions advanced by contributors.

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, if any. Please send an old address label, if possible. Allow 4 weeks for change.

New subscriptions and renewals are entered to begin with the first issue of the current volume. Should issues of the current volume be out of print at the time the subscription order is received, the pro rata value of such issues will be refunded to the subscriber.

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 1971: $20.00 per volume to members of the ACS and $40.00 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 $4.50 per subscription for Canada and countries belonging to the Postal Union, and $5.50 for all other countries.

Single copies for current year: $2.00. 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 15, 1971

THE JOURNAL OF Organic Chemistry®

VOLUME 36, NUMBER 3 FEBRUARY 12, 1971

K. GRANT TAYLOR, W. EDWARD HOBBS, AND MONIQUE SAQUET 369 Carbenoids with Neighboring Heteroatoms. II. Stereoselective Synthesis and Nucleophilic Reactions of α-Halocyclopropyllithium Reagents

D. W. SLOCUM, C. A. JENNINGS, T. R. ENGELMANN, B. W. ROCKETT, AND C. R. HAUSER 377 2-Metalation of Dimethylaminoethylferrocene with Butyllithium and Condensations with Electrophilic Reagents. Synthesis of 2-Substituted Vinylferrocenes

E. MARCUS, D. L. MACPEEK, AND S. W. TINSLEY 381 The Reaction of Triisobutylaluminum with 1,5-Cyclooctadiene

ARNOLD L. SCHULTZ 383 Hydrogenolysis of Cyclopropanes

HERBERT C. BROWN, CHANDRA P. GARG, AND KWANG-TING LIU 387 The Oxidation of Secondary Alcohols in Diethyl Ether with Aqueous Chromic Acid. A Convenient Procedure for the Preparation of Ketones in High Epimeric Purity

D. I. COFFEN AND D. G. KORZAN 390 Frangomeric and Anchimeric Processes in the Preparation and Reactions of α,β-Epoxy Ketones

JACOB B. BAUMANN 396 The Displacement of Nitrite Ion in Nitrobenzenes by Sodium Thiolates

SUE K. CORE AND F. J. LOTSPEICH 399 Neighboring-Group Replacement Reactions of Substituted Phenylcyclohexyl Tosylates

R. G. WEISS AND E. I. SNYDER 403 Stereochemistry of Displacement Reactions at the Neopentyl Carbon. Further Observations on the Triphenylphosphine–Polyhalomethane–Alcohol Reaction

WALDEMAR ADAM AND AGUSTIN RIOS 407 Ionic Peroxide Reactions. The Mechanism of the Reaction of Peroxycarbonates with Trivalent Phosphorus Nucleophiles

TOSHIFUMI HIRATA AND TAKAYUKI SUGA 412 Stereochemical Studies of Monoterpene Compounds. IX. Pinacol-Type Rearrangements of α-Pineneglycol Tosylate

E. J. EISENBRAUN, G. H. ADOLPHEN, K. S. SCHORNO, AND R. N. MORRIS 414 The Synthesis of the (3*S*)-Methylcyclopentane-1,2-dicarboxylic Acids (Nepetic Acids Related to the Nepetalactones)

CHARLES L. PERRIN 420 Relative Leaving Abilities and Isotope Effects in Electrophilic Aromatic Substitution

HIROSHI TANIDA AND SADAO MIYAZAKI 425 Substituent Effects on Solvolyses of 1,4-Ethano-1,2,3,4-tetrahydronaphthalen-2(*exo* and *endo*)-yl (Benzobicyclo[2.2.2]octen-2(*exo* and *endo*)-yl) Derivatives

LEO A. PAQUETTE, TSUYOSHI KAKIHANA, AND JOHN F. KELLY 435 The 1-Aza-2,4,6-cyclooctatriene–7-Azabicyclo[4.2.0]octadiene Valence Tautomeric Equilibrium. A Study of Substituent Effects and an Attempted Synthesis of Azetes (Azacyclobutadienes)

LEO A. PAQUETTE AND JOHN F. KELLY 442 Neighboring-Group Participation by Sulfonamide Nitrogen. The 7-Azabicyclo[4.2.0]oct-3-ene to 6-Azabicyclo[3.2.1]-oct-2-ene Rearrangement

TADASHI SASAKI, KEN KANEMATSU, AND MASAYASHI MURATA 446 Tetrazolo–Azide Isomerization in Heteroaromatics. I. Syntheses and Reactivities of Some Tetrazolopolyazines

BENJAMIN FRYDMAN, MARIO LOS, AND HENRY RAPOPORT 450 Synthesis of Substituted 1,5- and 1,7-Naphthyridines and Related Lactams

ELLIS V. BROWN AND RUSSELL J. MOSER 454 Further Evidence as to the Nature of the Transition State Leading to Decarboxylation of 2-Pyridinecarboxylic Acids. Electrical Effects in the Transition State

YUICHI KANAOKA, MASATO AIURA, AND SACHIKO HARIYA 458 Direct Conversion of *N*-Methylindoles into Indoxyl, Oxindole, and Dioxindole *O*-Benzoates

GORDON N. WALKER AND DAVID ALKALAY 461 New Synthesis of 4-Aryl-2,3-dihydro- and 2,3,4,5-Tetrahydro-2-(1*H*)-benzazepines and Corresponding 1,3-Diones

GORDON N. WALKER, DAVID ALKALAY, ALLAN R. ENGLE, AND ROBERT J. KEMPTON 466 Synthesis of 5-Oxo-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-10-carboxylic Acids, Corresponding Nitriles, and Related Bridged Lactones, Hemiketals, Lactams, Amines, Amidoximes, and Amidines (5,10-Epoxymethano and 5,10-Iminomethano Compounds)

EMIL J. MORICONI, THOMAS E. BRADY, AND ROBERT E. MISNER 479 Sulfur Dioxide Extrusion from Substituted 1,3-Dihydro-1,3-diphenylthieno[3,4-*b*]quinoxaline 2,2-Dioxides. Substituted 6-Phenylbenzo[*b*]phenazines

NOTES

NICOLAAS P. DU PREEZ, DANIEL P. VENTER, PETRUS JANSE VAN VUUREN, GERT J. KRUGER, AND JOHANNES DEKKER 485 A Study of the Bromination of Syn and Anti Photodimers of 1,4-Naphthoquinone. The Chemistry of the Brominated Derivatives

RICHARD G. HISKEY, LOWRIE M. BEACHAM, III, VICTOR G. MATL, J. NORTH SMITH, E. BRADY WILLIAMS, JR., A. M. THOMAS, AND ERIK T. WOLTERS 488 Sulfur-Containing Polypeptides. XIV. Removal of the *tert*-Butyloxycarbonyl Group with Boron Trifluoride Etherate

AUTHOR INDEX

Adam, W., 407
Adolphen, G. H., 414
Aiura, M., 458
Alkalay, D., 461, 466

Baumann, J. B., 396
Beacham, L. M., III, 488
Brady, T. E., 479
Brown, E. V., 454
Brown, H. C., 387

Coffen, D. I., 390
Core, S. K., 399

Dekker, J., 485
du Preez, N. P., 485

Eisenbraun, E. J., 414
Engelmann, T. R., 377
Engle, A. R., 466

Frydman, B., 450

Garg, C. P., 387

Hariya, S., 458
Hauser, C. R., 377
Hirata, T., 412
Hiskey, R. G., 488
Hobbs, W. E., 369

Jennings, C. A., 377

Kakihana, T., 435
Kanaoka, Y., 458
Kanematsu, K., 446
Kelly, J. F., 435, 442
Kempton, R. J., 466
Korzan, D. G., 390
Kruger, G. J., 485

Liu, K.-T., 387
Los, M., 450
Lotspeich, F. J., 399

MacPeek, D. L., 381
Marcus, E., 381
Matl, V. G., 488
Misner, R. E., 479
Miyazaki, S., 425
Moriconi, E. J., 479
Morris, R. N., 414
Moser, R. J., 454
Murata, M., 446

Paquette, L. A., 435, 442
Perrin, C. L., 420

Rapoport, H., 450
Rios, A., 407
Rockett, B. W., 377

Saquet, M., 369
Sasaki, T., 446
Schorno, K. S., 414
Schultz, A. L., 383
Slocum, D. W., 377
Smith, J. N., 488
Snyder, E. I., 403
Suga, T., 412

Tanida, H., 425
Taylor, K. G., 369
Thomas, A. M., 488
Tinsley, S. W., 381

van Vuuren, P. J., 485
Venter, D. P., 485

Walker, G. N., 461, 466
Weiss, R. G., 403
Williams, E. B., Jr., 488
Wolters, E. T., 488

THE JOURNAL OF Organic Chemistry®

VOLUME 36, NUMBER 3

FEBRUARY 12, 1971

Carbenoids with Neighboring Heteroatoms. II. Stereoselective Synthesis and Nucleophilic Reactions of α-Halocyclopropyllithium Reagents[1a,b]

K. GRANT TAYLOR,* W. EDWARD HOBBS,[1c] AND MONIQUE SAQUET

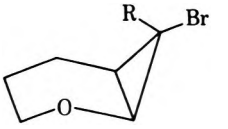
Department of Chemistry, University of Louisville, Louisville, Kentucky 40208

Received June 11, 1970

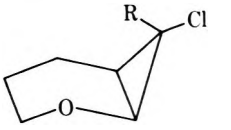
Exploratory investigations into the effect of neighboring n electron donors on the reactivity of carbenoid species were begun. The neighboring oxygen atoms in the 7,7-dihalo-2-oxabicyclo- and -3-oxabicyclo[4.1.0]heptyl ring systems were seen to direct halogen–metal interchange with methyl- and butyllithium to the more sterically hindered (endo) halogen. In addition, the neighboring oxygen stabilized the resulting α-halolithium compound toward α elimination rendering it useful as a nucleophilic reagent. This utility was investigated by reaction with the electrophiles H, D, benzophenone, benzaldehyde, phenyl isocyanate, methyl iodide, mercuric chloride, and carbon dioxide which afforded adducts **1c–h**, **2c–g**, **3**, **6c–f**, and **7d** in moderate to good yields. The 3-oxabicyclo[3.1.0]hexyl ring system was also investigated and found to yield the stable carbenoid **8b** but in low yield.

α-Halo organometallic compounds, particularly lithium reagents, are receiving increased attention both as proposed reactive intermediates in carbenoid reactions[2] and as synthetically useful organometallic reagents.[3] In brief summary, Miller and Whalen[2b] and Closs[2a,d] and Moss[2a] obtained firm evidence implicating α-haloalkyllithium compounds, not free carbenes, as the intermediates directly involved in cyclopropane formation when aryldihalo- and -polyhalomethanes were treated with alkyllithium reagents in the presence of olefins. The findings of Hoeg, Lusk, and Crumbliss[2c] essentially reinforced the conclusions of the previous authors regarding cyclopropane formation.[2e] In addition, they reported[2c] their discovery, made almost simultaneously with Köbrich,[3] that tetrahydrofuran solvent exhibited a marked stabilizing effect on α-haloalkyllithium compounds. Köbrich[3] has reported extensively on a variety of reactions of THF-stabilized lithium carbenoids. The direct intermediacy of lithium carbenoids in an intramolecular C–H insertion reaction has been indicated by the results of Goldstein and Dolbier[2f] who showed that the formation of hexadeuterated 1,1-dimethylcyclopropanes from 1-halo-2,2-di(methyl-d_3)-propyllithium was accompanied by a halogen-dependent (I, Br, Cl) deuterium isotope effect. Thus, the reactions of a number of the "carbenes" produced by α elimination are now attributable to organometallic compounds, and the study of such compounds has revealed that carbenoids can exhibit both nucleophilic and electrophilic reactivity. In this paper we discuss some exploratory work on the effect of oxygen as a neighboring n electron donor on carbenoid reactivity and report on a stereoselective synthesis of intramolecularly stabilized lithium carbenoids and some of their nucleophilic reactions. Their thermal and electrophilic reactions will be discussed at a later date.

The lithium carbenoids **1b**, **2b**, **6b**, **7b**, and **8b** were prepared by halogen–metal exchange between methyl- or butyllithium and the appropriate *gem*-dihalocyclopropane.[4] The dihalocyclopropanes were, with one exception, **1a**, distillable and obtainable in high purity from dihalocarbene additions to the corresponding ole-



1a, R = Br
b, R = Li
c, R = H
d, R = D
e, R = $(C_6H_5)_2COH$
f, R = C_6H_5NHCO
g, R = CH_3
h, R = Hg
i, R = COOH



2a, R = Cl
b, R = Li
c, R = H
d, R = D
e, R = $(C_6H_5)_2COH$
f, R = C_6H_5NHCO
g, R = Hg
h, R = COOH

(1) (a) Supported in part by Grant 970-G1 from the Petroleum Research Fund administered by the American Chemical Society. (b) Part I: K. G. Taylor and W. E. Hobbs, *Tetrahedron Lett.*, 1221 (1968), a preliminary account. (c) National Aeronautics and Space Administration Trainee, 1966–1968.

(2) (a) G. L. Closs and R. A. Moss, *J. Amer. Chem. Soc.*, **86**, 4042 (1964). (b) W. T. Miller and D. M. Whalen, *ibid.*, **86**, 2089 (1964). (c) D. F. Hoeg, D. I. Lusk, and A. L. Crumbliss, *ibid.*, **87**, 4147 (1965). (d) G. L. Closs, presented at the 20th National Organic Chemistry Symposium of the American Chemical Society, Burlington, Vt., June 1967, Abstracts, p 57. (e) Recent evidence indicates that free dichlorocarbene, however, is involved in electrophilic reactions of trichloromethyllithium: G. Köbrich, H. Büttner, and E. Wagner, *Angew. Chem., Int. Ed. Engl.*, **9**, 169 (1970). (f) M. J. Goldstein and W. R. Dolbier, *J. Amer. Chem. Soc.*, **87**, 2293 (1965).

(3) (a) G. Köbrich, *Angew. Chem., Int. Ed. Engl.*, **6**, 41 (1967), a review; (b) G. Köbrich and H. Büttner, *Tetrahedron*, **25**, 2223 (1969), a recent leading reference.

(4) W. R. Moore and H. R. Ward, *J. Amer. Chem. Soc.*, **82**, 6200 (1960).

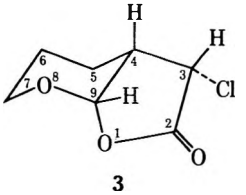
fin. Compound **1a** could not survive distillation but could be purified by column chromatography and low-temperature crystallization.

The 2-Oxabicyclo[4.1.0]heptyl System.—Some of the chemistry of **1b** was the subject of a preliminary communication[1b] and can be summarized as follows. The reaction of **1a** with ethereal methyllithium at −80 or −20° proceeded *via* exchange of the endo bromine giving **1b** in high yield as evidenced by the formation of **1c** or **1d** upon water or deuterium oxide quench, respectively. The stereochemistry of **1c** and **1d** was deduced from features of their nmr spectra. For **1c**, the C-7 H was a quartet at δ 2.83 with two trans couplings[5] (1.3 and 5.0 Hz) and the C-1 H was also a quartet, at δ 3.78 with a cis (8.0 Hz) and a trans (1.3 Hz) coupling. In the spectrum for **1d**, with the C-7 H signal gone, the C-1 H signal remained at δ 3.78 (indicating the same stereochemistry for Br) and was a sharp doublet with J = 8.0 Hz (loss of trans coupling). At −80°, **1c** was formed in 95% yield (by vpc) and could be isolated by distillation in 78% yield. At −20° the yield of **1c** was 60–70% by vpc (55% isolated). The above results indicated the presence of **1b** in the reaction mixture as a stable entity, and facets of its nucleophilic utility were studied. Reaction of **1b** with benzophenone, phenyl isocyanate, methyl iodide, and mercuric chloride gave **1e** (75%), **1f** (37%), **1g** (~90%), and **1h** (10%), respectively, with yields as indicated in parentheses. The ir spectrum of **1e** showed an intramolecularly hydrogen-bonded OH thereby confirming the expected endo configuration for the diphenylcarbinol moiety. The reduced yield of **1c** at −20° as opposed to −80° may reflect either thermal instability of **1b** or a decrease in the stereoselectivity of the exchange reaction with increasing temperature.

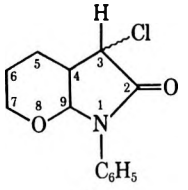
The chemistry of the chloro carbenoid **2b** was similar to that of **1b**. It was prepared from the known[6] **2a** by exchange with ethereal butyllithium at −20°. Water quench of **2b** afforded the known[6,7] monochloro derivative **2c** in 70% yield, and a deuterium oxide quench gave **2d**. Again, reaction of **2b** with benzophenone, phenyl isocyanate, and mercuric chloride gave the products **2e** (56%), **2f** (69%), and **2g** (2%), respectively.

Carbonation of **2b** gave an unexpected result in that a neutral product, lactone **3**, was isolated from the reaction after work-up.

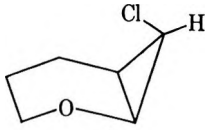
The structure and stereochemistry of **3** rests on the following data and reasoning. Elemental analysis indicated **3** to be isomeric with the anticipated acid **2h**. The ir spectrum of **3** had a strong band at 1780 cm^{-1} consistent with the presence of a γ lactone (1770 cm^{-1}) bearing an α-chloro group (+10 to 40 cm^{-1}).[8] The nmr signals could be assigned as follows: C-9, doublet (J = 4.0 cps), 1 H at δ 5.79; C-3, doublet (J = 6.5 cps), 1 H at 4.78; C-7, multiplet, 2 H centered at 3.83. The presence of a potential aldehyde function in **3** was indicated by a positive test using acidic dinitrophenylhydrazine reagent. Further, a cis ring juncture was indicated by the coupling constant (4.0 cps) of the C-9 proton located at that potential aldehyde site. An axial orientation for the lactone oxygen would be predicted on the basis of the relative conformational energies of an oxygen function as opposed to a carbon function attached to a six-membered ring.[9] Such a prediction found support in the ir spectrum of **3** which



3



4

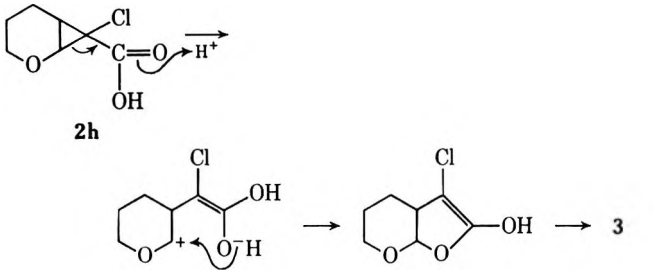


5

showed bands at 1160 (strong) and 1130 cm^{-1} (weak). Exactly this type of C–O stretch is seen in carbohydrate derivatives bearing axial C-1 acetate groups.[10] Inspection of a Dreiding model of **3** in the conformation shown revealed that an exo hydrogen (endo chlorine) at position 3 has an H-3–H-4 dihedral angle close to 30° which would predict a coupling constant close to 6.5 Hz, the experimental value. Conversely, an endo hydrogen (exo chlorine) at that position should have a dihedral angle of about 90° and, as a result, a coupling constant close to 0 Hz.

The lactone **3** can be envisioned as arising *via* a rearrangement of the initial carbonation product, acid **2h**, as shown in Scheme I. Such a pathway might be con-

SCHEME I



2h

sidered structurally analogous to the well-known vinylcyclopropane → cyclopentene and cyclopropanecarboxaldehyde → dihydrofuran thermal rearrangements.[11] The initial carbonation product was indeed **2h**. This could be seen from the nmr and ir spectra (Experimental Section) of the chloroform extract of the acidified carbonation reaction mixture. On evaporation of the above extract, an oil was produced which slowly crystallized with the evolution of considerable heat. The crystals were **3**.

Carbonation of the bromo carbenoid **1b** also produced an acidic oil which crystallized (mp 57–59°). The oil

(5) W. G. Dauben and T. Wipke, *J. Org. Chem.*, **32**, 2976 (1967); K. B. Wiberg and B. J. Nist, *J. Amer. Chem. Soc.*, **85**, 2788 (1963).

(6) W. E. Parham and E. E. Schweizer, *ibid.*, **82**, 4085 (1960).

(7) T. Ando, H. Yamanoka, and W. Funasaka, *Tetrahedron Lett.*, 2587 (1967), reports nmr data which shows that the chlorine atom of **2c** is exo. This is a reversal of the endo assignment originally made (without nmr) by Parham and Schweizer.[6]

(8) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, San Francisco, Calif., 1962, p 44.

(9) E. Eliel, N. Allinger, S. Angyal, and G. Morrison, "Conformational Analysis," Wiley, New York, N. Y., 1965, p 436.

(10) Reference 9, p 396.

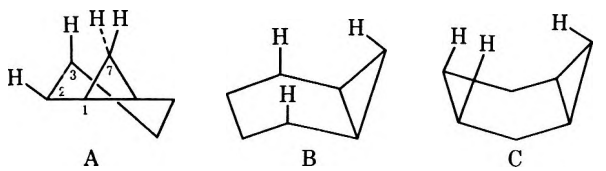
(11) R. Breslow in "Molecular Rearrangements," Vol. I, P. De Mayo, Ed., Wiley-Interscience, New York, N. Y., 1963, pp 236–239.

had ir features similar to those of **2h**, and the crystals had ir and nmr features similar to **3**. The crystals readily liberated HBr at room temperature and decomposition occurred while taking spectra. The crystals had been assigned structure **1h** in ref 1b prior to starting work on **2b**.

Interestingly, the anilide **2f** also appeared to rearrange under mild conditions. Thus, either warming a $CDCl_3$ solution of **2f** in the nmr probe or letting a chloroform solution of **2f** containing a trace of acid stand at room temperature resulted in the formation of a new product which can be formulated as **4** (or its isomeric iminolactone). Only spectral characterization is available for **4**: ir 1703 cm^{-1} consistent with an α-chloro-γ-lactam;[8] nmr loss of the NH proton seen at δ 8.24 in **2f**; appearance of signals of δ 5.9, 5.4, and 2.7 which could be assigned to the C-9, C-3, and C-4 protons of **4**, respectively. All attempts to purify **4** by recrystallization, column chromatography, or preparative tlc were unsuccessful. On one attempt to chromatograph **4** over silica gel a 15% yield of lactone **3** was obtained as the only pure component.

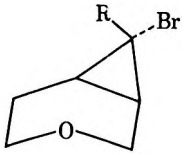
A brief study of the exchange reaction of **2a** with butyllithium in tetrahydrofuran solvent was done to allow a comparison with results in the 7,7-dichloronorcarane system studied by Köbrich and Goyert.[12] At both −20 and −80°, **2a** reacted with predominate exchange of its endo chlorine atom as evidenced by formation of both **2c** and its isomer, **5**,[7] in a 1.6 to 1 ratio upon water quench. In contrast, 7,7-dichloronorcarane reacts (at −115° in THF) with exo exchange predominating over endo exchange by a factor of 3 or 4 to 1. The above experiment with **2a** illustrates (1) the influential role of the ring oxygen in the exchange reaction, and (2) the marked stabilizing effect of THF on lithium carbenoids (due, presumably, to strong solvation of Li by the THF[3a]) and the stabilizing effect of the ring oxygen on **2b**. Thus, use of THF solvent stabilized the C-7 epimer of **2b** and allowed the isolation of **5**. When ether was the reaction solvent, the only monochloro compound formed was **2c** (70%) and no traces of **5** were seen, a fact which demonstrates the stabilized condition of **2b**. The stabilizing of **1b** and **2b** must be due, then, to intramolecular solvation of the lithium by the ring oxygen.

The 3-Oxabicyclo[4.1.0]heptyl System.—Inspection of the 3-oxabicyclo[4.1.0]heptyl system indicated that intramolecular solvation of the lithium atom should be stronger than in the 2-oxabicyclo system. Thus, using norcarane as a model, in the half-chair conformation A

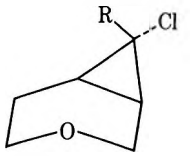


A B C

the C-7 and C-3 hydrogens can approach each other to within 2.1 Å without undue strain. In the same conformation the C-7 and C-2 hydrogens can approach to within 2.4 Å. Further, in the boat (or twist boat) form B, the C-7–C-2 hydrogen distance can shorten to about 2.2 Å, while in the boat form C, the C-7–C-3 hydrogen distance can be as short as 1.9 Å. The above would indicate that the oxygen n electrons in the 3-oxa system have a more favorable bonding distance and geometry for coordination with the C-7 lithium than would the oxygen n electrons of the 2-oxa system. It was deemed of interest, then, to determine what reactivity changes in the carbenoid would, in fact, result from this relatively minor structural change.



6a, R = Br
b, R = Li
c, R = H
d, R = D
e, R = C_6H_5CHOH
f, R = COOH



7a, R = Cl
b, R = Li
c, R = H
d, R = COOH

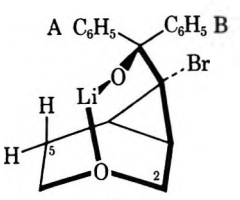
The stoichiometry of the exchange reaction of dibromocyclopropane **6a** with methyllithium was seen to change with change in reaction solvent. In ether solvent (at −80°) 1 equiv of methyllithium was sufficient to consume all of **6a**. In pentane, however, use of 1 equiv of methyllithium[13] for as long as 1.5 hr left 30% of starting **6a** unreacted. Use of 1.7 equiv of methyllithium reduced the amount of unreacted **6a** to about 10% and 2.0–2.5 equiv of methyllithium proved to be a practical quantity which ensured complete reaction of **6a**. On going from ether to pentane, the yield of the monobromo **6c** (obtained from a water quench of **6b**) increased from 60% by vpc (47% isolated) to 91% by vpc. In a like manner, the yield of carbonation product **6f** increased from 54 to 65%. Often, in practice, a 3:2 pentane–ether mixture, which gave good solubility for starting **6a**, a high yield of **6b**, and 1:1 stoichiometry for the exchange reaction, was used. These yield increases can logically be attributed to an increase in stereoselectivity in the exchange reaction in pentane solvent where the directing influence of the ring oxygen of **6a** would be more important. The change in stoichiometry with change in solvent requires a longer explanation. The following experiments were conducted to shed some light on the nature of the required second equivalent of methyllithium. The reaction of **6b** in ether–pentane (stoichiometry 1:1) with 1 equiv of benzaldehyde afforded the carbinol **6e** as a mixture of diastereomers in 40% yield. In pentane (stoichiometry 2:1), successive treatment of **6a** with 2.5 equiv of methyllithium and 2 equiv of benzaldehyde gave approximately equal amounts of carbinol **6e** and 1-phenylethanol. In addition, successive treatment of **6a** with 2.0 equiv of methyllithium, 1.0 equiv of water, and 1.0 equiv of benzaldehyde yielded (by vpc) about 50% of the monobromo **6c**, about 33% of 1-phenylethanol, and only 0–2% of carbinol **6e**. The above experiments showed that the second mole of methyllithium required for the exchange reaction in pentane was still reactive toward the electrophile benzaldehyde and apparently less reactive (less basic?) toward water than the carbenoid **6b**. The carbenoid **6b** appears insoluble in pentane at −80°, and most likely the second methyllithium is coordinated with it as **6b** precipitates from solution.

(12) G. Köbrich and W. Goyert, *Tetrahedron*, **24**, 4327 (1968).

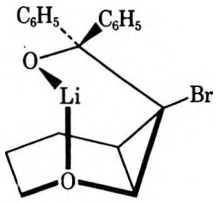
(13) Commercial methyllithium–lithium bromide 1.2 *M* in ether was used; hence, small amounts of ether were always present.

In ether wherein the carbenoid is soluble, the solvent may play the solvating role that methyllithium does in pentane.

Perhaps the most dramatic reactivity difference between **1b** and **6b** was seen in their reactivity toward benzophenone. While **1b** reacted smoothly at −80° to give **1e** in 63% yield, **6b** *failed* to react with benzophenone under a wide variety of concentration, solvent, and temperature conditions with side reactions, one of which was hydrogen abstraction, consuming **6b**.[14] The reasons for this failure must be steric in origin since, as mentioned above, **6b** reacted readily with benzaldehyde to yield **6e**. The failure of **6b** to react with benzophenone is striking when it is recalled that alkyllithium reagents have been seen to react ~10^3 times faster with ketones than Grignard reagents,[15] and also that ethereal *tert*-butyllithium affords an 81% yield of tri-*tert*-butylcarbinol upon reaction with hexamethylacetone at −65°.[16] If the assumptions are made that the addition step of **6b** to benzophenone is irreversible and that the lithium atom of **6b** (and **1b**) remains bonded to the ring oxygen in the transition state,[17] then the following might be suggested as an explanation for the reactivity difference between **6b** and **1b**. Using Drieding models to approximate the structure of the addition product, I,



I



II

of **6b** and benzophenone, the geometry of the seven-membered ring which incorporates the OLi–O link forces phenyl A over the pyran ring to within about 1.7 Å of H-5 (or phenyl B to within about 1.6 Å of H-2 if the 7-ring is inverted) and causes phenyl B to almost eclipse the bromine.[20] The six-membered OLi–O-containing ring in II, conversely, allows the two phenyls and the bromine to be staggered, and neither phenyl is forced over the pyran ring. Thus, if the unfavorable steric factors seen in I build up in the transition state leading to it, the rate of addition of **6b** may be retarded to the point where other reactions[22] of **6b** compete successfully.

(14) In one of seven attempts, a 0.7% yield of a product, mp 91–93°, was obtained whose faint nmr was not inconsistent with that expected for the desired carbinol product.

(15) S. G. Smith, *Tetrahedron Lett.*, 6075 (1966).

(16) P. D. Bartlett and E. B. Lefferts, *J. Amer. Chem. Soc.*, **77**, 2804 (1955).

(17) These assumptions appear intuitively valid but their importance to the success of the reaction with benzophenone can only, at present, be suggested. These suggestions, however, imply an additional significant role for basic solvents in the usual organolithium reactions, besides that of assistance in RLi aggregate dissociation,[18] and charge-transfer support in a one-electron process.[19]

(18) T. L. Brown, *Advan. Organometal. Chem.*, **3**, 392 (1966).

(19) C. G. Screttas and J. F. Eastham, *J. Amer. Chem. Soc.*, **88**, 5668 (1966).

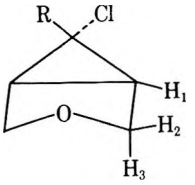
(20) An O–Li distance of 1.9 Å and O–Li–O angles of 100 and 109° were used.[21] The basic geometry of the tricyclic systems of I and II is relatively insensitive to these factors and the nonbonded interactions mentioned above cannot be relieved without imparting angle strain to the framework of the 3-oxabicyclo[4.1.0]heptane system.

(21) P. J. Wheatley, *Nature*, **185**, 681 (1960), reports for lithium methoxide a four-coordinate lithium with Li–O distance of 1.95 Å and O–Li–O angles of 131.7 and 101.7°.

(22) To be reported at a later date.

The preparation and reactions of the chloro carbenoid **7b** were only briefly investigated because the exchange reaction of **7a** with butyllithium proved quite complex with butyl groups becoming incorporated into several of the products formed. In fact, the monochloro derivative **7c**, although identifiable by nmr, could not be purified due to a butyl-containing impurity with a very similar vpc retention time. Carbonation of **7b**, however, gave the carboxylic acid **7d** in 40% yield.

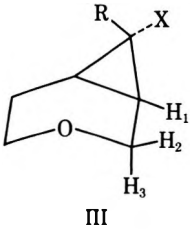
The 3-Oxabicyclo[3.1.0]hexyl System.—Again, the chemistry of carbenoid **8b** was studied only briefly due



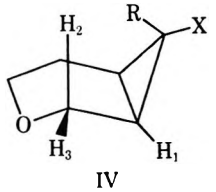
8a, R = Cl
b, R = Li
c, R = H
d, R = COOH

to the relative tediousness in obtaining the known **8a** in sufficient quantity and purity and due to the complex nature of its reactions with butyllithium. A water quench of a preparation of **8b** in ether at −80°, however, did afford **8c**, readily identified by its C-6 H nmr signal at δ 2.88 (triplet, J_{trans} = 2.5 Hz) but only in about 10% yield (starting material remained and butyl-containing products were beginning to form). Carbonation of a similar preparation of **8b** yielded the carboxylic acid **8d** in 9% yield.

Nmr Spectra.—The nmr spectra of the 3-oxabicyclo systems had some common features which bear further comment on two aspects. First, the nmr spectra of **8c** and **8d** were more consistent with a boat, rather than chair, conformation for those compounds. Thus, one hydrogen on C-2 was seen as a sharp doublet with J_{gem} = −9.0 Hz and J_{21} = 0 Hz indicating a vicinal dihedral angle close to 90°. In a boat conformation the H_2 hydrogen describes such an angle with H_1, and in this conformation better staggering of the vicinal C–H's and cyclopropane C–C bonds occurs. In a chair conformation no 90° dihedral angle occurs and eclipsing exists between H_2 and the vicinal (banana) bonds of the cyclopropane ring, and between H_3 and H_1. Boat conformations have been observed for the 3-oxa-6-azabicyclo[3.1.0]hexane[23] and 6-azabicyclo[3.1.0]hexane[24] ring systems in the solid state. A similar analysis allows the assignment of half-chair conformation III rather than IV as the predominate one for the com-



III



IV

pounds **6c–f** and **7c,d**. Thus H_2 is generally seen as a sharp doublet, J_{12} = 0 Hz and J_{23} = −12 Hz, with H_3 somewhat upfield as a quartet, J_{13} = 3 Hz. An H_1–H_2

(23) L. M. Trefonas and T. Sato, *J. Heterocycl. Chem.*, **3**, 404 (1966).

(24) H. M. Zacharis and L. M. Trefonas, *ibid.*, **5**, 343 (1968).

dihedral angle approaching 80° can be accommodated in chair III, but not in chair IV, without increase in nonbonded interactions.

The second feature of the nmr spectra of the 3-oxabicyclo systems that was somewhat unusual was the chemical shift changes of H_2 and H_3 that occurred upon changing the substitution on the cyclopropane ring. As can be seen from Table I, when the substituents on

TABLE I

CHEMICAL SHIFTS (δ) OF H_2 AND H_3 IN THE 3-OXABICYCLO[*n*.1.0] RING SYSTEMS

Compd	H_2	H_3	$\Delta\delta$ H_3–H_2
9[a]	3.77		~0
6a[a]	~3.98		<0.06
6c[a]	4.08	3.77	0.31
7a[b]	4.08		~0
7c[a]	4.09	3.78	0.31
10[c]	3.54	3.41	0.13
8a[d,e]	~4.17		~0
8c[d]	4.08	3.79	0.28

[a] CCl_4 solvent, internal TMS. [b] Neat, external TMS. [c] Taken from ref 25, in CCl_4. [d] $CDCl_3$ solvent, internal TMS. [e] In CCl_4, δ 4.08; ref 25.

the cyclopropane methylene group were both halogen (**6a**, **7a**, **8a**), the chemical shifts of H_2 and H_3 were nearly identical, with the signal appearing as a sharp narrowly spaced doublet, or, as in the case of **9a**, a narrow triplet (half-height width, 6 Hz). This held true, also, when the substituents were both hydrogen. In the case of 3-oxabicyclo[4.1.0]heptane (**9**), the signal was a narrow doublet, and for 3-oxabicyclo[3.1.0]hexane (**10**),[25] the signal was reported as a narrow quartet. However, when the substituents were not identical, as exemplified by the monohalo compounds **6c**, **7c**, and **8c**, H_2 always appeared distinctly downfield from H_3. In another way of looking at the data of Table I, when the endo halogen was replaced by hydrogen, it was H_3, the hydrogen further removed from the substituent change, which was affected the most. An attempt was made to calculate the H_2–H_3 chemical-shift difference, by methods previously used with some success by others, to see if the observed shifts could easily be accounted for.

Using the method of Tori and Kitahonoki,[26] the shielding effect of the cyclopropane ring on H_2 and H_3 of **9** and **10** was calculated. For conformation III of **9** and the boat form of **10**, H_2–H_3 differences of δ 0.28 and 0.34, respectively, were calculated with H_3 predicted to be downfield from H_2. The effect of a neighboring ether oxygen atom cannot be reliably calculated,[27] but it can be predicted from data from numerous sources[28] that H_3, anti to a nonbonding electron pair of oxygen in the conformations chosen, should be shifted upfield relative to H_2. To fit the observed spectra, the compensating upfield shifts needed to offset the calculated effect of the cyclopropane ring are about δ 0.30 for H_3 of **9** and about δ 0.45 for H_3 of **10**, values which are well within the usually observed range of δ 0.20–0.5.[27,28] By way of contrast, for conformation IV of **9** and the chair form of **10**, H_2–H_3 shift differences due to the cyclopropane ring of δ 1.31 and 1.07, respectively, are calculated. Here, again, H_3 is predicted to be downfield from H_2, and this difference should be accentuated rather than cancelled by the effect of the neighboring oxygen since H_2 is now anti to a nonbonding electron pair. Thus, the observed similarity in chemical shifts for H_2 and H_3 of **9** and **10** can be readily rationalized on the basis of conformation III for **9** and a boat for **10**.

On the basis of the above, it would appear to follow that the observed H_2–H_3 shift differences in **6c**, **7c**, and **8c** should be attributable to the effect of the exo halogen. Zürcher[29] has, with some success, calculated the chemical-shift changes of methyl groups in rigid, aliphatic molecules. He found that, in the compounds studied, changes induced by the neighboring chlorine could be satisfactorily accounted for on the basis of electrical effects alone. Calculations by the method of Zürcher, when applied to conformation III of **6c** and the boat form of **8c**, predicted that H_2 and H_3 should be deshielded by the chlorine substituent to practically the same extent (δ 0.18–0.20) and consequently should differ in chemical shift by only δ 0.02 in both compounds. Assuming conformation IV for **6c** and a chair for **8c** yielded different predictions but no better a correlation. A number of reasons could be cited for the above failure of Zürcher's method. Further comment, however, should be reserved until further work, such as variable temperature nmr studies, testing the flexibility of **6c** and **8c** is done.

Experimental Section

General.—All melting points were taken on a Thomas–Hoover melting point apparatus and are uncorrected. Vpc analyses were performed on an F & M Scientific Corp. instrument, Model 5750, fitted with a flame ionization detector, or Model 700, fitted with a thermal conductivity detector. The following columns were used: A, 15% polytetramethylene ether glycol 3000 on Chromosorb G-NAW; B, 10% Carbowax 20M on Chromosorb G-NAW; C, 2% polytetramethylene ether glycol on Chromosorb G-NAW; D, 10% silicone rubber UCW 98 on Chromosorb G-NAW; E, 2% silicone rubber UCW 98 on Chromosorb G-NAW; F, 2% silicone rubber UCW 98 on Diatoport S; G, 5% ethylene glycol adipate on Diatoport S; H, 20% SE 52 silicone on Chromosorb G-NAW. When necessary, peak identification was done by spiking with known compounds. Nmr spectra were obtained with a Varian Associates A-60A spectrometer with tetramethylsilane as an internal standard and, unless otherwise specified, deuteriochloroform was the solvent. Infrared spectra were determined on a Perkin-Elmer Model 337 grating spectrophotometer. Ultraviolet spectra were obtained with a Cary Model 14 spectrophotometer in 95% ethanol. Elemental analyses were performed as direct analyses by Midwest Microlab, Inc., Indianapolis, Ind.

All the reactions which involved the use of potassium metal, carbene addition, or the use of alkyllithium reagents were conducted in an atmosphere of dry nitrogen. The methyllithium and butyllithium reagents were titrated when required by the method of Gilman and Haubein substituting ethylene dibromide for benzyl chloride.[30]

7,7-Dibromo-2-oxabicyclo[4.1.0]heptane (1a).—To 250 ml of *tert*-butyl alcohol (distilled from sodium) was added 8.6 g (0.22 g-atom) of potassium. The mixture was heated until dissolution occurred. The excess *tert*-butyl alcohol was removed *in*

(25) T. Shono, A. Oku, T. Morikawa, M. Kimura, and R. Oda, *Bull. Chem. Soc. Jap.*, **38**, 940 (1965).

(26) K. Tori and K. Kitahonoki, *J. Amer. Chem. Soc.*, **87**, 386 (1965).

(27) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1969, pp 80–81.

(28) (a) C. Altona and E. Havinga, *Tetrahedron*, **22**, 2275 (1966); (b) C. B. Anderson and D. T. Sepp, *ibid.*, **24**, 1707 (1968); (c) D. T. Sepp and C. B. Anderson, *ibid.*, **24**, 6873 (1968); (d) F. W. Nader and E. L. Eliel, *J. Amer. Chem. Soc.*, **92**, 3050 (1970), and references therein; (e) L. D. Hall, *Tetrahedron Lett.*, 1457 (1964).

(29) R. F. Zürcher in "Progress in Nuclear Magnetic Resonance Spectroscopy," Vol. 2, J. W. Emsley, J. Feeny, and L. H. Sutcliffe, Ed., Pergamon Press, New York, N. Y., 1967, Chapter 5.

(30) H. Gilman and A. H. Haubein, *J. Amer. Chem. Soc.*, **66**, 1515 (1944).

vacuo with mild heating. The remaining potassium *tert*-butoxide was broken up and 25.22 g (0.3 mol) of 3,4-dihydro-2*H*-pyran in 90 ml of pentane was added. The resulting slurry was cooled to −20° (ice–acetone) and 38.4 g (0.15 mol) of bromoform in 75 ml of pentane was added dropwise over a period of 1 hr. The mixture was stirred an additional hour at −20° and quenched with water. The organic layer was washed with two portions of water, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was evacuated to 0.8 mm and heated (50–60°) until vigorous boiling occurred. The heating bath was removed and the compound was allowed to cool under reduced pressure. The remaining yellow oil was dissolved in pentane and passed over a column (40.0 g) of neutral alumina. The first 150 ml of eluent was collected and concentrated *in vacuo*. This yielded 28.8 g (75%) of a clear colorless oil: $n^{27}D$ 1.5514; nmr δ 3.84 (d, J = 8.0 Hz, H_1), 3.57 (m, CH_2O), 1.67 (m, 5 H).

It was subsequently found that this compound could be purified by low-temperature (−80°) recrystallization from pentane in about a 40.0% yield. The recrystallized material when stored at −20° was a white crystalline solid and appeared to be stable indefinitely at that temperature.

exo-7-Bromo-2-oxabicyclo[4.1.0]heptane (1c).—To a cooled (−20°) solution of 10.0 g (38.4 mmol) of 1a in 150 ml of ether was added methyllithium–lithium bromide (55.5 mmol) during a period of 30 min. The solution was stirred for an additional 15 min and quenched by the slow addition of water. The organic layer was washed with two portions of water, dried ($MgSO_4$), and concentrated *in vacuo* (the usual work-up). This yielded a yellow oil. Distillation gave 3.97 g (55.5%) of 1c: bp 58–61.5° (0.32 mm); ir (neat) 3050 cm^{-1} (–CH, cyclopropane); nmr δ 3.78 (q, J = 1.3 and 8.0 Hz, H_1), 3.4 (m, $-CH_2O-$), 2.83 (q, J = 1.3 and 5.0 Hz, H_7), 1.8 (m, 5 H); d^{27}_4 1.55.

When the above procedure was repeated at −80° using 5.0 g of 1a, the isolated yield was 77.8%.

The yield at −20° was determined by vpc (column A, 6 ft × 0.25 in.), using ethylene glycol as an internal standard, to be 62.0%. At −80° the yield was 95.0%.

Anal. Calcd for C_9H_9BrO: C, 40.70; H, 5.12; Br, 45.13; O, 9.03. Found: C, 40.99; H, 5.12; O, 9.28.

exo-7-Bromo-*endo*-7-deuterio-2-oxabicyclo[4.1.0]heptane (1d).—The above procedure was repeated and quenched by the slow addition of deuterium oxide (99.8%). The major component was collected from preparative vpc (column A, 6 ft × 0.25 in.): ir (neat) 2270 cm^{-1} (w) (C–D); the 3050 cm^{-1} (w) (CH, cyclopropane) absorption which was present in 1c was absent; nmr δ 3.78 (d, J = 8.0 Hz, H_1), 3.57 (m, $-CH_2O-$), 1.67 (m, 5 H).

exo-7-Bromo-*endo*-7-(diphenylmethanol)-2-oxabicyclo[4.1.0]-heptane (1e).—To a cooled (−80°) solution of 4.0 g (15.64 mmol) of 1a in 60 ml of ether was added methyllithium–lithium bromide (15.64 mmol) during a period of 15 min. A precipitate formed after about 3 min and the slurry was stirred for an additional 7 min. After this period 2.84 g (15.64 mmol) of benzophenone dissolved in 20 ml of ether was added. The reaction mixture was stirred 1 hr at −80° and quenched by addition of methanol. The usual work-up yielded a clear colorless oil which crystallized on standing. Recrystallization from methanol yielded 4.20 g (75.0%) of white prisms: mp 88–90.0°; ir (CCl_4) 3450 cm^{-1} (OH) which did not change upon dilution; nmr (CCl_4) δ 7.4 (m, phenyl H), 4.33 (s, –OH), 4.05 (d, J = 7.0 Hz, H_1), 3.58 (m, CH_2O), 1.64 (m, 5 H).

Anal. Calcd for $C_{19}H_{19}BrO_2$: C, 63.51; H, 5.33; O, 8.90. Found: C, 63.66; H, 5.45; O, 8.83.

exo-7-Bromo-*endo*-7-(*N*-phenylcarboxamido)-2-oxabicyclo-[4.1.0]heptane (1f).—To a cooled (−80°) solution of 4.0 g (15.64 mmol) of 1a in 60 ml of ether was added methyllithium–lithium bromide (15.64 mmol) during a period of 15 min. The mixture was stirred for an additional 10 min and 1.86 g (15.64 mmol) of phenyl isocyanate in 20 ml of ether was added. The mixture was stirred at −80° for 1 hr and quenched by addition of methanol. The reaction mixture was filtered to yield a white microcrystalline solid. The usual work-up yielded an additional amount of white solid. Recrystallization of the combined solids from methanol yielded 1.73 g (37.4%) of white needles: mp 112.5–113°; ir ($CHCl_3$) 3400 and 3350 (broad) (–NH–), 1680 and 1600 cm^{-1} (amide I and II); nmr δ 8.1 (broad, NH), 7.39 (m, phenyl), 4.05 (d, J = 7.5 Hz, H_1), 3.64 (m, CH_2O), 1.34 (m, 5 H).

Anal. Calcd for $C_{13}H_{14}BrNO_2$: C, 52.70; H, 4.77; O, 10.80. Found: C, 52.89; H, 4.73; O, 10.89.

exo-7-Bromo-2-oxabicyclo[4.1.0]heptyl-*endo*-7-carboxylic Acid (1i).—To a cooled (−80°) solution of 4.14 g (16.2 mmol) of 1a in 60 ml of ether was added methyllithium–lithium bromide (16.8 mmol) during a period of 10 min. The solution was stirred for an additional 10 min and dry carbon dioxide was passed into the stirred solution for a period of 1 hr. The reaction was quenched by the addition of methanol. After it was washed with ether the basic water layer was acidified with concentrated hydrochloric acid and extracted with ether. The ether extracts of the acidic layer were dried ($MgSO_4$) and concentrated *in vacuo* to yield an oil [ir (neat) 3600–2300 (OH) and 1698 cm^{-1} (C=O)] which crystallized to a white solid. Recrystallization from cold benzene–hexane yielded 3.14 g (87.5%) of white crystals: mp 57.5–59.5°; ir (KBr) 1750 cm^{-1} broad (C=O); nmr δ 1.7, 2.6, 3.9, 5.7, and 6.9. The compound was too unstable for further characterization.

exo-7-Bromo-*endo*-7-methyl-2-oxabicyclo[4.1.0]heptane (1g).—To a cooled (−80°) solution of 1.3 g (5.12 mmol) of 1a in 20 ml of ether was added methyllithium–lithium bromide (5.2 mmol) during a period of 10 min. The mixture was stirred for an additional 10 min and 5.7 g (40 mmol) of methyl iodide in 20 ml of ether was added. The bath was removed and the solution was allowed to attain 25°. The solution was stirred at 25° for a period of 1 hr and quenched with water. The usual work-up gave a major component which was collected from preparative vpc (column H, 6 ft × 0.25 in.). The yield was about 90.0% as estimated from vpc: nmr δ 3.82 (d, J = 8.0 Hz, H_1), 3.52 (m, CH_2O), 1.79 (s, CH_3), 1.88 (m, 5 H).

Anal. Calcd for $C_7H_{11}BrO$: C, 44.00; H, 5.80; O, 8.37. Found: C, 44.22; H, 5.78; O, 8.60.

2-Oxabicyclo[4.1.0]heptane (9). A. From 2a.—To a cooled (−80°) mixture of 5.0 g (0.22 g-atom) of sodium in 60 ml of liquid ammonia was added 5.96 g (35.7 mmol) of 2a in 20 ml of ether during a period of 2 hr. The bath was removed and the ammonia allowed to evaporate. An additional 50 ml of ether was added followed by the careful addition of 2 ml of ethanol. Decomposition was completed by addition of ammonium chloride. The usual work-up gave a major component which was collected from preparative vpc (column A, 6 ft × 0.25 in.): $n^{26}D$ 1.4489 (lit.[19] $n^{25}D$ 1.4488); the ir was identical with that of the published spectrum;[19] nmr δ 3.42 (m, 3 H), 1.84 (m, 2 H), 1.41 (m, 2 H), 0.72 (m, 3 H).

B. From 1a.—From 3 g (0.13 g-atom) of sodium, 35 ml of liquid ammonia, and 3.0 g (11.7 mmol) of 1a in 20 ml of ether at −80° was obtained 9 as the major component of the reaction, collected from preparative vpc (column H, 6 ft × 0.25 in.). The ir of 9 was identical with that of 9 obtained from the reduction of 2a.

C. From 1c.—From 0.5 g (21.7 g-atom) of sodium in 10 ml of liquid ammonia and 0.39 g (2.22 mmol) of 1c in 10 ml of ether at −80°, 9 was obtained and was collected from preparative vpc (column H, 6 ft × 0.25 in.). The ir of 9 was identical with that of 9 obtained from the reduction of 2a.

Bis[*endo*-7-(*exo*-7-bromo-2-oxabicyclo[4.1.0]heptyl)]mercury (1h).—To a cooled (−80°) solution of 0.5 g (1.9 mmol) of 1a in 8 ml of ether was added methyllithium–lithium bromide (2.0 mmol) during a period of 5 min. The mixture was stirred for an additional 10 min and 0.26 g (0.97 mmol) of mercuric chloride in 5 ml of tetrahydrofuran was added dropwise. The mixture was stirred for 45 min and quenched by the addition of water. An insoluble yellow solid (60 mg, mp >225°) was filtered from the two-phase reaction mixture. The usual work-up yielded an oily white solid. Recrystallization from ethanol (95%) yielded 84 mg (10.5%) of white needles, mp 154–155°.

Anal. Calcd for $C_{12}H_{16}Br_2HgO_2$: C, 26.08; H, 2.92. Found: C, 26.12; H, 3.14.

7,7-Dichloro-2-oxabicyclo[4.1.0]heptane (2a)[6] had the following nmr: δ 3.78 (d, J = 8.0 Hz, H_1), 3.52 (m, CH_2O), 1.66 (m, 5 H).

exo-7-Chloro-2-oxabicyclo[4.1.0]heptane (2c).—To a cooled (−20°) solution of 1.0 g (5.98 mmol) of 2a in 15 ml of ether was added butyllithium (5.98 mmol) during a period of 10 min. The solution was stirred for an additional 30 min and quenched by the slow addition of water. The usual work-up yielded an oil. The vpc yield of 2c was determined (column D, 6 ft × 1/8 in.), using an internal standard (acetophenone), to be 69.5%. The major component was collected: its ir was identical with that of the published spectrum;[6] nmr δ 3.69 (q, J = 1.3 and 8.0 Hz, H_1), 3.4 (m, CH_2O), 2.91 (q, J = 1.3 and 4.5 Hz, H_7), 1.94 (m,

2 H), 1.33 (m, 3 H), is in agreement with previously published features.[7]

exo-7-Chloro-*endo*-7-deuterio-2-oxabicyclo[4.1.0]heptane (2d). —To a cooled (−20°) solution of 1.0 g (5.98 mmol) of 2a in 15 ml of ether was added butyllithium (5.98 mmol) during a period of 10 min. The solution was stirred for an additional 30 min and quenched by the slow addition of deuterium oxide (99.8%). The major component was collected from preparative vpc (column H, 6 ft × 0.25 in.): ir (neat) 2270 (w) (C–D), the 3050 cm^{-1} (w) –CH band which was present in 2c was absent; nmr δ 3.69 (d, J = 8.0 Hz, H_1), 3.4 (m, CH_2O), 1.57 (m, 5 H).

exo-7-Chloro-*endo*-7-(diphenylmethanol)-2-oxabicyclo[4.1.0]-heptane (2e).—To a cooled (−20°) solution of 2.0 g (12.0 mmol) of 2a in 30 ml of ether was added butyllithium (12.0 mmol) during a period of 10 min. The solution was stirred for an additional 30 min and 2.16 g (12.0 mmol) of benzophenone dissolved in 15 ml of ether was added. The reaction mixture was stirred 1 hr at −20° and quenched with water. The usual work-up yielded a yellow oil. Trituration with pentane produced a white crystalline solid. Recrystallization from methanol yielded 2.14 g (56.7%) of white prisms: mp 93.5–95.0°; ir 3430 cm^{-1} (OH); nmr (CCl_4) δ 7.42 (m, phenyl H's), 4.33 (s, OH), 4.05 (d, J = 7.5 Hz, H_1), 3.63 (m, CH_2O), 1.74 (m, 5 H).

Anal. Calcd for $C_{19}H_{19}ClO_2$: C, 72.48; H, 6.08; O, 10.16. Found: C, 72.28; H, 6.06; O, 10.43.

exo-7-Chloro-2-oxabicyclo[4.1.0]heptyl-*endo*-7-carboxylic acid (2h).—To a cooled (−20°) solution of 2.0 g (12.0 mmol) of 2a in 30 ml of ether was added butyllithium (12.0 mmol) during a period of 10 min. The solution was stirred for an additional 30 min and dry carbon dioxide was passed into the stirred (magnetic) solution for a period of 1 hr. The reaction was quenched with water. The basic water layer was acidified with concentrated hydrochloric acid and extracted with chloroform. The chloroform extract was dried ($MgSO_4$) and used for spectral determinations: ir 3600–3400 (OH) and 1715 cm^{-1} (–C=O); nmr ($CHCl_3$) δ 9.23 (s, OH), 3.97 (d, J = 7.5 Hz, H_1).

2-Oxo-3-chlorotetrahydrofuro[2,3-*b*]tetrahydropyran (3).—The chloroform extract from above was concentrated *in vacuo*. This yielded a yellow oil which solidified on standing with evolution of heat to yield pale yellow crystals. Recrystallization from ether–pentane yielded 1.17 g (55.2%) of white needles: mp 88–89°; ir 1780 (–C=O), 1160 (s) and 1130 cm^{-1} (w) (axial –CO); nmr δ 5.79 (d, J = 4.0 Hz, H_9), 4.78 (d, J = 6.5 Hz, H_3), 3.83 (m, CH_2O), 2.72 (m, H_4), 1.76 (m, 4 H).

Anal. Calcd for $C_7H_9ClO_3$: C, 47.60; H, 5.14; O, 27.17. Found: C, 47.48; H, 5.07; O, 27.17.

exo-7-Chloro-*endo*-7-(*N*-phenylcarboxamide)-2-oxabicyclo-[4.1.0]heptane (2f).—To a cooled (−20°) solution of 5.0 g (29.5 mmol) of 2a in 75 ml of ether was added butyllithium (29.5 mmol) during a period of 15 min. The solution was stirred for an additional 30 min and 3.52 g (29.5 mmol) of phenyl isocyanate in 15 ml of ether was added. The resulting slurry was stirred for a period of 1 hr and quenched with water. The reaction mixture was filtered to yield a white microcrystalline solid. The usual work-up of the organic layer yielded an additional amount of white solid. Recrystallization of the combined solids from ether yielded 5.14 g (69.3%) of white needles: mp 111–113°; ir 3400 and 3320 (broad) (NH), 1680 and 1601 cm^{-1} (amide I and II); nmr δ 8.23 (broad, NH), 7.37 (m, phenyl), 3.99 (d, J = 7.0 Hz, H_1), 3.62 (m, CH_2O), 1.64 (m, 5 H).

Anal. Calcd for $C_{13}H_{14}ClNO_2$: C, 62.03; H, 5.61; O, 12.71. Found: C, 62.30; H, 5.85; O, 12.94.

2-Oxo-3-chloro-*N*-phenylpyrrolidino[2,3-*b*]tetrahydropyran (4).—To 0.5 g of 2h dissolved in chloroform was added one drop of isopropyl alcohol saturated with hydrogen chloride. The solution was stored at room temperature for 12 hr. The solvent was stripped *in vacuo* yielding 0.51 g of a tan oil: ir 1703 cm^{-1} (–C=O for γ-lactam); nmr δ 7.32 (m, phenyl), 5.85 (d, J = 1.5 Hz, H_9), 5.34 (s, H_3), 3.86 (m, CH_2O), 2.27 (m, 5 H).

Bis{*endo*-7-(*exo*-7-chloro-2-oxabicyclo[4.1.0]heptyl)}mercury (2g).—To a cooled (−20°) solution of 0.5 g (2.9 mmol) of 2a in 8 ml of ether was added butyllithium (2.9 mmol) during a period of 5 min. The solution was stirred for an additional 30 min and 0.26 g (0.97 mmol) of mercuric chloride in 5 ml of tetrahydrofuran was added dropwise. The mixture was stirred for 15 min at −20° and allowed to attain 25° during 15 min. The mixture was then quenched by the addition of water. An insoluble, high melting, grayish green solid was filtered from the two-phase mixture. The ether layer was washed with two portions of water and concentrated *in vacuo*. This yielded a yellow oil which when triturated with pentane produced a white crystalline solid. The crystals were filtered and recrystallized from ethanol (95%) to yield 20 mg (1.85%) of white needles, mp 131–132°.

Anal. Calcd for $C_{12}H_{16}ClHgO$: C, 31.08; H, 3.48. Found: C, 31.12; H, 3.68.

endo-7-Chloro-2-oxabicyclo[4.1.0]heptane (5).—To a cooled (−80°) solution of 1.0 g (5.98 mmol) of 2a in 8 ml of tetrahydrofuran was added butyllithium (5.98 mmol) during a period of 10 min. The solution was stirred for an additional 30 min and quenched by the slow addition of methanol. The organic layer was washed with two portions of water, dried ($MgSO_4$), and concentrated *in vacuo*. Vpc (column D, 6 ft × 1/8 in.) showed 2c to be 60% of a two-component mixture. The second component was collected using preparative vpc (column D, 6 ft × 0.25 in.). Its nmr was identical with that of the published spectrum[7] for 5.

6,6-Dichloro-3-oxabicyclo[3.1.0]hexane (8a).—A modification of the method of Anderson and Reese was used.[31] A stirred slurry of 42.4 g (0.6 mmol) of 2,5-dihydrofuran and 39.0 g (0.72 mol) of sodium methoxide in 200 ml of pentane at 0° was treated dropwise with 134 g (0.70 mol) of ethyl trichloroacetate during 1 hr. The mixture was stirred at 0–5° for 15 hr, at room temperature for 4 hr, cooled, and quenched with water. This resulted in a dark emulsion and it was necessary to add Norit and filter the mixture before the layers could be distinguished. The organic layer was washed with one portion of water, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was distilled to yield 17.12 g (18.4%) of a colorless liquid, bp 73.5–75° (17 mm). Vpc (column C, 6 ft × 1/8 in.) showed a two-component mixture in a 1:2.1 ratio. The title compound was the more abundant component. An aliquot of 15.08 g of the above mixture was dissolved in 150 ml of methanol and enough water was added to produce cloudiness. To this cooled, stirred solution was added 25 g of potassium hydroxide. The mixture was stirred at room temperature for 6 days. Vpc (column C, 6 ft × 0.25 in.) showed that the hydrolysis of the 2-dichloromethyl-2,5-dihydrofuran isomer was essentially complete. The mixture was saturated with sodium chloride and extracted with two portions of ether. The ether extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Distillation of the residue yielded 8.09 g of a colorless liquid: bp 73–77.5 (20 mm); the nmr [δ 4.11 (d, 4 H), 2.55 (m, 2 H)] agreed with published[25,31] spectra; ir 3060 cm^{-1} (–CH, cyclopropane).

exo-6-Chloro-3-oxabicyclo[3.1.0]hexyl-*endo*-6-carboxylic Acid (8d).—To a cooled (−80°) solution of 0.5 g (3.3 mmol) of 8a in 8 ml of ether was added butyllithium (6.6 mmol) during a period of 5 min. The mixture was stirred for 1 hr and dry carbon dioxide was passed into the stirred solution for a period of 1 hr. The reaction was quenched by the slow addition of methanol. The reaction was allowed to warm and water was added. The basic water layer was acidified with concentrated hydrochloric acid and extracted with ether. The ether extracts were dried ($MgSO_4$) and concentrated *in vacuo* to yield a pale yellow semicrystalline solid, which had a strong odor of valeric acid. Recrystallization from ether–petroleum ether (bp 30–60°) yielded 46 mg (8.6%) of white crystals: mp 174–175°; ir (KBr) 3650–2350 (–OH), 1730 cm^{-1} (–C=O); nmr (D_2O, Na_2CO_3, external TMS) δ 2.38 (m, 2 H), 4.30 (d, J_{gem} = −9.0 and J_{vic} = 0 Hz, $H_{2,4}$ endo), 3.91 (d, J_{gem} = −9.0 and J_{vic} = 1.0 Hz, $H_{2,4}$ exo).

Anal. Calcd for $C_6H_7ClO_3$: C, 44.32; H, 4.34; O, 29.52. Found: C, 44.50; H, 4.49; O, 29.26.

exo-6-Chloro-3-oxabicyclo[3.1.0]hexane (8c).—To a cooled (−80°) solution of 0.5 g (3.3 mmol) of 8a in 7.5 ml of ether was added butyllithium (6.6 mmol) during a period of 10 min. The reaction was stirred for an additional 20 min and quenched by the slow addition of methanol. The mixture was allowed to warm to 25° and water was added. The ether layer was washed with two portions of water, dried ($MgSO_4$), and concentrated *in vacuo*. Vpc (column C, 6 ft × 1/8 in.) showed starting 8a and a component with a lower retention time. The first component was collected from preparative vpc (column F, 6 ft × 0.25 in.): nmr δ 4.08 (d, J_{gem} = −9.0 and J_{vic} = 0 Hz, H_2), 3.79 (d, J_{gem} = −9.0 and J_{vic} = ∼1.0 Hz, H_3), 2.88 (t, J = 2.5 Hz, H_6), 2.02 (m, 2 H).

7,7-Dibromo-3-oxabicyclo[4.1.0]heptane (6a).—A slurry of solid potassium *tert*-butoxide (prepared by dissolving 6 g (0.15 g-atom) of potassium in *tert*-butyl alcohol, evaporating the solvent, and drying under N_2 at room temperature *in vacuo*) in 50

(31) J. C. Anderson and C. B. Reese, *Chem. Ind. (London)*, 575 (1963).

ml of pentane and 8.4 g (0.10 mol) of 5,6-dihydro-2*H*-pyran[32] at −20° was treated dropwise with 25.3 g of bromoform in 25 ml of pentane over 45 min. After stirring overnight at room temperature, water was added and the organic layer separated, washed with saturated NaCl solution, and dried ($MgSO_4$). Evaporation of the pentane *in vacuo* yielded 18.3 g of a yellow liquid (which contained starting olefin, 31%; **6a**, 47%; and bromoform, 22%) which was fractionated *in vacuo*. The second fraction, bp 122° (14 mm), was redistilled to yield 7.53 g (30%) of **6a**, bp 122° (14 mm), of about 95% purity: nmr (CCl_4) δ 3.98 (t, $W_{1/2}$ = 6 Hz, $H_{2,3}$), 3.55 (m, 1 H), 3.10 (m, 1 H), 1.9 (m, 4 H). A third distillation yielded an analytical sample, bp 95° (4 mm)

Anal. Calcd for $C_5H_8Br_2O$: C, 28.15; H, 3.15; Br, 62.44 Found: C, 28.35; H, 3.20; Br, 61.46.

***exo*-7-Bromo-3-oxabicyclo[4.1.0]heptane (6c).**—A solution of 2.4 g (9.3 mmol) of **6a** in 45 ml of ether was cooled to −80° and ethereal methyllithium–lithium bromide (9.4 mmol) was added. The mixture was stirred for 20 min at −80° and then quenched with water. The organic layer was dried ($MgSO_4$), the ether evaporated, and the liquid residue distilled to yield 0.8 g of a colorless liquid, bp 94° (30 mm), which was shown by vpc (column G) to be 94% pure **6c**: yield 47%; nmr (CCl_4) δ 4.08 (d, J_{gem} = −12.0, J_{vic} = 0 Hz, H_2), 3.77 (q, J_{gem} = −12.0, J_{vic} = 3.5 Hz, H_3), 3.4 (m, 2 H), 2.85 (t, J_{trans} = 3.5 Hz, HCBr), 1.85 (m, 2 H), 1.4 (m, 2 H).

The vpc yield of **6c** prepared as above was determined to be 60% (column G, with bromobenzene as internal standard). Using 0.26 g (1 mmol) of **6a** in 10 ml of pentane at −80° required 2.5 mol equiv (~2 ml) of ethereal methyllithium–lithium bromide for complete reaction of **6a**. After the resulting slurry stirred at −80° for 30 min, a water quench afforded **6c** in 91% yield by vpc (columns B, D, G; bromobenzene internal standard; average of three reactions). When the results were corrected for purity of **6a**, the yield of **6c** was 96%. Preparative vpc (column F) afforded an analytical sample.

Anal. Calcd for C_6H_9BrO: C, 40.70; H, 5.12; Br, 45.13. Found: C, 40.67; H, 5.21; Br, 44.95.

***exo*-7-Bromo-*endo*-7-deuterio-3-oxabicyclo[4.1.0]heptane (6d).**—A solution of 0.512 g (2 mmol) of **6a** in 10 ml of ether at −80° was treated with 1 equiv of methyllithium–lithium bromide, added all at once. After stirring at −80° for 30 min, the reaction was quenched with D_2O (99.5%). The organic layer separated, dried ($MgSO_4$), and evaporated to yield 0.23 g of a colorless oil, the nmr and vpc (column F) of which indicated that it was almost entirely a mixture of **6c** and **6d** in 33:67 ratio. Preparative vpc (column F) afforded a pure sample, and nmr integration confirmed the presence of 33% of **6c** in **6d**:[33] nmr (CCl_4) δ 4.08 (d, J = −12 Hz, 1 H) 3.77 (q, J = −12 and 3.5 Hz, 1 H), 3.4 (m, 2 H), 2.80 (t, J = 3.5 Hz, 0.3 HCBr), 1.85 (m, 2 H), 1.4 (m, 2 H).

***exo*-7-Bromo-*endo*-7-(phenylmethanol)-3-oxabicyclo[4.1.0]heptane (6e).**—A solution of 0.51 g (2 mmol) of **6a** in 15 ml of pentane and 10 ml of ether was cooled to −80° and treated with 1 equiv of methyllithium–lithium bromide. After stirring at −75° for 30 min, 0.26 g (2.4 mmol) of benzaldehyde in 10 ml of ether was added, and the mixture was allowed to warm to room temperature during 1 hr. After a water quench, the organic layer was washed twice with water, dried ($MgSO_4$), and evaporated to yield 0.45 g (80%) of crude, yellow crystals of **6e**, mp 69–75°. One recrystallization from pentane–ether afforded 0.216 g (40%) of white crystals, mp 80–83°. A second recrystallization gave an analytical sample: mp 84.5–85.5; ir (CCl_4) 3550 (with shoulder at 3570, free OH), 3440 cm^{-1} (broad, intramolecularly bonded OH) which did not change upon dilution; nmr (on **6e**, mp 80–83°) δ 7.3 (m, C_6H_5), 5.08 (broad d, J = 6 Hz, OH), 4.37 (d, J_{gem} = −12 Hz, 0.3 H endo on C_2), 4.12 (d, J_{gem} = −12 Hz, 0.7 H endo on C_2), 3.67 (m, 2 H), 3.17 (d, J = 6 Hz, 0.3 H benzylic), 2.88 (m, 1.7 H), 1.9 (m, 2 H) 1.6 (sextet, cyclopropane H). The spectrum is best interpreted as a mixture of diastereomers of **6e**.

Reactions of 6b–Methyllithium Complex. A. With 2 Equiv of Benzaldehyde.—A solution of 0.095 g (0.37 mmol) of **6a** in 5 ml of pentane at −80° was treated with 2.5 equiv (about 0.9 ml) of methyllithium–lithium bromide. After stirring at −80° for 30 min, 0.079 g (0.74 mmol) of benzaldehyde in 2 ml of ether was added, and the mixture was allowed to warm to room temperature during 1 hr. A water quench followed by the usual work-up afforded 0.075 g of a yellow oil. Vpc of the oil (columns A and D, no internal standard) indicated three major components: **6c** (7%), **6e** (40%), and 1-phenylethanol (51%).

B. With 1 Equiv of H_2O Followed by 1 Equiv of Benzaldehyde.—A solution of 0.105 g (0.41 mmol) of **6a** in 5 ml of pentane at −80° was treated with 2.0 equiv of methyllithium–lithium bromide and stirred at −80° for 30 min. A solution of 0.0074 g (0.41 mmol) of H_2O in 1 ml of ether was added, and the mixture was allowed to stir without the cooling bath for 15 min. At this point, 0.0435 g (0.41 mmol) of benzaldehyde in 1 ml of ether was added and stirring continued for 1 hr. Work-up as in part A yielded 0.050 g of yellow oil. Vpc (columns A and D, no internal standard) indicated two major peaks: **6c** (50%) and 1-phenylethanol (33%). Less than 2% of **6e** was detected.

***exo*-7-Bromo-3-oxabicyclo[4.1.0]heptyl-*endo*-7-carboxylic Acid (6f).**— Carbenoid **6b** was prepared in 20 ml of pentane from 0.43 g (1.7 mmol) of **6a** at −80°. Carbon dioxide was passed through the reaction mixture for 1 hr at −80°. A water quench, followed by extraction with ether, yielded 0.21 g of white, crystalline **6f**. Acidification of the aqueous layer followed by ether extraction yielded an additional 0.03 g, total yield 65%, mp 153–155°. Recrystallization from ether gave an analytical sample: mp 155°; ir (KBr) 3000 (broad, OH), 1725 cm^{-1} (strong, C=O); nmr δ 9.35 (s, COOH), 4.58 (d, J_{gem} = −12 Hz, endo H on C_2), 3.93 (m, 1 H), 3.87 (q, J_{gem} = −12 Hz, J_{vic} = 3 Hz, exo H on C_2), 3.28 (sextet, 1 H), 2.55 (m, 1 H), 1.8 (m, 3 H).

Anal. Calcd for $C_7H_9BrO_3$: C, 38.03; H, 4.10; O, 21.71. Found: C, 38.15; H, 4.22; O, 21.66.

7,7-Dichloro-3-oxabicyclo[4.1.0]heptane (7a).—Using the method of Parham,[6] dichlorocarbene, generated from 28.7 g of ethyl trichloroacetate, was added to 12.6 g of 5,6-dihydro-2*H*-pyran[32] at −15° yielding a crude product which on fractionation yielded 8.25 g (33%) of colorless **7a**: bp 103–105° (28 mm); nmr (neat, external TMS) δ 4.08 (d, $H_{2,3}$), 3.5 (m, 2 H), 2.1 (m, 4 H). A redistillation afforded an analytical sample, bp 105° (30 mm).

Anal. Calcd for $C_6H_8Cl_2O$: C, 43.14; H, 4.82. Found: C, 42.88; H, 4.86.

***exo*-7-Chloro-3-oxabicyclo[4.1.0]heptyl-*endo*-7-carboxylic Acid (7d).**—A solution of 1.51 g (9.00 mmol) of **7a** in 50 ml of tetrahydrofuran at −80° was treated with 1.4 equiv of butyllithium in hexane. The reaction turned yellow but remained homogeneous during stirring for 30 min. Dry CO_2 was bubbled through the reaction for 1 hr after which the reaction was quenched with water and the aqueous and organic layers separated. The aqueous layer was acidified and extracted with ether. Drying ($MgSO_4$) and evaporation of the ether yielded 0.88 g of yellow crystals, mp 130–138°. Recrystallization from petroleum ether–ether gave white, crystalline **7a**, mp 138–141°, 0.53 g (30%). Further recrystallization from ether gave an analytical sample: ir (KBr) 3000 (broad and strong, OH), 1740 cm^{-1} (C=O); nmr (D_2O, Na_2CO_3, external TMS) δ 4.42 (d, J_{gem} = −12 Hz, endo H on C_2), 4.10 (q, J_{gem} = −12, J_{vic} = 4 Hz, exo H on C_2), 3.58 (m, 2 H), 2.13 (m, 2 H), 1.83 (m, 2 H).

Anal. Calcd for $C_7H_9ClO_3$: C, 47.60; H, 5.13; Cl, 20.07; O, 27.18. Found: C, 47.66; H, 5.12; Cl, 20.08; O, 26.91.

***exo*-7-Chloro-3-oxabicyclo[4.1.0]heptane (7c).**—A solution of 0.50 g (3.0 mmol) of **7a** in 9 ml of tetrahydrofuran was treated at −80° with 2 equiv of butyllithium in hexane. After stirring for 90 min at −80°, a water quench produced an organic layer which after drying and evaporation gave 0.63 g of a yellow liquid. Preparative vpc (column F) of the major component (64%) yielded impure **7c**, contaminated by a butyl-containing product of identical retention time: nmr (CCl_4) δ 4.09 (d, J_{gem} = −12 Hz, H_2), 3.78 (q, J_{gem} = −12, J_{vic} = 3.5 Hz, H_3), 3.5 (m, 2 H), 2.95 (t, J_{trans} = 3 Hz, HCCl), 1.9 (m, 2 H), 1.3 (m, 2 H), 0.8 (m, ~1 H).

3-Oxabicyclo[4.1.0]heptane (10).—A solution of 2.0 g of **6a** in 32 ml of ether was added dropwise to a solution of 8 g of sodium in 100 ml of liquid ammonia. After the addition the solution was stirred at −80° for 1 hr and at reflux (about −30°) for 30 min. Addition of NH_4Cl discharged the color, and evaporation of the ammonia left a residue which was partitioned between 80 ml of ether, 5 ml of methanol, and 60 ml of H_2O. The organic layer was dried ($MgSO_4$) and evaporated to 5 g at 0° under modest vacuum. Preparative vpc (column D) of the one major component (90% of the total excluding solvent) yielded **10**: ir (neat)

(32) J. Colonge and P. Boisde, *Bull. Soc. Chim. Fr.*, 824 (1956).

(33) Incorporation of H into **1d** after stirring at −20° for 70 min was only about 8%. The source of H which is incorporated into **6d** is, at present, not known.

3060, 3020 cm^{-1} (cyclopropane, CH); nmr (CCl_4) δ 3.77 (d, $H_{2,3}$), 3.4 (m, 2 H), 1.8 (m, 2 H), 0.8 (m, 2 H), 0.35 (m, 1 H).

Anal. Calcd for $C_6H_{10}O$: C, 73.42; H, 10.27; O, 16.30. Found: C, 73.11; H, 10.18; O, 16.43.

Registry No.—**1a**, 27024-90-4; **1c**, 17879-78-6; **1d**, 17879-77-5; **1e**, 17879-76-4; **1f**, 17879-75-3; **1g**, 17879-74-2; **1h**, 27024-96-0; **1i**, 18022-11-2; **2d**, 27024-98-2; **2e**, 27024-99-3; **2f** 27025-00-9; **2g**, 27062-09-5; **2h**, 27025-01-0; **3**, 27025-02-1; **4**, 27025-03-2; **6a**, 27025-04-3; **6c**, 27025-05-4; **6d**, 27025-06-5; **6e**, 27025-07-6; **6f**, 27025-08-7; **7a**, 932-61-6; **7c**, 27193-01-7; **7d**, 27193-02-8; **8a**, 931-28-2; **8c**, 27025-11-2; **8d**, 27025-12-3; **10**, 286-10-2.

Acknowledgment.—The authors acknowledge some helpful nmr discussions with Dr. J. C. Deck, and partial financial support from the College of Arts and Sciences Research Committee, University of Louisville. The Varian A60-A nmr spectrometer was purchased with funds provided by the National Science Foundation.

2-Metalation of Dimethylaminoethylferrocene with Butyllithium and Condensations with Electrophilic Reagents. Synthesis of 2-Substituted Vinylferrocenes[1a]

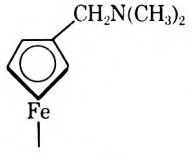
D. W. SLOCUM,*[1b] C. A. JENNINGS,[1c] T. R. ENGELMANN,[1d] B. W. ROCKETT,[1e] AND C. R. HAUSER[1f]

Departments of Chemistry, Southern Illinois University, Carbondale, Illinois 62901, and Duke University, Durham, North Carolina 27706

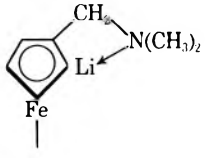
Received June 18, 1970

N,N-Dimethylaminoethylferrocene (DMAEF) was metalated in good yield with *n*-butyllithium in ether–hexane, and the intermediate 2-lithioamine was condensed with benzophenone, benzonitrile, phenyl isocyanate, phenyl isothiocyanate, hexachloroethane, and mercuric chloride to form the corresponding 2 derivatives. Methiodides of the above 2 derivatives were formed and converted to the corresponding 2-substituted vinylferrocene derivatives by treatment with potassium hydroxide. Metalation of DMAEF for extended time with excess *n*-butyllithium gave fair yields of the 2,1′-dilithioamine intermediate. That metalation occurred at the 2 position was established by converting the 2-benzoyldimethylaminomethylferrocene methiodide salt with KNH_2–NH_3 to give *via* a Stevens rearrangement the identical phenone derivative obtained from metalation of DMAEF. The successful 2-lithiation reported here for dimethylaminoethylferrocene is in direct contrast to the poor yield of lithiation found in the analogous benzene derivative, *N,N*-dimethyl-β-phenethylamine. The difference in behavior is attributed to the relative acidities of the 2 position and α protons in the respective systems.

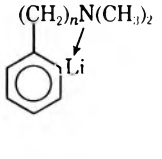
Recently, we reported that metalation of dimethylaminomethylferrocene (DMAMF) (**1**) with *n*-BuLi apparently proceeded *via* the cyclic 2-lithiated species **1a**.[2] The analogous 2 position lithiation of benzyldimethylamine (**2**) to give the lithio intermediate **2a** had



1

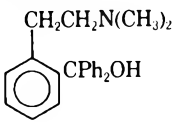


1a

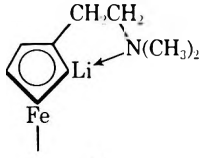


2a, $n = 1$
3a, $n = 2$

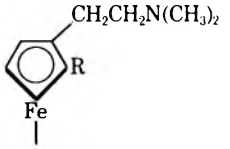
been reported earlier.[3] Hauser and other coworkers also published a study of the metalation of the homologous β-phenethyldimethylamine system but record only a tarry product from the reaction of β-phenethyldimethylamine (**3**) with *n*-BuLi followed by treatment with benzophenone.[4] In contrast to this are two recent observations[5] that metalation of β-phenethyldimethylamine (**3**) with *n*-BuLi apparently does proceed through the six-membered cyclic lithioamine intermediate (**3a**) to give the anticipated carbinolamine **4** when treated with benzophenone, although the yield of such an intermediate must be very low. In a noteworthy extension of this method, the oxygen analog of amine **1**, namely, ferrocenylmethyl methyl ether, has been found to undergo the 2-lithiation reaction.[6]



4



5a



5, R = –H
6, R = –CPh_2OH
8, R = –CONHPh
9, R = –CSNHPh
10, R = –COPh
11, R = –Cl
12, R = –HgCl

We would now like to report that metalation of dimethylaminoethylferrocene (DMAEF) (**5**) with *n*-BuLi for 2 hr gave an optimum yield of 68% of the 2-lithio intermediate **5a** as demonstrated by its condensation with benzophenone to produce carbinolamine **6** (*cf.* Table I). Longer metalation periods brought considerable concentration of dilithio intermediate **5b**. Struc-

(1) (a) Parts of this work were supported by the Office of Army Research (Durham) and by the Petroleum Research Fund; (b) Southern Illinois University, author to whom requests for reprints should be directed; (c) NSF Undergraduate Research participant; (d) NASA Fellow, Southern Illinois University, 1966–1969; (e) Wolverhampton College of Technology, Wolverhampton, England; (f) Duke University, deceased Jan 6, 1970.

(2) D. W. Slocum, B. W. Rockett, and C. R. Hauser, *J. Amer. Chem. Soc.*, **87**, 1241 (1965).

(3) (a) F. N. Jones, M. F. Zinn, and C. R. Hauser, *J. Org. Chem.*, **28**, 663 (1963); (b) F. N. Jones, R. L. Vaulx, and C. R. Hauser, *ibid.*, **28**, 3461 (1963).

(4) R. L. Vaulx, F. N. Jones, and C. R. Hauser, *ibid.*, **30**, 58 (1965).

(5) (a) N. S. Narasimhan and A. C. Ranade, *Tetrahedron Lett.*, 603 (1966); (b) D. W. Slocum, T. R. Engelmann, and C. A. Jennings, *Aust. J. Chem.*, **21**, 2319 (1968).

(6) D. W. Slocum and B. P. Koonsvitsky, *Chem. Commun.*, 846 (1969).

TABLE I

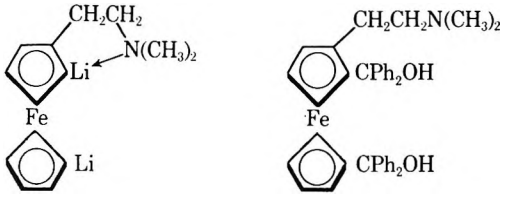
METALATION OF DIMETHYLAMINOETHYLFERROCENE (5) WITH *n*-BUTYLLITHIUM IN A MIXTURE OF HEXANE AND ETHER. CONDENSATION WITH BENZOPHENONE TO GIVE CARBINOLAMINE 6 AND DICARBINOLAMINE 7[a]

Mol ratio, 5:*n*-BuLi	Lithiation period, hr	Yield, % 6	Yield, % 7
1:1.5	1	36[b]	
1:1.5	2	68[b]	4[b]
1:1.5	10	32,[b] 36[c]	16,[b] 18[c]
1:1.5	14	36[d]	21[c]
1:1.5	20	13,[b] 16[c]	28,[b] 36[c]
1:3.0	20	45[b]	28[b]

[a] Each condensation period 4 hr. [b] Purified by column chromatography. [c] Yield based on unrecovered starting material. [d] Recrystallized from 95% ethanol.

ture **6** for the benzophenone adduct was supported by elemental analysis and absorption spectra. In the infrared spectrum absorption bands were evident at 9.08 and 10.0 μ; such bands are indicative of an unsubstituted cyclopentadienyl ring in a ferrocene (*cf.* Table II).[7] An nmr spectrum of **6** in $CDCl_3$ exhibited a 5-proton singlet at τ 5.86 (unsubstituted cyclopentadienyl ring) and a 6-proton singlet at τ 8.02 [$N(CH_3)_2$]. Broad unresolved absorption from τ 7.4 to 8 integrated as 4.1 protons and was assigned to the $-CH_2CH_2-$ portion of the molecule (*cf.* Table III).

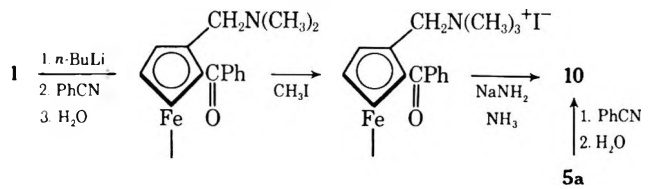
Metalation with *n*-BuLi of DMAEF (**5**) over extended periods of time gave dilithiated species **5b**; condensation with benzophenone led to dicarbinolamine **7** (Table I). That two benzophenone molecules had been substituted into dicarbinolamine **7** was supported by its elemental analysis. In addition, its infrared spectrum failed to show the characteristic absorptions of an unsubstituted cyclopentadienyl ring.[7]



5b **7**

Demonstration That the Site of Lithiation of DMAEF Is the 2 Position.—The 1,2 disposition of substituents in the DMAEF series was demonstrated by rearrangement of the methiodide of the 2-substituted phenone in the dimethylaminomethylferrocene (DMAMF) series[2] with $NaNH_2$–NH_3 (Stevens rearrangement) to give the identical phenone (**10**) as prepared in the DMAEF series. These paths are outlined in Scheme I. Inas-

SCHEME I



(7) M. Rosenblum, Ph.D. Thesis, Harvard University, 1953; M. Rosenblum, *Chem. Ind.* (*London*), 953 (1958); P. L. Pauson, *Quart. Rev.* (*London*), 391 (1955).

TABLE II

ANALYTICAL AND SPECTRAL DATA

Compd	Calcd, % C	H	N	Fe	Other	Found, % C	H	N	Fe	Other	Infrared absorptions, μ[a,b] "9–10-μ rule"	Substituent absorption	Chemical shifts[c] of pertinent nmr absorptions[d-f] Unsubstituted $-N(CH_3)_2$	C_5H_5	H_a[g]	H_b[g]	H_c[g]
6	73.79	6.65	3.19			73.73	6.70	3.09			9.08 (s) 10.00 (s)		8.02 (s)	5.86 (s)			
7	77.29	6.32	2.25			77.62	6.57	2.40									
8	67.03	6.43	7.45	14.85		66.85	6.51	7.34	14.26		9.01 (m)[h] 9.95 (m)[h]	6.04 (bs) (–CONPh)[h]	7.83 (s)	5.88 (s)			
9	64.29	6.16	7.14		S, 8.17	64.55	6.01	7.30		S, 8.04	9.02 (m) 9.96 (m)	3.82 (b) (–NH)	7.92 (s)	5.82 (s)			
10	69.82	6.42	3.88	15.46		69.82	6.68	3.69	15.25		9.03 (m) 9.96 (m)	6.12 (s) (–COPh)	7.83 (s)	5.97 (s)			
11	57.66	6.22	4.80	19.15	Cl, 12.16	58.84[i]	6.66	4.45	17.90	Cl, 11.33	9.02 (m) 9.95 (m)		7.79 (s)	5.89 (s)			
12	34.16	3.68	2.85			34.42	3.51	2.89			9.03 (m) 9.94 (m)		7.75 (s)	5.85 (s)			
20	76.15	5.62		14.16		76.46	5.78		14.34		9.04 (m) 9.98 (s)	2.92 (m) (–OH)		5.83 (s)	5.13	4.74	3.47
21	68.90	5.17	4.23	16.86		68.54	5.26	4.36	16.46		9.04 (m) 10.01 (s)	6.16 (s) (–CONHPh)		5.63 (s)	4.51	4.25	...[j]
22	72.18	5.10		17.66	O, 5.06	72.15	5.50		17.46	O, 5.15	9.01 (m)	6.10 (s) (–COPh)		5.94 (s)	4.83	4.52	...[j]
23	58.47	4.50		22.65	Cl, 14.38	56.21[i]	4.56		22.03	Cl, 13.66	9.03 (m) 9.97 (m)			5.83 (s)	4.76	4.50	3.33

[a] Spectra of crystalline compounds determined as Nujol mulls; oils (**8**, **10**, **11**, **22**, **23**) as neat liquid films between sodium chloride plates. Spectra were recorded on a Perkin-Elmer Model 137 Infracord spectrometer. All spectra unless otherwise indicated were standardized against polystyrene. [b] s = strong, m = medium, b = broad. [c] Chemical shifts are expressed in τ units: s = singlet, t = triplet. [d] All spectra were run in $CDCl_3$ using tetramethylsilane as an internal standard. [e] Methylene protons appeared as a broad 4-proton multiplet in the τ 6.8–8.0 region. [f] We are unable at this time to unequivocally make assignments to the observed chemical shifts of the substituted cyclopentadienyl ring protons. [g] These protons constitute an ABX system. No analysis of these systems was performed; hence, recorded values are approximate. [h] Standardized against 7.26-μ band of Nujol. [i] This was the best analysis. [j] This proton is apparently situated under the benzene ring protons.

TABLE III

2-SUBSTITUTED METHIODIDES AND 2-SUBSTITUTED VINYL COMPOUNDS OF CONDENSATION PRODUCTS 6 AND 8–11

Methiodide[a]	Mp, °C[b,c]	Vinyl compd	Mp, °C[c]	Yield, %
15	239–246	Vinylcarbinol 20	163–164.5	96
16	220–225	Vinylcarboxamide 21	97.5–99.0[d]	82
			127.0–130.0[d]	
17	223–226	...	...	..
18	196–208.5	Vinylphenone 22	Oil	80
19		Vinylchloro compound 23	Oil	83

[a] Methiodides were formed from parent amines in essentially quantitative yields. [b] Melts with decomposition. [c] All melting points are corrected. [d] These two samples gave superimposable infrared spectra. [e] Attempted elimination of the elements of trimethylammonium iodide from the methiodide 17 of the thiocarboxamide 9 apparently led to decomposition.

much as 2-lithiation has been unequivocally demonstrated in the DMAMF series,[2] the fact that a product from this series can be transformed into a product from the DMAEF series means that the *site of lithiation in DMAEF* (**5**) *must also be the 2 position.*

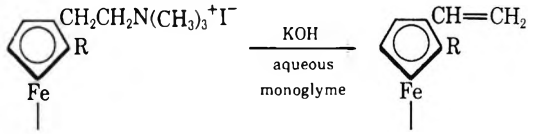
Attempts to cyclize carbinolamine **6** to the six-membered ring cyclic ether in a manner similar to that utilized in the DMAMF series[2] proved fruitless.

Condensations of Lithioamine 5a with Electrophilic Compounds.—In addition to benzophenone, 2-lithioamine **5a** has been condensed with phenyl isocyanate, phenyl isothiocyanate, benzonitrile, and hexachloroethane[8] to afford the carboxamide **8** (35%), thiocarboxamide **9** (33%), phenone **10** (62%), and chloro derivative **11** (30%), respectively. Infrared spectra of each of these compounds possessed adsorption at 9 and 10 μ[7] in accord with their assigned structures (Table II).

Lithioamine **5a** underwent a transmetalation reaction with mercuric chloride to produce the chloromercuri derivative **12** (12%). This compound is of interest because it contains both a σ- and a π-bonded metal atom. It also represents a potentially useful intermediate from which a number of other 1,2-disubstituted ferrocenes might be prepared.

Reaction of Methiodides of 2-Substituted DMAEF's with Base. Formation of 2-Substituted Vinylferrocenes.—The methiodides of each of the condensation products described in the preceding section were prepared using methyl iodide (Table III). Elimination of the elements of trimethylammonium iodide from the respective molecules was effected with an aqueous KOH–monoglyme system to afford the 2-substituted vinyl compound (Tables II and III). The reaction is illustrated for the conversion of the methiodide **18** of phenone **10** to the 2-substituted vinyl compound **22** (Scheme II).

SCHEME II



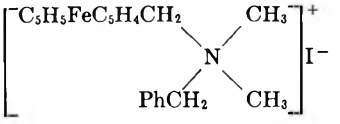
Methiodide	R	Vinyl compd
15	$-CPh_2OH$	20
16	–CONHPh	21
17	–CSNHPh	..
18	–COPh	22
19	–Cl	23

(8) R. L. Gay, T. F. Crimmins, and C. R. Hauser, *Chem. Ind. (London)*, 1635 (1966).

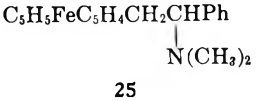
Discussion

It is of interest to compare the lithiation of dimethylaminoethylferrocene (**5**) with that of dimethylaminomethylferrocene (**1**). Whereas maximum lithiation of amine **1** took place within 1 hr,[2] that of amine **5** required at least 2 hr; both ferrocene derivatives were metalated much more rapidly than benzyldimethylamine (**2**) which requires 20–30 hr.[3] That amine **1** is metalated faster than amine **5** is apparently a reflection of the well-known greater stability of the five-membered chelate ring in lithioamine **1a**. Longer metalation periods for **5** appear to allow significant formation of dilithiated species such as **5b**. Similar behavior was reported for lithiation of the dimethylaminomethyl compound **1**,[2] but only to the extent of a very few per cent. Possibly, random lithiation competes much more efficiently in the case of **5**.

Some suggestion is in order as to why the dimethylaminoethyl derivative of ferrocene can be significantly lithiated in the 2 position while that of benzene evidently cannot.[4,5] An explanation of this difference may lie in the relative acidities of the ring protons and the methylene protons α to the ring in β-phenethyldimethylamine (**3**) and dimethylaminoethylferrocene (**5**). Lithiation of amine **3** apparently involves a competing E_2 reaction which results in the formation of styrene and thence polystyrene.[4,5] No comparable material was found among the products from the lithiation of amine **5** followed by various condensations. It must be concluded that the methylene protons α to the benzene system are much more acidic than those α to the ferrocene system. Some support for this statement can be found in the observations of Ustynyuk and Perevalova.[9] These authors have demonstrated that benzyl(ferrocenylmethyl)dimethylammonium chloride (**24**) rearranged exclusively to *N*,*N*-dimethyl-α-phenylferrocene ethylamine (**25**) under Stevens rearrangement condi-



24



25

tions; *i.e.*, ionization with strong base apparently took place at the benzyl methylene protons. Interestingly enough, the Stevens rearrangement of the methiodide of DMAMF which was used to prepare the DMAEF utilized in this study brings out the fact that a $-CH_3$ group must be ionized in preference to the methylene protons adjacent to the ring system. A recent study

(9) Yu. A. Ustynyuk and E. G. Perevalova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 62 (1964).

has shown that ferrocene acting as a substituent is electron donating.[10] One other point might be made: the fact that ferrocene ring protons are more acidic than benzene ring protons should allow lithiation of the aromatic ring in the ferrocene system (**5**) to compete much more effectively with the elimination reaction. Thus relative acidity of the ring protons and relative nonacidity of the α protons in DMAEF seem to offer a fair explanation for the coordinate directed lithiation reaction being observed in this ferrocene system.

These results continue our studies of synthetic routes to produce 1,2-disubstituted ferrocenes. Not only can a variety of 1,2-disubstituted derivatives be prepared by this method, but it is also evident that 1,2,1′-trisubstituted ferrocenes can be prepared in fair yield when longer metalation periods are employed.

Curiously, attempts to effect addition reactions at the double bond of vinylcarbinol **20** were fruitless. Several such reactions for vinyl ferrocene itself have been recorded in the literature.[11] This may be a simple steric effect caused by the substituent in the 2 position of compound **20**.

Experimental Section

Elemental analyses were performed by Alfred Bernhardt, Microanalytical Laboratories, Mülheim, West Germany, and by Galbraith Laboratories, Nashville, Tenn. Melting points were determined on a Hoover melting point apparatus and are corrected. Chromatograms were obtained using Fisher alumina. All infrared spectra were run on a Perkin-Elmer 137 sodium chloride spectrophotometer and are standardized against polystyrene unless otherwise indicated. All nmr spectra were run on a Varian A-56/60 spectrometer.

Metalated Dimethylaminoethylferrocene (5a) Solution.—In general, 10–20 mmol of amine **5a** in ether was treated with 1.5 equiv (condition A) or 2.4 equiv (condition B) of *n*-butyllithium for 1.5–2 hr. The metalation reaction was carried out with stirring under argon at room temperature.

Carbinolamine 6 and Dicarbinolamine 7.—A solution of 7.2 g (40 mmol) of benzophenone in 20 ml of dry ether was slowly added to a solution of 20 mmol of lithioamine **5a** metalated by condition A. Water (10 ml) was added and the solution stirred for 2 hr. The ether layer and ether extracts of the aqueous layer were combined and stripped. The resulting brown oil was chromatographed on alumina III. The fraction eluted with 50% petroleum ether–benzene contained 6.0 g of dark oil which crystallized on standing. Recrystallization from 95% ethanol gave 4.9 g (68%) of carbinolamine **6**, orange crystals, mp 122–125°. Repeated recrystallization of **6** produced an analytical sample, mp 125–126°.

A fraction eluted with benzene(80%)–ether (20%) gave a small amount of crystals (4%) of dicarbinolamine **7**, mp 156–160°. Recrystallization of **7** from ether–hexane produced an analytical sample, mp 163–166°. Higher yields of **7** were obtained using much longer lithiation periods (*cf.* Table I).

Carboxamide 8.—A solution of 4.3 ml (40 mmol) of phenyl isocyanate in 10 ml of dry ether was slowly added to a mixture of 10 mmol of lithioamine **5a** metalated by condition B. The resulting suspension was hydrolyzed after 4 hr with 10 ml of water. The aqueous and ether phases were separated and the aqueous layer was extracted with benzene. The organic layers were combined and extracted with 1:10 H_3PO_4. These extracts were combined and made basic with solid Na_2CO_3. An oil separatd which was extracted into benzene, stripped again to an oil, and chromatographed on alumina III. A dark orange oil representing a 33% yield of carboxamide **8** was eluted with benzene. This oil could not be induced to crystallize. Elemental analysis and spectral data supported assignment of its structure (*cf.* Table II).

Thiocarboxamide 9.—A solution of 4.3 ml (36 mmol) of phenyl isocyanate in 10 ml of ether was added to a mixture of lithioamine **5a** metalated under condition A. This product solution was hydrolyzed with water after stirring for 4 hr, the ether layer was separated, and the aqueous layer extracted with ether several times. The ether layer and ether extracts of the aqueous layer were combined, stripped, and chromatographed on alumina III. A red band which was eluted with petroleum ether (30%)–benzene(70%) solution was collected. Recrystallization from hexane–benzene gave a 33% yield of red crystals of thiocarboxamide **9**, mp 147.5–149.5°. Elemental analysis and spectral data are recorded in Table II.

Phenone 10.—A solution of 4.12 g (40 mmol) of benzonitrile in 25 ml of dry ether was added to a mixture of 20 mmol of lithioamine **5a** metalated by condition B. The resulting dark solution was stirred 12 hr and hydrolyzed with 10 ml of water. The ether layer and ether extracts of the aqueous layer were combined, stripped, and chromatographed on alumina III. A dark red oil was eluted with 20% ether–benzene. A yield of 62% of phenone **10** was obtained. This material seemed somewhat sensitive to light. Elemental analysis and various spectral data supported assignment of its structure (*cf.* Table II).

Chloroamine 11.—A solution of 4.8 g (20 mmol) of hexachloroethane in 50 ml of dry ether was added to a mixture of 10 mmol of lithioamine **5a** metalated by condition A. After stirring for 16 hr, the mixture was hydrolyzed with water. The ether layer and ether extracts were combined, stripped, and chromatographed on alumina III. A yellow band was eluted with 50% petroleum ether–benzene and stripped to give 0.87 g (30%) of a dark red oil which was chloroamine **11**, bp 135–145° (0.25 mm). Chloroamine **11** appeared to be contaminated with dimethylaminoethylferrocene. Elemental analysis of this compound were not totally acceptable (*cf.* Table II). Evidence for the presence of DMAEF in this product is presented in the experimental section on the vinyl derivatives.

Chloromercuriamine 12.—Solid mercuric chloride (27.2 g, 10 mmol) was added to 10 mmol of lithioamine **5a** metalated under condition A. After stirring for 15 hr, 20 ml of water was added and the solution stirred for 2 hr. The ether layer and ether extracts were combined, dried over $MgSO_4$, and stripped. The crude product was taken up in petroleum ether and excess mercuric chloride filtered off. Chromatography on alumina yielded 5.8 g (12%) chloromercuriamine **12** upon elution with benzene. Recrystallization from hexane gave analytical material having mp 122.5–124.0°. Spectral and analytical data are recorded in Table II.

Formation of the Methiodide Salt of 2-(Dimethylaminomethyl)ferrocenylphenone.[2] Treatment of Methiodide with KNH_2–NH_3 to Give Phenone 10.—2-(Dimethylaminomethyl)ferrocenylphenone was treated with methyl iodide (5 equiv) in ether with stirring for 4 hr to afford an orange precipitate of the methiodide salt. After washing several times with dry ether and drying in a vacuum desiccator orange crystals, mp 160–166° dec, were obtained in 94% yield.

The above methiodide (9.8 g, 20 mmol) was added to a solution obtained by adding 3.9 g of potassium metal (100 g-atoms) to 150 ml of liquid NH_3 and stirring with a trace of $Fe(NO_3)_3$ for 1 hr. After addition of the methiodide, the mixture was stirred for 6 hr (150 ml additional NH_3 added after 3 hr). Ether (350 ml) and 30 g of NH_4Cl were added and the mixture was stirred until all the NH_3 had evaporated. The ether layer and ether extracts of the aqueous layer were combined, dried over $MgSO_4$, stripped, and chromatographed on alumina III. A dark red oil was eluted with 20% ether–benzene in 20% yield. The spectral, physical, and chemical properties of the compound were identical with those of phenone **10** prepared *via* condensation of lithioamine **5a** with benzonitrile.

Formation of Methiodide Salts of Amines 6 and 8–11.—The above 2-substituted amine derivatives were treated for 1 hr with a 5–10 *M* excess of methyl iodide in ether. The methiodide salts were recrystallized from ether–methanol (*cf.* Table III).

Treatment of Methiodides 15–19 with Base to Give Vinyl Derivatives 20–23.—The above methiodide salts were treated with excess 10–25% aqueous KOH–monoglyme (1:1 volume ratio) for 3 days at reflux temperature to give the crude vinyl materials. Each product was chromatographed on alumina III. The chlorovinyl product was analyzed in a benzene solution on a Varian Model 90-P gas chromatograph using a column of 3% silicon rubber SE-30 on Chromosorb P operating at 178° with a gas flow of 60 cc/min. Two peaks besides benzene appeared at 4.0 and 5.0 min with relative integration of 3–5% and 95–97%, respec-

(10) A. N. Nesmayanov, E. G. Perevalova, S. P. Gubin, K. I. Grandberg, and A. G. Koslovsky, *Tetrahedron Lett.*, 2381 (1966).

(11) (a) G. R. Buell, W. E. McEwen and J. Kleinberg, *ibid.*, 16 (1959); (b) G. R. Buell, W. E. McEwen and J. Kleinberg, *J. Amer. Chem. Soc.*, **84**, 40 (1962).

tively. The first peak was shown to be vinylferrocene by enrichment of the mixture with an authentic sample of vinylferrocene. Apparently this impurity resulted from contamination of chloroamine 11 with amine 5. The method of formation and the analytical data identify the main chromatographic component to be 2-chlorovinylferrocene. For melting point and analytical and spectral data, see Table II.

Registry No.—Butyllithium, 109-72-8; **1**, 1271-86-9; **6**, 12441-23-5; **7**, 12441-25-7; **8**, 12441-17-7; **9**, 12441-18-8; **10**, 12441-16-6; **11**, 12441-13-3; **12**, 12441-12-2; **15**, 12441-24-6; **16**, 12441-20-2; **17**, 12441-21-3; **18**, 12441-19-9; **20**, 12441-22-4; **21**, 12441-15-5; **22**, 12441-14-4; **23**, 12441-11-1.

The Reaction of Triisobutylaluminum with 1,5-Cyclooctadiene[1]

E. MARCUS,*[2] D. L. MACPEEK, AND S. W. TINSLEY

Research and Development Department, Union Carbide Corporation, Chemicals and Plastics, South Charleston, West Virginia 25303

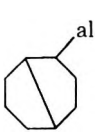
Received June 8, 1970

Hydrolysis of the reaction product derived from triisobutylaluminum and 1,5-cyclooctadiene gave rise to *cis*- and *trans*-1-ethyl-2-methylcyclopentane as well as some cyclooctene, but no cyclooctane. Treatment of the reaction product with ethylene in the presence of nickel acetylacetonate afforded 1-methylene-2-vinylcyclopentane.

The unexpected results obtained from the investigation of the triisobutylaluminum–butadiene reaction[3] prompted us to study reactions of other diolefins with triisobutylaluminum (TIBA). 1,5-Cyclooctadiene (**1**) looked like an especially interesting case, because its two double bonds would not necessarily be expected to behave as independent units in this type of reaction.

Isobutylene was not displaced efficiently until a reaction temperature of about 145° was reached. After hydrolysis of the reaction product, a saturated C_8H_{16} hydrocarbon boiling at about 120–125° was obtained in 60% yield based on TIBA. Gas chromatography showed the presence of two peaks. The major component of this cut was proven to be *cis*-1-ethyl-2-methylcyclopentane (**2**) by comparison with a National Bureau of Standards sample. Although a similar reference sample of *trans*-1-ethyl-2-methylcyclopentane (**3**) is not available, there is little doubt that the other component is the trans isomer; besides, hydrogenation of 1-methylene-2-vinylcyclopentane gave the same two 1-ethyl-2-methylcyclopentanes, one of which was the cis isomer and the other one was identical with the trans isomer in question. Furthermore, the infrared spectrum of **3** was identical with the spectrum of *trans*-1-ethyl-2-methylcyclopentane published by Natalis.[4] No cyclooctane was observed and only a small amount of cyclooctene was obtained.

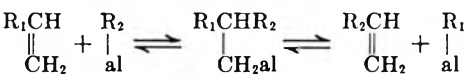
Formation of the ethylmethylcyclopentanes was unexpected. The unusual step is the breakage of a carbon–carbon single bond at some stage. Initial formation of aluminobicyclo[3.3.0]octane (**4**) appeared at first sight a likely possibility (al = $^1/_3$Al).



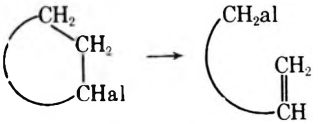
4

The reversibility of the following reaction, where R_1 and R_2 are alkyl, has been proven (Scheme I).[5] However, this type of reaction with an aluminocycloalkane has never been reported (Scheme II). Therefore, it would have been interesting to subject bicyclo[3.3.0]-oct-2-ene to the reaction with TIBA. Since this material was not available, the structurally related tricyclo-[5.2.1.$0^{2,6}$]dec-3-ene was treated with TIBA at 150–190°. However, the desired ring opening did not occur; tricyclo[5.2.1.$0^{2,6}$]decane was the only product we could detect after hydrolysis of the reaction product. We also attempted unsuccessfully the conversion of cyclooctene with an excess of TIBA at 150–190° into 1,8-dialuminooctane; cyclooctane was the only product formed after hydrolysis. Hence, it is unlikely that aluminobicyclooctane (**4**) is involved in the formation of **2** and **3**.

SCHEME I



SCHEME II



Although we do not have experimental support for a satisfactory explanation of the observed results, Scheme III may be looked upon as an alternative interesting speculation. The critical step in Scheme III involves, of course, the intermediacy of 3-alumino-1,7-octadiene. The pyrolysis of cyclooctene to 1,7-octadiene can be accomplished in high efficiencies at 500°.[6] This reaction depends on the rupture of a carbon–hydrogen bond in the 5 position of cyclooctene.[7,8] The con-

(1) A part of this work has been described by E. Marcus and D. L. MacPeek, U. S. Patent 3,388,180 (June 11, 1968).

(2) Author to whom correspondence should be directed.

(3) E. Marcus, D. L. MacPeek, and S. W. Tinsley, *J. Org. Chem.*, **34**, 1931 (1969).

(4) P. Natalis, *Bull. Soc. Chim. Belg.*, **72**, 178 (1963); *Chem. Abstr.*, **59**, 7346 (1963).

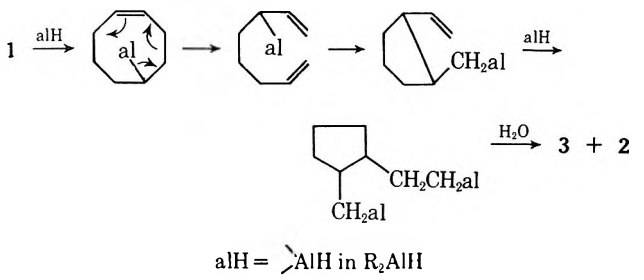
(5) K. Ziegler, K. Nagel, and W. Pfohl, *Justus Liebigs Ann. Chem.*, **629**, 210 (1960).

(6) S. W. Tinsley and E. A. Rick, U. S. Patent 3,388,182 (June 11, 1968).

(7) G. S. Denning, Jr., *Diss. Abstr.*, **21**, 1731 (1961).

(8) A. T. Blomquist and G. S. Denning, Jr., 139th National Meeting of the American Chemical Society, St. Louis, Mo., March 1961, Abstract 29-O

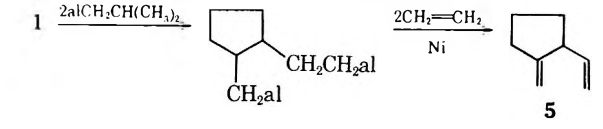
SCHEME III



version of 5-aluminocyclooctene to 3-alumino-1,7-octadiene would necessitate breaking of the much weaker carbon–aluminum bond at a considerably lower temperature; this, in our opinion, is a reasonable possibility. Further transformation of 3-alumino-1,7-octadiene to a cyclopentane derivative is straightforward. 1-Alumino-5-hexenes are known to cyclize rapidly to (aluminomethyl)cyclopentanes.[3,9,10] The fact that 3-alumino-1,7-octadiene is an allylic aluminum derivative should enhance the reactivity of this intermediate even further.[3]

When the TIBA–1,5-cyclooctadiene reaction product was treated with ethylene in a bomb in the presence of nickel acetylacetonate as catalyst and benzene as solvent, the C_8 fraction contained as major product the expected 1-methylene-2-vinylcyclopentane (**5**). The overall reaction can be described by Scheme IV.

SCHEME IV



The infrared absorption spectrum showed intense bands at 10.1, 11.0, and 11.35 μ, which confirmed the presence of both a vinyl and a vinylidene group. According to mass spectroscopy it was a C_8H_{12} hydrocarbon. Catalytic reduction over platinum oxide produced both of the 1-ethyl-2-methylcyclopentane isomers.

It is of interest to note that the TIBA–1,5-cyclooctadiene reaction product was soluble in the excess of cyclooctadienes as well as in benzene, which indicates that the polymer was cross-linked only slightly or not at all.

It should also be mentioned that **2** and **3** have been obtained before by catalytic conversion of cyclooctane in the presence of hydrogen;[11,12] the precursor for the ethylmethylcyclopentanes seems to be bicyclo[3.3.0]-octane. However, it is difficult to see any close relationship between this reaction and the reaction discussed in the present article.

Experimental Section

The gas chromatograph used for analyzing the composition of a certain fraction was the Barber–Coleman capillary gas chromatograph IDS Model 20, with a 200-ft UCON 50 HB 2000 column and a strontium-90 detector.

The gas chromatograph used for isolating a component from a certain fraction was the Beckman GC-2 analytical gas chromatograph with a packed column containing a UCON-P substrate on firebrick. The amount of material injected varied from 0.03 to 0.05 ml. The desired component was collected by condensation of the effluent from the exit port. Usually the amount collected was sufficient for an infrared or a mass spectral determination. However, in a few cases where the material contained too little of the desired component, collections had to be repeated until a sufficient amount was available.

The yields reported are based on calculations derived from the gas chromatographic spectra. Since the assumption was made that "area %" equals "weight %," yields given are only approximate. Most probably this assumption is fairly valid for similar hydrocarbons.

1,5-Cyclooctadiene–TIBA Reaction Product and Its Hydrolysis.—TIBA (132 g, 0.67 mol) was added with stirring during a period of 190 min to **1** (216 g, 2.0 mol), while the temperature was maintained between 122 and 149°. Heating with stirring was continued for another 50 min at 145°. During the reaction time isobutylene (106 g, 95%) was collected in a Dry Ice trap. Cyclooctadiene (52 g, 24%) was recovered by distillation under reduced pressure at 55°. The reaction product was hydrolyzed with ethanol and then with dilute hydrochloric acid. The organic layer was separated; the aqueous layer was extracted with petroleum ether, bp 35–37°. The combined organic layers were washed with water, dilute sodium hydroxide solution, again with water, dried over calcium chloride, decanted, and distilled through a 15-in. column to give the following fractions: 24 g from 110 to 122°, 57 g from 122 to 125°, 28 g from 62° (50 mm) to 45° (10 mm), 24 g from 65° (0.75 mm) to 92° (1 mm), and 5 g of residue. The first two fractions contained mostly the two ethylmethylcyclopentanes, some cyclooctene, and cyclooctadiene. The third fraction contained mainly cyclooctene and cyclooctadiene. The last fraction is believed to contain C_{16} hydrocarbons. The first three fractions were analyzed by gas chromatography and found to contain four main peaks. The compound of the first peak is believed to be **3**. The second peak is caused by **2**. The third peak represents cyclooctene, and the fourth peak is caused by **1**. The yields on TIBA given in Table I have been obtained assuming that 2 equiv of TIBA are required for the formation of ethylmethylcyclopentane after hydrolysis.

TABLE I

Compd	Yield, g	Yield, %, based on 1	Yield, %, based on TIBA
trans-1-Ethyl-2-methylcyclopentane	26.5	12	24
cis-1-Ethyl-2-methylcyclopentane	41.3	18	37
Cyclooctene	16.4	7.5	7.5
Cyclooctadienes recovered[a]	69.5	32	
C_{16} hydrocarbons	24	11	

[a] Was shown to be a mixture of 1,3-, 1,4-, and 1,5-cyclooctadiene.

The products represented by peaks I and II were isolated by gas chromatography. Peak II was identified as the cis isomer by comparing its infrared and mass spectra with those of an authentic National Bureau of Standards sample. The reported[4] boiling points for **2** and **3** are 128.4 and 121.35°, respectively.

1-Methylene-2-vinylcyclopentane.—TIBA (264 g, 1.34 mol) was added to **1** (432 g, 4.0 mol) under conditions similar to those described in the previous experiment to give 475 g of a reaction product. After removal of the excess of **1**, which contained now significant amounts of the 1,3 and 1,4 isomers, by distillation under vacuum, there was left 339 g of a colorless polymer. Of this polymer 320 g, which is equivalent to 1.25 mol of initial TIBA, was used for the following run.

A mixture of the TIBA–cyclooctadiene polymer (320 g), benzene (500 ml), and nickel acetylacetonate (0.15 g) was charged to a 3-l. stainless-steel bomb. After the addition of ethylene (351 g, 12.5 mol), the bomb was heated with rocking to 74° within 15 min to give a pressure of 1080 psi. Heating with rocking was continued between 69 and 74° for 17 hr. The pressure had dropped to 680 psi at 70°. The bomb was vented and its

(9) K. Ziegler, *Angew. Chem.*, **68**, 721 (1956).
(10) G. Hata and A. Miyake, *J. Org. Chem.*, **28**, 3237 (1963).
(11) A. Kazanskiĭ, E. A. Shokova, S. I. Khromov, V. I. Aleksanyan, and Kh. E. Sterin, *Dokl. Akad. Nauk SSSR*, **133**, 1090 (1960); *Chem. Abstr.*, **54**, 24442 (1960).
(12) S. I. Khromov, E. A. Shokova, Kh. E. Sterin, and B. A. Kazanskiĭ, *Dokl. Akad. Nauk SSSR*, **136**, 1112 (1961); *Chem. Abstr.*, **55**, 17534 (1961).

content was transferred under nitrogen to a distillation flask. The product was not soluble in benzene. The benzene and other low-boiling material were removed by distillation without rectification by lowering the pressure gradually to 10 mm at 40°. Most of the benzene was separated by distillation through a 36-in. column. The residue was distilled through a 20-in. spiral wire column to give 28 g, bp 121° at atmospheric pressure to 110° at 200 mm. Gas chromatography showed that it contained about 70% of one material and several other products in small amounts. A fraction boiling between 122 and 124°, which was about 85% pure according to gas chromatography, was analyzed, n^{30}D 1.4572, d^{20}_{20} 0.814 (lit.[13] bp 118°, n^{27}D 1.4557).

Anal. Calcd for C_8H_{12}: C, 88.82; H, 11.18; mol wt, 108. Found: C, 88.55; H, 11.39; mol wt (largest parent peak by mass spectroscopy), 108.

The product was purified further by gas chromatography. Its infrared absorption spectrum showed bands at 6.06, 6.10, 10.12, 11.0, and 11.35 μ indicating the presence of both a vinyl and a vinylidene group. All of the positions of the absorption peaks were identical with the positions reported for 5.[14]

(13) W. D. Huntsman and R. P. Hall, *J. Org. Chem.*, **27**, 1988 (1962).
(14) R. P. Hall, M.S. Thesis, Ohio University, Athens, Ohio, 1961, p 10.

Reduction of 1-Methylene-2-vinylcyclopentane.—1-Methylene-2-vinylcyclopentane (2 ml), which was about 85% pure, was hydrogenated over platinum oxide in a Parr hydrogenator at 40 psi and room temperature. After 1 hr the pressure had decreased to 37.5 psi. Gas chromatography showed the presence of two major peaks: 35% of peak I and 54% of peak II. A comparison with the two 1-ethyl-2-methylcyclopentanes obtained by hydrolysis of the TIBA–cyclooctadiene reaction product showed that peak I and peak II had the same retention times as **3** and **2**, respectively. Further support was obtained from the infrared and mass spectra of the products which had been purified by gas chromatography.

Hydrogenation of **5** over prereduced platinum oxide in acetic acid has been reported to give 66% of **2** and 34% of **3**.[13]

Registry No.—TIBA, 100-99-2; **1**, 111-78-4.

Acknowledgment.—The authors wish to express thanks to Messrs. H. R. Harless and C. M. Lovell of Union Carbide Corporation for interpretations of spectral data.

Hydrogenolysis of Cyclopropanes

ARNOLD L. SCHULTZ[1]

Department of Chemistry, University of Colorado, Boulder, Colorado 80302

Received September 2, 1970

Several cyclopropane derivatives bearing unsaturated functional groups directly on the three-membered ring, including ketones, acids, and esters, were prepared and subjected to hydrogenolysis at room temperature and atmospheric pressure over a palladium-on-carbon catalyst. Exclusive C_1–C_2 bond cleavage was observed for all cyclopropyl methyl ketones studied. Predominant C_1–C_2 bond cleavage (>70%) was observed for the cyclopropanecarboxylic acids and cyclopropanecarboxylic acid esters. For cyclopropanes bearing phenyl groups as the only unsaturated substituent, exclusive cleavage adjacent to the phenyl-substituted carbon atom was observed. This preference for C_1–C_2 bond cleavage may be due to polarization effects of the unsaturated substituents and/or binding of the unsaturated functional groups to the catalyst surface.

Although the cyclopropyl system is one that has been extensively studied, relatively few investigations have been carried out involving the ability of cyclopropanes to undergo hydrogenolysis.[2] In the previous studies only a small percentage of the work has dealt with the hydrogenolysis of cyclopropane rings adjacent to unsaturated groups. In addition, comparisons of the effect of structure on reactivity are often difficult to make because different catalysts as well as various reaction temperatures and pressures have been used. Cyclopropyl methyl ketone has been hydrogenated using copper–chromium, Raney nickel, zinc, zinc–copper, and copper catalysts. Various products result depending upon the catalyst employed.[2a] Several alkenylcyclopropanes have been hydrogenated,[2] but the only systematic study of the effect of structure upon the nature of the hydrogenation products has dealt with the differences observed in the behavior of 2-cyclopropyl-1- and -2-alkenes.[3] The only report of the effect of phenyl substituents was concerned with the relative reactivities of phenylcyclopropane and the various diphenylcyclopropanes.[4]

In an attempt to elucidate the effect of adjacent unsaturated groups on the direction of ring opening of the three-membered ring, several such cyclopropanes were prepared and hydrogenated at room temperature and atmospheric pressure in the presence of palladium on carbon. In all the cases studied hydrogenolysis of the cyclopropane ring could result in various products determined by the direction of bond cleavage. The results of these hydrogenolyses and their implications are discussed.

Results and Discussion

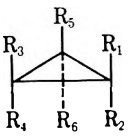
The results of the present study into the mode of ring opening of unsaturated cyclopropane derivatives upon hydrogenation at room temperature and atmospheric pressure over 10% palladium-on-carbon catalyst are presented in Table I.

Upon hydrogenation all the cyclopropanes bearing an adjacent carbonyl group preferentially undergo ring opening at the C_1–C_2[5] bond of the three-membered ring. In the case of the cyclopropyl methyl ketones hydrogenolysis occurs exclusively at the C_1–C_2 bond of the cyclopropane ring, while with the esters and acids a minimum of 70% of the ring-opened products results from rupture of the C_1–C_2 bond of the three-membered ring. The results of the hydrogenolyses of the cyclopropylcarbinols (**19**–**21**), acetates (**22**–**24**), *trans*-1,2-diphenylcyclopropane (**25**), and 1,1-dimethyl-2-phenylcyclopropane (**26**) indicate that, in those compounds in which a benzene ring is the only unsaturated moiety in conjugation with the three-membered ring, exclusive

(1) This work is taken in part from the M.S. Thesis of A. L. S.
(2) For reviews see (a) M. Yu. Lukina, *Russ. Chem. Rev.*, **31**, 419 (1962); (b) J. Newham, *Chem. Rev.*, **63**, 123 (1963).
(3) V. A. Slabey and P. H. Wise, *J. Amer. Chem. Soc.*, **74**, 3887 (1952).
(4) B. A. Kazanskii, M. Yu. Lukina, and I. L. Safonova, *Dokl. Akad. Nauk SSSR*, **130**, 322 (1960); *Chem. Abstr.*, **54**, 10953 (1960).
(5) See Table I for numbering system.

TABLE I

DIRECTION OF RING OPENING UPON HYDROGENOLYSIS OF CYCLOPROPANES



Compd	R_1	R_2	R_3	R_4	R_5	R_6	Bond cleaved, %[a,b] C_1–C_2	C_1–C_3	C_2–C_3
1	$COCH_3$	H	H	H	H	H	50	50	
2	$COCH_3$	H	H	C_4H_8[c]	H	...[c]	50	50	
3	$COCH_3$	H	H	C_6H_5	H	H	100		
4	$COCH_3$	H	CH_3	C_6H_5	H	H	100		
5	$COCH_3$	C_6H_5	H	CH_3	H	CH_3	50	50	
6	$COCH_3$	C_6H_5	CH_3	H	H	CH_3	50	50	
7	$COCH_3$	CH_3	C_6H_5	C_6H_5	H	H	100		
8	$COCH_3$	CH_3	H	C_6H_5	H	H	100[d]		
9	$COCH_3$	H	C_6H_5	C_6H_5	H	H	100[e]		
10	$CO_2C_2H_5$	H	H	C_6H_5	H	H	100		
11	CO_2CH_3	CH_3	C_6H_5	C_6H_5	H	H	89	11	
12	CO_2CH_3	CH_3	H	C_6H_5	H	H	85[d]	15[d]	
13	CO_2CH_3	H	C_6H_5	C_6H_5	H	H	80[e]		20[e]
14	CO_2H	H	H	C_6H_5	H	H	100		
15	CO_2H	H	C_6H_5	C_6H_5	H	H	100		
16	CO_2H	CH_3	C_6H_5	C_6H_5	H	H	100		
17	CO_2H	H	C_6H_5	H	H	H	100[d]		
18	CO_2H	CH_3	H	C_6H_5	H	H	70[d]	30[d]	
19	CH_2OH	CH_3	C_6H_5	C_6H_5	H	H	100		
20	CH_2OH	CH_3	H	C_6H_5	H	H			100[d]
21	CH_3CHOH	H	C_6H_5	C_6H_5	H	H			100[e]
22	$OCOCH_3$	C_6H_5	C_6H_5	H	H	H	100[f]		
23	$OCOCH_3$	CH_3	CH_3	CH_3	H	H		No reaction	
24	$OCOCH_3$	CH_3	H	C_6H_5	H	H			100[d,f]
25	C_6H_5	H	H	C_6H_5	H	H	100[e]		
26	CH_3	CH_3	C_6H_5	H	H	H			100[d]

[a] C_1 is the carbon atom bearing R_1 and R_2, C_2 is the carbon atom bearing R_3 and R_4, and C_3 is the carbon atom bearing R_5 and R_6. [b] All percentages are ±5% as analysis was by nmr. [c] A tetramethylene grouping bridges R_4 and R_6. [d] Dr. W. Wiedemann, unpublished results. [e] Dr. B. Plummer, unpublished results. [f] The acetoxy group was also cleaved.

cleavage of a carbon–carbon bond adjacent to the aromatic ring takes place.

The hydrogenolysis of alkylcyclopropanes typically occurs with cleavage of the bond between those two carbon atoms of the three-membered ring which carry the largest number of hydrogen atoms.[2] Inspection of Table I reveals that the behavior of cyclopropane derivatives containing an adjacent carbonyl function under conditions of hydrogenolysis is quite different from that exhibited by alkylcyclopropanes under similar reaction conditions as evidenced by the predominance of C_1–C_2 bond cleavage observed in this study.

Palladium was chosen for the catalyst because of reports that many other hydrogenation catalysts cause isomerization of alkylcyclopropanes to open-chain alkenes which are then hydrogenated, whereas palladium leads only to direct hydrogenolysis of the three-membered ring.[2] Palladium is also a specific catalyst for the hydrogenolysis of conjugated cyclopropane compounds. For example, phenylcyclopropane is hydrogenolyzed 90 times more rapidly in the presence of palladium than in the presence of platinum. In the former case the only product is *n*-propylbenzene, whereas in the latter case *n*-propylbenzene and possibly cyclopropylcyclohexane are also formed.[6]

The mechanisms of hydrogenolysis of cyclopropanes are not well understood.[2] There are, however, some studies in the literature which lend some understanding to the present results. The rates of hydrogenolysis of phenylcyclopropanes on palladium at 20° have been found to be *trans*-1,2-diphenylcyclopropane > phenylcyclopropane > *cis*-1,2-diphenylcyclopropane > 1,1-diphenylcyclopropane.[4] It was reported that under these conditions 1,1-diphenylcyclopropane fails to react. The Raman spectra of these compounds show a corresponding decrease in the conjugation of the substrate as the rate of hydrogenolysis decreases.[7] This was taken as evidence that polarization or conjugative effects and not steric hindrance are the important factors in determining the direction and rate of cleavage of phenyl-substituted cyclopropanes.

When unsaturated substituents are present on a cyclopropane ring, the point(s) of adsorption on the catalyst surface is not as well defined as with alkyl-substituted cyclopropanes.[2b] The possibility that phenylcyclopropane is initially adsorbed at the aromatic ring and that hydrogenolysis occurs by way of a migration of the adsorbed site to the cyclopropyl ring does not seem likely based on deuterium exchange studies.[2b] It has been suggested that the hydrogenation of alkenes in conjugation with a phenyl substituent proceeds *via* a species in which the olefinic bond is adsorbed on the catalyst surface while the aromatic ring is simultane-

(6) B. A. Kazanskiĭ, M. Yu. Lukina, and I. L. Safonova, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 95 (1958).

(7) V. T. Aleksanyan and Kh. Sterin, *Dokl. Akad. Nauk SSSR*, **131**, 1373 (1960); *Chem. Abstr.*, **57**, 7929 (1962).

ously π complexed to the metal.[8] Such a phenyl effect could conceivably be operative in the case of phenylcyclopropanes. Although 1,4-conjugate addition has been proposed for some of the hydrogenolyses of cyclopropyl methyl ketone,[2a] no supportive evidence has been provided. It has also been suggested that 1,4-conjugate addition may be involved in the hydrogenolysis of alkenylcyclopropanes.[2a] However, in a study of the hydrogenolysis of isopropenylcyclopropane over palladium it was shown that the product that would result from 1,4-conjugate addition could be formed by the isomerization by palladium of the product that would result from 1,2 addition of hydrogen to the cyclopropyl ring.[9]

The most probable explanations for the formation of the major hydrogenolysis products observed in this study resulting from the rupture of the bond between C_1 and C_2 thus appear to be based upon (1) the action of polarization effects acting through conjugative or inductive forces tending to weaken the C_1–C_2 bond of the cyclopropane ring and leading to chemisorption with simultaneous ring cleavage, and (2) an interaction of the unsaturated functional groups on C_1 and C_2 with the catalyst surface in such a manner as to properly orient the cyclopropyl ring for cleavage of the C_1–C_2 bond. These two effects may operate separately or in conjunction with one another. Steric effects do not appear to be of any consequence as is most noticeably shown by the fact that 2,2-diphenyl-1-methylcyclopropyl methyl ketone (**7**) readily undergoes hydrogenolysis at the sterically shielded C_1–C_2 bond.

The formation of the minor products observed in the hydrogenolysis of some of the acids and esters does not show a definite pattern at this time. As there are many factors that could affect the formation of these products, no attempt will be made to interpret these results until further work is performed to determine if a definite pattern does exist.

The observation that 1-methyl-*trans*-2-phenylcyclopropyl acetate (**24**) undergoes cleavage of the acetoxy group as well as hydrogenolysis of the three-membered ring while 1,2,2-trimethylcyclopropyl acetate (**23**) fails to react suggests that the acetoxy function is lost in the former case from a species in which the cyclopropane ring is bound to the catalyst.

Experimental Section

General.—Melting points were taken on a Fisher–Johns melting point apparatus and are uncorrected. Boiling points are uncorrected. The ir spectra were recorded with a Beckman IR-10. Nmr spectra were determined with a Varian A-60 spectrometer using TMS as an internal standard. Glpc analyses were performed on either an Aerograph Model 200 or an F & M Model 700. Preparative scale glpc was performed on an Aerograph Autoprep Model A-700. All elemental analyses were performed by A. Bernhardt, Mülheim, Germany.

The hydrogenolyses of substituted cyclopropanes were carried out in an atmospheric pressure hydrogenation apparatus of essentially the same design as that described by Wiberg,[10] the principal difference being that water rather than mercury was used in the 500-ml buret. The hydrogenations were carried out using 10% palladium on carbon as the catalyst in 95% ethanol unless otherwise noted. In a typical experiment 1 g of the cyclopropane compound was dissolved in 25 ml of solvent and, along with 150 mg of catalyst, was charged to a hydrogenation flask equipped with a magnetic stirring bar. The system was alternately evacuated and filled with hydrogen five times and then the magnetic stirrer was started. When the uptake of hydrogen ceased, the catalyst was removed by filtration, and after the removal of solvent by distillation at atmospheric pressure, the crude reaction product was analyzed by nmr and ir spectroscopy. The product distribution is based entirely on nmr analysis and is therefore accurate to ±5%. The overall yield of ring-opened products was 90% or greater unless otherwise stated. In general, the ketones took up the theoretical amount of hydrogen in a few hours, whereas the acids and esters required several days for complete hydrogenolysis of the cyclopropane ring.

Diphenyldiazomethane was prepared by the method of Smith and Howard,[11] employing a modification described by Miller.[12]

Cyclopropyl methyl ketone (**1**) was commercially available and was used without purification. Hydrogenolysis of **1** produced 2-pentanone as the only product: ir (CCl_4) 1715 cm^{-1}; nmr (CCl_4) δ 0.98 (t, 3), 1.48 (m, 2), 2.07 (s, 3), 2.35 (t, 2). A mixture melting point of the 2,4-dinitrophenylhydrazone prepared from the product with an authentic sample showed no melting point depression. The ir spectra of the two derivatives were identical.

***exo*-7-Norcaryl methyl ketone** (**2**)[13] gave only cyclohexylacetone upon hydrogenolysis: ir (CCl_4) 1715 cm^{-1}; nmr (CCl_4) δ 1.37 (m, 11), 2.02 (s, 3), 2.20 (d, 2). A 2,4-dinitrophenylhydrazone derivative of the reaction product was prepared, mp 117–118° (lit.[14] mp 115–117°).

***trans*-2-Phenylcyclopropyl methyl ketone** (**3**)[15] gave only 5-phenyl-2-pentanone upon hydrogenolysis: ir (CCl_4) 1720 cm^{-1}; nmr (CCl_4) δ 1.92 (s, 3), 2.15 (m, 6), 7.13 (s, 5). The spectroscopic identification of the product was supported by preparation of two derivatives: 2,4-dinitrophenylhydrazone, mp 77.5–79° (lit.[16] mp 78°); semicarbazone, mp 130–133.5° (lit.[17] mp 135–136°).

***cis*-2-Methyl-*trans*-2-phenylcyclopropyl methyl ketone** (**4**) was prepared in 14% yield from *cis*-2-methyl-*trans*-2-phenylcyclopropanecarboxylic acid and methyllithium using the method described by Tegner,[18] bp 52–57° (0.4–0.5 mm). A 2,4-dinitrophenylhydrazone derivative was prepared yielding orange crystals (ethanol), mp 161.5–163.5°.

Anal. Calcd for $C_{18}H_{18}N_4O_4$: C, 61.01; H, 5.12; N, 15.81. Found: C, 60.83; H, 5.26; N, 15.64.

Hydrogenolysis of **4** produced only 5-phenyl-2-hexanone: ir (CCl_4) 1722 cm^{-1}; nmr (CCl_4) δ 1.21 (d, 3), 1.88 (s, 3), 2.28 (m, 5), 7.15 (s, 5). A semicarbazone of the product was prepared, mp 146–148° (lit.[19] mp 147°).

***trans,trans*-2,3-Dimethyl-1-phenylcyclopropyl methyl ketone** (**5**)[20] gave only 4-methyl-3-phenyl-2-hexanone upon hydrogenolysis: ir (CCl_4) 1720 cm^{-1}; nmr (CCl_4) δ 0.93 (m, 9), 1.97 (s, 3), 3.38 (d, 1), 7.20 (s, 5).

***cis,trans*-2,3-Dimethyl-1-phenylcyclopropyl Methyl Ketone** (**6**).[20]—The hydrogenation product was shown to be the same as that resulting from the isomeric ketone, **5**, based on ir, nmr, and glpc (5-ft 15% Apiezon L on 60–80 Chromosorb W at 185°) comparisons.

2,2-Diphenyl-1-methylcyclopropyl methyl ketone (**7**)[21] gave 5,5-diphenyl-3-methyl-2-pentanone as the only hydrogenolysis product: ir (CCl_4) 1710 cm^{-1}; nmr (CCl_4) δ 0.93 (d, 3), 1.75 (s, 3), 2.32 (m, 3), 3.83 (m, 1), 7.05 (s, 10).

1-Methyl-*trans*-2-phenylcyclopropyl methyl ketone (**8**)[22] gave

(8) G. V. Smith and J. A. Roth, *J. Amer. Chem. Soc.*, **88**, 3879 (1966).

(9) B. A. Kazanskiĭ, M. Yu. Lukina, A. I. Malyshev, V. T. Aleksanyan, and Kh. E. Sterin, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 35 (1956).

(10) K. B. Wiberg, "Laboratory Technique in Organic Chemistry," McGraw-Hill, New York, N. Y., 1960, p 228.

(11) L. I. Smith and K. L. Howard, "Organic Syntheses," Coll. Vol. III, Wiley, New York, N. Y., 1955, p 351.

(12) J. B. Miller, *J. Org. Chem.*, **24**, 560 (1959).

(13) M. Mousseron, R. Jacquier, and R. Fraisse, *C. R. Acad. Sci., Ser. C*, **243**, 1880 (1956).

(14) J. G. Baldinus and I. Rothberg, *Anal. Chem.*, **34**, 924 (1962).

(15) C. H. DePuy, G. M. Dappen, K. L. Eilers, and R. A. Klein, *J. Org. Chem.*, **29**, 2813 (1964).

(16) C. M. Clark and J. D. A. Johnson, *J. Chem. Soc.*, 126 (1962).

(17) A. I. Lebedeva and V. A. Shlyakova, *Zh. Obshch. Khim.*, **19**, 1290 (1949); *Chem. Abstr.*, **44**, 1054 (1950).

(18) C. Tegner, *Acta Chem. Scand.*, **6**, 782 (1952).

(19) J. Cologne and L. Pichat, *Bull. Soc. Chim. Fr.*, 853 (1949).

(20) C. H. DePuy, W. C. Arney, Jr., and Dorothy H. Gibson, *J. Amer. Chem. Soc.*, **90**, 1830 (1968).

(21) F. J. Impastato and H. M. Walborsky, *ibid.*, **84**, 4838 (1962).

(22) C. H. DePuy, F. W. Breitbeil, and K. R. DeBruin, *ibid.*, **88**, 3347 (1966).

only 3-methyl-5-phenyl-2-pentanone upon hydrogenolysis: nmr (CCl_4) δ 1.04 (d, 3), 2.00 (s, 3), 2.06 (m, 5), 7.12 (s, 5).

2,2-Diphenylcyclopropyl methyl ketone (9)[21] gave only 5,5-diphenyl-2-pentanone: ir (CCl_4) 1720 cm^{-1}; nmr (CCl_4) δ 1.95 (s, 3), 2.20 (m, 4), 3.78 (t, 1), 7.10 (s, 10).

Ethyl *trans*-2-phenylcyclopropanecarboxylate (10)[15] gave only ethyl 4-phenylbutanoate upon hydrogenolysis: ir (CCl_4) 1745 cm^{-1}; nmr (CCl_4) δ 1.20 (t, 3), 2.03 (m, 4), 2.60 (t, 2), 4.05 (quartet, 2), 7.15 (s, 5).

Methyl 2,2-diphenyl-1-methylcyclopropanecarboxylate (11)[23] gave a mixture of products upon hydrogenolysis. The reaction mixture exhibited ir (CCl_4) 1738 cm^{-1}; nmr (CCl_4) δ 1.27 (m), 2.28 (m), 3.20 (s), 3.33 (s), 3.45 (s), 3.88 (m), 7.23 (m). Interpretation of these data along with the observed nmr integrated peak areas led to the conclusion that the reaction mixture consisted of 26% unreacted starting material, 66% methyl 4,4-diphenyl-2-methylbutanoate, and 8% methyl 3,3-diphenyl-2-methylbutanoate.

Methyl 1-methyl-*trans*-2-phenylcyclopropanecarboxylate (12) was prepared from the corresponding acid, **18**, by treatment with diazomethane. The crude product was subjected directly to hydrogenolysis and gave an 85:15 mixture of methyl 2-methyl-4-phenylbutanoate–methyl 2-methyl-3-phenylbutanoate as shown by ir and nmr spectroscopy and glpc analysis.

Methyl 2,2-diphenylcyclopropanecarboxylate (13)[23] gave a mixture of 80% methyl 4,4-diphenylbutanoate and 20% methyl 3,3-diphenyl-2-methylbutanoate upon hydrogenolysis: nmr (CCl_4) δ 1.08 (d), 2.20 (m), 3.34 (s), 3.48 (s), 3.86 (m), 7.10 (s).

Ethyl *cis*- and *trans*-2-Methyl-2-phenylcyclopropanecarboxylates.—These isomeric esters were prepared by a method analogous to that used by Burger and Yost[24] to prepare ethyl 2-phenylcyclopropanecarboxylate. In this case α-methylstyrene and ethyl diazoacetate were the reagents used. The mixture of isomers was obtained in 44% yield, bp 70–78° (0.75 mm). The ratio of ethyl *trans*-2-methyl-*cis*-2-phenylcyclopropanecarboxylate to ethyl *cis*-2-methyl-*trans*-2-phenylcyclopropanecarboxylate was found to be 1:3 by glpc analysis (5-ft Apiezon L on 60–80 Chromosorb W at 160°). Separation of the isomers was effected by initial enhancement of the isomer ratio by use of a Nester–Faust annular Teflon spinning-band distillation column followed by preparative scale glpc (20-ft SE-30 on 30–60 Chromosorb P).

Anal. Calcd for $C_{13}H_{16}O_2$ (ethyl *cis*-2-methyl-*trans*-2-phenylcyclopropanecarboxylate): C, 76.44; H, 7.90. Found: C, 76.41; H, 7.74.

Anal. Calcd for $C_{13}H_{16}O_2$ (ethyl *trans*-2-methyl-*cis*-2-phenylcyclopropanecarboxylate): C, 76.44; H, 7.90. Found: C, 76.24; H, 7.70.

Structure assignments for the geometrical isomers were made using the chemical shift of the methylene protons in the carboethoxy group as a criterion.[25] Thus the structure of ethyl *cis*-2-methyl-*trans*-2-phenylcyclopropanecarboxylate was assigned to the compound with nmr (CCl_4) δ 1.22 (t, 3), 1.40 (m, 2), 1.50 (s, 3), 1.90 (doublet of doublets, 1), 4.13 (quartet, 2), 7.20 (s, 5), and the structure of ethyl *trans*-2-methyl-*cis*-2-phenylcyclopropanecarboxylate to the compound with nmr (CCl_4) δ 0.85 (m, 4), 1.37 (s, 3), 1.72 (m, 2), 3.74 (quartet, 2), 7.17 (s, 5).

***trans*-2-Phenylcyclopropanecarboxylic acid (14)**[15] gave only 4-phenylbutanoic acid upon hydrogenolysis: ir (CCl_4) 2940, 1720 cm^{-1}; nmr (CCl_4) δ 2.12 (m, 4), 2.67 (t, 2), 7.17 (s, 5), 12.09 (s, 1).

2,2-Diphenylcyclopropanecarboxylic acid (15)[23] gave only 4,4-diphenylbutanoic acid upon hydrogenolysis in ethyl acetate: ir ($CHCl_3$) 3020, 1710 cm^{-1}; nmr ($CDCl_3$) δ 2.33 (m, 4), 3.77 (m, 1), 7.17 (s, 10), 11.30 (s, 1).

1-Methyl-2,2-diphenylcyclopropanecarboxylic acid (16)[22] was hydrogenated using a 2:3 mixture of ethanol–ethyl acetate as the solvent to give 4,4-diphenyl-2-methylbutanoic acid as the only product: ir (CCl_4) 2950, 1705 cm^{-1}; nmr (CCl_4) δ 1.15 (d, 3), 2.17 (m, 3), 3.83 (t, 1), 6.90 (s, 10), 11.73 (s, 1).

***cis*-2-Phenylcyclopropanecarboxylic acid (17)**[15] gave only 4-phenylbutanoic acid upon hydrogenolysis: nmr (CCl_4) δ 2.10 (m, 4), 2.67 (t, 2), 7.17 (s, 5), 12.41 (s, 1).

1-Methyl-*trans*-2-phenylcyclopropanecarboxylic acid (18)[22] gave a mixture of 70% 2-methyl-4-phenylbutanoic acid and 30% 2-methyl-3-phenylbutanoic acid: nmr (CCl_4) δ 1.19 (m), 1.77 (m), 2.53 (m), 3.48 (m), 7.08 (s), 10.50 (s).

***cis*-2-Methyl-*trans*-2-phenylcyclopropanecarboxylic acid** was prepared by saponification of the corresponding ethyl ester in ethanol in 66% yield, mp 46–48° (lit.[26] mp 52.5–53°) from petroleum ether (bp 35–60°).

2,2-Diphenyl-1-methylcyclopropylcarbinol (19)[27] gave only 4,4-diphenyl-2-methyl-1-butanol upon hydrogenolysis: ir (CCl_4) 3600, 3345 cm^{-1}; nmr (CCl_4) δ 0.83 (d, 3), 1.81 (m, 3), 2.70 (s, 1), 3.22 (d, 2), 3.88 (m, 1), 7.10 (s, 10).

1-Methyl-*trans*-2-phenylcyclopropylcarbinol (20) was prepared by reduction of the corresponding acid, **18**, with lithium aluminum hydride.[28] 2,2-Dimethyl-3-phenylpropanol was the only product obtained upon hydrogenation: nmr (CCl_4) δ 0.84 (s, 6), 2.49 (s, 2), 2.56 (s, 1), 3.17 (s, 2), 7.15 (s, 5).

2,2-Diphenylcyclopropylmethylcarbinol (21) was prepared by sodium borohydride reduction of the corresponding ketone, **9**, and was hydrogenated without purification to give 1,2-dimethyl-3,3-diphenyl-1-propanol as the only product: ir (CCl_4) 3380 cm^{-1}; nmr (CCl_4) δ 0.88 (m, 6), 2.37 (m, 1), 2.47 (s, 1), 3.65 (m, 2), 7.15 (m, 10).

***cis*-1,2-Diphenylcyclopropyl acetate (22)** was prepared as previously described by Freeman.[29] The isomers were separated[30] by distillation through a Nester–Faust 24-in. spinning-band distillation column. The fraction with bp 100–110° (0.06 mm) was found to be greater than 95% *cis*-1,2-diphenylcyclopropyl acetate by glpc analysis. Crystallization of this material from hexane yielded pure **22**, mp 74.5–75.0°.

Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.94; H, 6.39. Found: C, 81.05; H, 6.61.

The hydrogenation of this acetate in a 2:3 mixture of ethanol–ethyl acetate required 2 mol of hydrogen per mol of cyclopropyl compound. The ir and nmr spectra of the product was identical with those of an authentic sample of 1,3-diphenylpropane.

1,2,2-Trimethylcyclopropyl acetate (23)[20,29] failed to undergo hydrogenolysis in either ethyl acetate or acetic acid.

1-Methyl-*trans*-2-phenylcyclopropyl acetate (24)[29] gave only 2-methyl-1-phenylpropane upon hydrogenolysis: nmr (CCl_4) δ 0.89 (d, 6), 1.71 (m, 1), 2.41 (d, 2), 7.09 (s, 5).

***trans*-1,2-Diphenylcyclopropane (25)**[31] gave only 1,3-diphenylpropane upon hydrogenolysis: nmr (CCl_4) δ 1.93 (m, 2), 2.58 (t, 4), 7.15 (s, 10).

1,1-Dimethyl-2-phenylcyclopropane (26)[28] was prepared from the corresponding carbinol, **20**, and yielded only 2,2-dimethyl-1-phenylpropane upon hydrogenation: nmr (CCl_4) δ 0.91 (s, 9), 2.40 (s, 2), 7.09 (s, 5).

Registry No.—**1**, 765-43-5; **2**, 10330-36-6; **3**, 14063-86-6; **4**, 15967-24-5; **5**, 27067-36-3; **6**, 27067-37-4; **7**, 27067-38-5; **8**, 27067-39-6; **9**, 27067-40-9; **10**, 946-39-4; **11**, 6975-21-9; **12**, 27067-43-2; **13**, 19179-60-3; **14**, 939-90-2; **15**, 7150-12-1; **16**, 27067-47-6; **17**, 939-89-9; **18**, 13005-22-6; **19**, 27067-50-1; **20**, 27067-51-2; **21**, 27067-52-3; **22**, 27067-53-4; **23**, 16526-20-8; **24**, 16526-24-2; **25**, 1138-47-2; **26**, 7653-94-3; ethyl *cis*-2-methyl-*trans*-2-phenylcyclopropanecarboxylate, 27070-05-9; ethyl *trans*-2-methyl-*cis*-2-phenylcyclopropanecarboxylate, 27070-06-0.

Acknowledgments.—Support of this study by the U. S. Army Research Office (Durham) under Grant No. DA-ARO-D-31-124-G-583 is gratefully acknowledged. The author wishes to thank Dr. Charles H. DePuy for the use of his research laboratory to carry out this study.

(23) H. M. Walborsky and F. M. Hornyak, *J. Amer. Chem. Soc.*, **77**, 6026 (1955).

(24) A. Burger and W. L. Yost, *ibid.*, **70**, 2198 (1948).

(25) G. L. Kreueger, F. Kaplan, M. Orchin, and W. H. Faul, *Tetrahedron Lett.*, 3979 (1965).

(26) J. Smejkal and J. Farkas, *Collect. Czech. Chem. Commun.*, **28**, 1577 (1963).

(27) H. M. Walborsky and L. Plonsker, *J. Amer. Chem. Soc.*, **83**, 2138 (1961).

(28) I. Tömösközi, *Tetrahedron*, **22**, 179 (1966).

(29) J. P. Freeman, *J. Org. Chem.*, **29**, 1379 (1964).

(30) J. P. Clark, Ph.D. Thesis, University of Colorado, 1967.

(31) C. G. Overberger, R. E. Zangaro, and J-P. Anselme, *J. Org. Chem.*, **31**, 2046 (1966).

The Oxidation of Secondary Alcohols in Diethyl Ether with Aqueous Chromic Acid. A Convenient Procedure for the Preparation of Ketones in High Epimeric Purity[1]

HERBERT C. BROWN,* CHANDRA P. GARG,[2] AND KWANG-TING LIU[2]

Richard B. Wetherill Laboratory, Purdue University, Lafayette, Indiana 47907

Received July 1, 1970

Convenient procedures have been developed to convert secondary alcohols into ketones in excellent yield and high epimeric purity utilizing oxidation of the alcohol in diethyl ether with aqueous chromic acid. In one procedure (procedure A) the stoichiometric amount of sodium dichromate and sulfuric acid in water is added to the diethyl ether solution of alcohol at 25–30° and the reaction is continued for 2 hr. In the second procedure (procedure B), especially applicable to strained bicyclic alcohols, a 100% excess of the oxidation agent is used. In this case the reaction is complete in 15 min at 0°. These procedures offer especial promise for the preparation of ketones without accompanying epimerization or loss of isotopic purity.

The oxidation of secondary alcohols by hexavalent chromium derivatives is the most commonly employed method to prepare ketones. Although the oxidation with aqueous chromic acid has long been a standard method,[3] many modified procedures have been developed to simplify the isolation process, to achieve certain selectivity, and to improve the yield as well as the purity of the products.[4]

In the course of studying the direct chromic acid oxidation of organoboranes to ketones in the usual hydroboration solvents (diglyme, tetrahydrofuran, and diethyl ether),[5] it became desirable to explore the oxidation of secondary alcohols in these solvents. To our surprise, the oxidation of secondary alcohols proceeded very simply and cleanly in a two-phase system involving diethyl ether and a water solution of sodium dichromate and sulfuric acid. There appeared to be significant advantages to such an oxidation procedure. Consequently, we decided to undertake a detailed study.

In one early experiment we observed that, when a solution of cyclohexanol was contacted at 25° with an aqueous solution of the calculated quantity of sodium dichromate and sulfuric acid, the cyclohexanol disappeared almost immediately from the ether phase. Evidently, the cyclohexanol must be rapidly esterified and the chromic acid ester is extracted into the aqueous phase. Ketone then begins to appear at a moderate rate and is extracted into the ether phase as it forms. The ether phase then protects the ketone from undesirable side reactions, such as further oxidation or epimerization. Indeed, it proved possible to develop procedures which give nearly quantitative yields of ketones from a wide variety of secondary alcohols, with remarkably low epimerization for derivatives subject to this side reaction.

Results and Discussion

Since the preliminary results with diethyl ether were so promising, we decided to explore a representative range of solvents in order to see which one might be preferable for such oxidations. For these studies *l*-menthol was employed as a representative substrate to explore the relative efficacy of the different solvents. For these initial experiments we utilized the stoichiometric quantity of sodium dichromate and sulfuric acid. This had the advantage that any further oxidation of the ketone or of the solvent by the chromic acid[6,7] could readily be detected through decreased yields of the ketone. Finally, analysis of the product for isomenthone indicated the presence of undesired epimerization.

Gas chromatographic analyses revealed that the use of certain water-miscible solvents, such as diglyme or tetrahydrofuran, was undesirable because they were attacked by chromic acid, resulting in decreased yields of menthone, with considerable epimerization. Water-miscible solvents, relatively stable to chromic acid, gave almost complete oxidation to ketone, but the product contained several per cent of the epimerized ketone, isomenthone. Water-immiscible solvents, such as benzene[8] and *n*-pentane, were stable to the chromic acid but formed severe emulsions which hindered isolation of the product. Finally, we tried a number of oxygen containing solvents immiscible with the aqueous phase. Among these were solvents such as diisopropyl ether, ethyl acetate, and diethyl ketone. However, in these cases there was significant attack by the chromic acid, resulting in considerable amounts of alcohol in the ketone product.

Among the solvents examined, diethyl ether was clearly superior In the presence of this second phase the oxidation proceeded smoothly, with no problem from emulsions. Separation of the ether layer provided for an exceptionally simple recovery of the product from the reaction mixture. Attack of the ether by aqueous chromic acid is evidently quite low, since the menthone product contained only 1.5% of residual alcohol. (Use of excess chromic acid was unfavorable, since a decrease in yield was observed, presumably arising from further oxidation of the ketone product.)

* To whom correspondence should be addressed.

(1) A preliminary report of a portion of this study has been published: H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, **83**, 2952 (1961).

(2) Based in part on the Ph.D. Theses of C. P. Garg (1962) and K.-T. Liu (1968), Purdue University, Lafayette, Ind.

(3) E. Beckmann, *Justus Liebigs Ann. Chem.*, **250**, 322 (1889); L. T. Sandborn, "Organic Syntheses," Coll. Vol. I, Wiley, New York, N. Y., 1941, p 340.

(4) For concise reviews, see L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, pp 142–147; S. R. Sandler and W. Karo, "Organic Functional Group Preparations," Academic Press, New York, N. Y., 1968, pp 169–176. For more recent work, see J. C. Collins, W. W. Hess, and T. J. Katz, *Tetrahedron Lett.*, 3363 (1968).

(5) H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, **83**, 2951 (1961).

(6) K. B. Wiberg, Ed., "Oxidation in Organic Chemistry," part A, Academic Press, New York, N. Y., 1965, Chapter 2.

(7) J. Rocek and A. Riehl, *J. Amer. Chem. Soc.*, **88**, 4749 (1966); **89**, 6691 (1967); *J. Org. Chem.*, **32**, 3569 (1967).

(8) W. F. Bruce, "Organic Syntheses," Coll. Vol. II, Wiley, New York, N. Y., 1943, p 139.

Finally, the *l*-menthone recovered was exceptionally free of isomenthone.

The effect of variations in temperature and reaction times was then explored. The reaction at room temperature (25–30°) appeared to be more favorable than reaction at lower temperatures. At 25° the reaction is essentially over in 45 min. However, longer reaction times were not deleterious. Consequently, it appeared desirable to standardize on a 2-hr reaction time to allow for less reactive alcohols. A standard procedure (procedure A) was then developed. In this procedure, a stoichiometric amount of sodium dichromate and sulfuric acid was dissolved in water and this solution was added over a 15-min period to a solution of the secondary alcohol in diethyl ether at 25–30°. After 2 hr, the organic layer was separated and the product isolated (for details, see Experimental Section). Application of this procedure to some representative alcohols gave, in general, yields of 85–97%. Only in the case of bicyclic alcohols, such as *exo*-norbornanol, were the yields significantly lower. Fortunately, as will be described later, it proved possible to overcome this difficulty through a modified procedure (procedure B). The experimental results with the above procedure are summarized in Table I.

TABLE I

OXIDATION OF ALCOHOLS IN DIETHYL ETHER WITH EQUIVALENT AQUEOUS CHROMIC ACID AT 25°

Alcohol	Yield of ketone, % Glpc	Isolated
3-Methyl-2-butanol	85	
Cyclopentanol	87	
Cyclohexanol	92	
Cyclooctanol	93	
2-Methylcyclohexanol[a]	97	87
l-Menthol[b]	97	84[d]
Isopinocampheol[c]	94	80[e]
exo-Norbornanol	61	

[a] 58% *cis*- and 42% *trans* alcohols. [b] $[\alpha]D$ −48.7°. [c] $[\alpha]D$ −32.4°. [d] $[\alpha]D$ −29.9°. [e] $[\alpha]D$ +10.04°.

It was of interest to compare the epimeric purities of the products from this procedure with those realized in other commonly utilized procedures in the literature.

TABLE II

OXIDATION OF *l*-MENTHOL AND ISOPINOCAMPHEOL BY VARIOUS PROCEDURES

Procedure[a]	Product from *l*-menthol, %[b]		
	Menthol	Isomenthone	Menthol
A	97	Trace	1.5
C	86	4	2
D	90	3	Trace
E	71	3	0
	Product from isopinocampheol, %		
	Isopinocamphone	Pinocamphone	Isopinocampheol
A	94	Trace	0
C	84	4	1
D	86	4	1
E	78	3	0

[a] Procedure A, stoichiometric amount of aqueous chromic acid with alcohol in diethyl ether. Procedure C, chromic acid in acetone: K. Bowden, I. M. Heilborn, E. R. H. Jones, and B. C. L. Weeden, *J. Chem. Soc.*, 39 (1946). Procedure D, aqueous chromic acid.[3] Procedure E, chromic acid in 90% acetic acid at 25°: B. Gastamide, *Ann. Chim. (Paris)*, 9, 257 (1954). [b] Determined by glpc.

l-Menthol and isopinocampheol were selected as test substrates. The results are summarized in Table II.

Alkyl- and aryl-substituted, and deuterium-tagged norbornanones are the necessary starting materials for synthesizing various bicyclo[2.2.1]heptyl alcohols, ester, halides, and olefins, employed in our studies of the nature of norbornyl cation. It follows that the comparatively low yield of ketone in the oxidation of norbornanol and related bicyclic alcohols by the present oxidation procedure constituted a severe handicap. Consequently, we undertook to develop an improved method which would be applicable to these strained bicyclic alcohols. We were led to a satisfactory procedure by the following considerations.

Chromic acid oxidation of secondary alcohol has been considered to proceed *via* the following sequence.[6,9–13]

$$Cr_2O_7^{2-} + H_2O \rightleftharpoons 2HCrO_4^-$$

$$HCrO_4^- + HA + H^+ \rightleftharpoons HCrO_3A + H_2O$$

$$R_2CHOH + HCrO_3A \rightleftharpoons R_2CHOCrO_2A + H_2O$$

$$R_2CHOCrO_2A \xrightarrow{\text{slow}} R_2CO + Cr(IV)$$

$$Cr(IV) + Cr(VI) \xrightarrow{\text{fast}} 2Cr(V)$$

$$R_2CHOH + Cr(V) \xrightarrow{\text{fast}} R_2CO + Cr(III)$$

The Cr(V) species is more powerful than Cr(VI) in the oxidation reaction. Under ordinary conditions it may be responsible for as much as two-thirds of the total oxidation and may lead to unwanted side reactions, such as C–C bond cleavage of secondary alcohols.[6,14] On the other hand, recent findings have

$$(CH_3)_3CCH(OH)C_6H_5 \longrightarrow (CH_3)_3COH + C_6H_5CHO$$

indicated that Cr(IV) may be responsible for the cleavage reaction.[15–17] Consequently, the strained norbornyl derivatives might be easily cleaved by Cr(V) or Cr(IV). Such a side reaction might be decreased in the presence of excess Cr(VI). However, the previous results (*vide supra*) indicated that the use of excess chromic acid decreased the yield of ketone. It appeared that this difficulty might be overcome by running the reaction at lower temperatures and/or shorter time.

Indeed, a series of experiments based on our standard procedure revealed that the yield of norbornanone from *exo*-norbornanol increased when excess chromic acid was used at lower temperature and the reaction was run for shorter periods. The most suitable conditions adopted for such oxidations appeared to be the use of 0°. The oxidizing agent is added to the diethyl ether solution of alcohol over a period of 10 min, the reaction mixture is stirred for 5 min, and the product is recovered by separating the ether layer

(9) D. G. Lee and R. Stewart, *J. Amer. Chem. Soc.*, **86**, 3051 (1964).
(10) K. B. Wiberg and H. Schäfer, *ibid.*, **89**, 455 (1967); **91**, 927, 933 (1969).
(11) R. Stewart and D. G. Lee, *Can. J. Chem.*, **42**, 439 (1964).
(12) D. G. Lee, W. L. Downey, and R. M. Maass, *ibid.*, **46**, 441 (1968).
(13) D. G. Lee and R. Stewart, *J. Org. Chem.*, **32**, 2868 (1967).
(14) J. J. Cawley and F. H. Westheimer, *Chem. Ind. (London)*, 656 (1960).
(15) J. Rocék and A. E. Radkowsky, *J. Amer. Chem. Soc.*, **90**, 2986 (1968).
(16) W. A. Mosher and G. L. Driscoll, *ibid.*, **90**, 4189 (1968).
(17) P. M. Nave and W. S. Trahanovsky, *ibid.*, **92**, 1120 (1970).

and removing the ether (for details, see Experimental Section).

This modified procedure not only gives excellent yields in the oxidation of bicyclo[2.2.1]heptyl alcohols (Table III), but also is applicable to many other

Table III

Oxidation of Alcohols in Diethyl Ether with 100% Excess Aqueous Chromic Acid at 0°

Alcohol	Yield of ketone, % Glpc	Isolated
Cyclohexanol	98	
exo-Norbornanol[a]	85	80
endo-Norbornanol	90	
1-Methyl-*exo*-norbornanol	76	70
1-Methyl-*endo*-norbornanol	89	81
1-Phenyl-*exo*-norbornanol	74	68
7,7-Dimethyl-*exo*-norbornanol[b]	90	80
Isoborneol	99	
Borneol	99	
endo-Fenchyl alcohol	95	

[a] *exo*-3-*d*-*exo*-Norbornanol yielded *exo*-3-*d*-norbornanone retaining over 98% isotopic purity. [b] *exo*-3-*d*-7,7-Dimethyl-*exo*-norbornanol yielded *exo*-3-*d*-7,7-dimethylnorbornanone retaining over 98% isotopic purity.

strained or labile systems, such as bicyclo[3.2.0]heptan-2-ol[18] and 2-isocaranol,[19] for which other oxidation methods proved unsatisfactory, as well as to the more usual alcohols for which the previous procedure is applicable (Table I). More important, no epimerization[19] or loss of isotopic purity has been observed. The yield of ketone is, in general, higher than that realized from other commonly used procedures. A comparison of representative cases is summarized in Table IV.

Table IV

Comparison of Yield of Bicyclo[2.2.1]heptanones from Various Oxidation Procedures

Procedure[a]	Yield of ketone,[b] % *exo*-Norbornanol	*endo*-Norbornanol	1-Methyl-*exo*-norbornanol	1-Phenyl-*exo*-norbornanol
A	61[c]	76[c]	59[d]	
B	85[c]	90[c]	70[d]	68[d]
C		85[e,f]	67[d,f]	51[d,g]
D		79[d,h]		
F		74[c]		

[a] Procedures A, C, and D are described in Table II. Procedure B, 100% excess aqueous chromic acid with alcohol in diethyl ether. Procedure F, chromium trioxide and alcohol in pyridine [Sarett's reagent, see G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 722 (1953)]. [b] Present work unless otherwise mentioned. [c] Determined by glpc. [d] Isolation. [e] Crude product. [f] Reference 23. [g] Reference 25. [h] H. K. Hall, Jr., *J. Amer. Chem. Soc.*, **82**, 1209 (1960).

In applying this procedure to 5,6-dehydronorbornanol, the yield dropped to approximately 60%. Consequently, it would appear that for the oxidation of such acid-sensitive structures this procedure may not be so satisfactory as the application of Sarett's reagent.[20]

(18) W. J. Hammer, Ph.D. Thesis, Purdue University, Lafayette, Ind., 1967.

(19) S. P. Acharya and H. C. Brown, *J. Amer. Chem. Soc.*, **89**, 1925 (1967).

(20) J. G. Atkinson, M. H. Fisher, D. Horley, A. T. Morse, R. S. Stuart, and E. Synnes, *Can. J. Chem.*, **43**, 1614 (1965).

Experimental Section

Glpc Analysis.—All analyses were carried out on a Perkin-Elmer Model 154 vapor fractometer equipped with appropriate columns.

Materials.—Cyclooctanol was obtained by the reduction of cyclooctanone with sodium borohydride. Isopinocampheol was synthesized from the hydroboration–oxidation of α-pinene,[21] and the isopinocamphone prepared by chromic acid oxidation of the alcohol. Isomerization of isopinocamphone gave a mixture of pinocamphone and isopinocamphone.[21] The reduction with lithium trimethoxyaluminohydride[22] yielded 98% pure *endo*-norbornanol, 99% pure 1-methyl-*endo*-norbornanol, and 97% pure *endo*-fenchyl alcohol, respectively, from the corresponding ketones. 1-Methyl-*exo*-norbornanol was prepared by modified procedures of Berson and coworkers.[23,24] Direct oxidation of *exo*-2-methyl-*endo*-norbornanol gave 1-methylnorbornanone.[24] 1-Phenyl-*exo*-norbornanol and 1-phenylnorbornanone were synthesized by modified procedures of Kleinfelter and Schleyer.[24,25] 7,7-Dimethylnorbornanone was prepared *via* hydroboration and oxidation.[26] From *cis*-*exo*-3-acetoxy-7,7-dimethyl-2-norbornylmercuric chloride[26] 7,7-dimethyl-*exo*-norbornanol was obtained from reduction with 2% sodium amalgam in sodium hydroxide and the 3-*exo*-*d* isomer was obtained from reduction with 2% sodium amalgam in sodium deuterioxide.[24] Similarly, 3-*exo*-*d*-*exo*-norbornanol was prepared from *cis*-*exo*-3-hydroxy-2-*exo*-norbornylmercuric chloride.[24] Other alcohols and ketones utilized were commercial samples used without further treatment.

Chromic Acid Solution.—The chromic acid solution used for the oxidation was prepared from the appropriate amount of sodium dichromate and sulfuric acid as indicated by the following equation.

$$3R_2CHOH + Na_2Cr_2O_7 + 4H_2SO_4 \longrightarrow 3R_2CO + Na_2SO_4 + Cr_2(SO_4)_3 + 7H_2O$$

The chromic acid solution is prepared by dissolving 100 g (0.33 mol) of sodium dichromate dihydrate in 300 ml of water. The sulfuric acid (97%), 136 g (1.34 mol), was then added. The solution was then diluted to 500-ml total volume. This solution will oxidize 1.00 mol of secondary alcohol by procedure A or 0.05 mol of secondary alcohol by procedure B.

Oxidation of *l*-Menthol in Diethyl Ether with Stoichiometric Amount of Chromic Acid. A Representative Procedure A.—Diethyl ether, 20 ml, and 7.80 g (50 mmol) of *l*-menthol were placed in a 100-ml three-necked flask fitted with a stirrer, a condenser, and an addition funnel. Chromic acid solution (25 ml) was added to the stirred solution over 15 min, maintaining the temperature at 25–30°. After 2 hr at room temperature, the upper ether layer was separated and the aqueous phase was extracted with two 10-ml portions with ether. The combined ether extracts were washed with saturated sodium bicarbonate and then water. Gas chromatographic analysis on a Carbowax 4000 column indicated 97% *l*-menthone, a trace of isomenthone, and 1.5% menthol. Vacuum distillation through a short Vigreux column gave 6.45 g, 84% yield, of *l*-menthone, bp 66–67° (4 mm), $n^{20}D$ 1.4500, $[\alpha]D$ −29.9° (lit. $n^{20}D$ 1.45038,[27] $[\alpha]D$ −29.6°[28]). Other alcohols listed in Table I were oxidized in the same manner.

Oxidation of 1-Phenyl-*exo*-norbornanol in Diethyl Ether with 100% Excess of Chromic Acid. A Representative Procedure B.—Diethyl ether, 25 ml, and 9.43 g (50 mmol) of 1-phenyl-*exo*-norbornanol were placed in a 300-ml three-necked flask fitted with a stirrer, a condenser, and an addition funnel. This flask was chilled in an ice bath for about 30 min. Chromic acid solution (50 ml) was also cooled in an ice bath for 30 min. This chilled chromic acid solution (25 ml) was added to the stirred solution of alcohol over 5 min while the other portion of chromic acid was still kept in ice bath. Then the second 25 ml of chromic acid was added in another 5 min. After the completion of addi-

(21) G. Zweifel and H. C. Brown, *J. Amer. Chem. Soc.*, **86**, 393 (1964).

(22) H. C. Brown and H. R. Deck, *ibid.*, **87**, 5620 (1965).

(23) J. A. Berson, *et al.*, *ibid.*, **83**, 3986 (1961).

(24) K.-T. Liu, Ph.D. Thesis, Purdue University, Lafayette, Ind., 1968.

(25) D. C. Kelinfelter and P. v. R. Schleyer, *J. Org. Chem.*, **26**, 3740 (1961).

(26) H. C. Brown, J. H. Kawakami, and S. Misumi, *ibid.*, **35**, 1360 (1970).

(27) O. Zeitschel and H. Schmidt, *Chem. Ber.*, **59**, 2298 (1926).

(28) T. Read and G. J. Robertson, *J. Chem. Soc.*, 2209 (1926).

tion, vigorous stirring was continued for an additional 5 min. Then the upper layer was separated, and the lower aqueous layer was extracted with two 15-ml portions of ether. The combined ether extracts were washed once with 5% sodium carbonate and then four times with water. Gas chromatographic analysis on a Carbowax 20M column with benzil as internal standard showed 74% yield of 1-phenylnorcamphor in the absence of any starting alcohol. After the solvent was removed, the remaining oil was carefully fractionally distilled through a 10-cm Vigreux column and the ketone, bp 132–135° (1.5 mm), solidified in the receiver. The yield of this glpc homogeneous 1-phenylnorboranone, mp 41–42° (lit.[25] 40.2–41.0), was 6.37 g (68%).

Other alcohols listed in Table III were oxidized in the same way.

Registry No.—3-Methyl-2-butanol, 598-75-4; cyclopentanol, 96-41-3; cyclohexanol, 108-93-0; cyclooctanol, 696-71-9; *cis*-2-methylcyclohexanol, 7443-70-1; *trans*-2-methylcyclohexanol, 7443-52-9; *l*-menthol, 2216-51-5; isopinocampheol, 1196-00-5; *exo*-norbornanol, 497-37-0; *endo*-norbornanol, 497-36-9; 1-methyl-*exo*-norbornanol, 766-25-6; 1-methyl-*endo*-norbornanol, 3588-21-4; 1-phenyl-*exo*-norbornanol, 14182-93-5; 7,7-dimethyl-*exo*-norbornanol, 26908-71-4; isoborneol, 124-76-5; borneol, 507-70-0; *endo*-fenchyl alcohol, 14575-74-7; chromic acid, 7738-94-5.

Acknowledgment.—Financial support from the Office of Ordnance Research (Contracts DA-33-008-ORD-992 and -2002) and the National Science Foundation (Grant G 19878) is gratefully acknowledged.

Frangomeric and Anchimeric Processes in the Preparation and Reactions of α,β-Epoxy Ketones[1]

D. L. COFFEN* AND D. G. KORZAN

Department of Chemistry, University of Colorado, Boulder, Colorado 80302

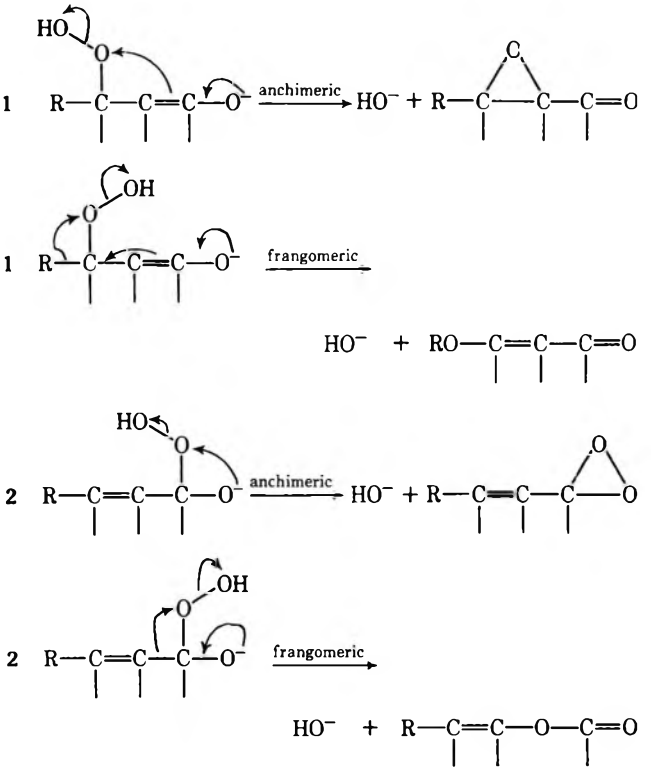
Received July 9, 1970

Four pathways are considered for the reaction of the hydrogen peroxide anion with α,β-unsaturated ketones. One of these pathways leading to α,β-epoxy ketones is well known. Examples of a second pathway, Baeyer–Villiger oxidation, are described with 2-arylmethylene-3-quinuclidinones. The reactions of hydrazine with α,β-epoxy ketones yield either hydroxypyrazolines or allylic alcohols depending on whether the intermediate epoxyhydrazones follow an anchimeric process or a frangomeric process. The former is shown to be preferred with α,β-epoxy ketones in which the β-carbon atom is benzylic and in which a cisoidal conformation of epoxide and ketone functions is accessible.

Heterolytic processes involving interaction between two functional groups may formally proceed by either of two pathways. Electron pairs may shift through an existing framework of chemical bonds or they may move through space, forming a new bond in the process. These two pathways have been described as frangomeric and anchimeric processes, respectively,[2] as an extension of the concept of frangomeric[3] and anchimeric[4] effects. In a formal sense, four reaction pathways could be defined for the reaction of alkaline hydrogen peroxide[5] with an α,β-unsaturated ketone.[6] The hydrogen peroxide anion could add in either the conjugate or direct mode giving either intermediate **1** or **2** and each of these could collapse to products *via* an anchimeric or a frangomeric process (Scheme I).

The first of these pathways leading to α,β-epoxy ketones is familiar and clearly preferred in most systems. The second pathway corresponds to a vinylogous Baeyer–Villiger oxidation but has never, to our knowledge, been observed. The migration of the group R formally entails heterolysis of the R—C bond whence the analogy with the generalized frangomeric process is valid. The third pathway leading to a dioxirane is unknown. The fourth pathway is a normal Baeyer–Villiger oxidation which virtually never occurs under these conditions.[7] However, one possible exception and some low-yield Baeyer–Villiger oxidations of simple ketones under these conditions have been reported.[8] The pathway is

SCHEME I



(1) Synthetic Quinine Analogs. III. Supported by the U. S. Army Medical Research and Development Command, Contract DADA-17-68-C-80-45. Part II: D. L. Coffen and T. E. McEntee, *J. Org. Chem.*, **35**, 503 (1970).

(2) J. W. Wilt and W. J. Wagner, *J. Amer. Chem. Soc.*, **90**, 6135 (1968).

(3) C. A. Grob, *Bull. Soc. Chim. Fr.*, 1360 (1960); *Angew. Chem., Int. Ed. Engl.*, **8**, 535 (1969).

(4) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt-Dryden, New York, N.Y., 1959, Chapter 14.

(5) (a) E. Weitz and A. Scheffer, *Chem. Ber.*, **54**, 2327 (1921); (b) for recent discussion, see R. D. Temple, *J. Org. Chem.*, **35**, 1275 (1970).

(6) With care the reagent can be used to epoxidize base sensitive unsaturated aldehydes: G. B. Payne, *J. Amer. Chem. Soc.*, **81**, 4901 (1959).

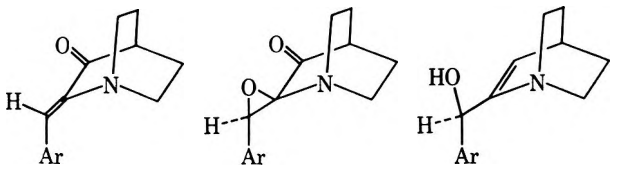
(7) C. H. Hassall, *Org. React.*, **9**, 81 (1957).

(8) H. O. House and R. L. Wasson, *J. Org. Chem.*, **22**, 1157 (1957).

labeled frangomeric purely for the convenience of this discussion.

Although all four of these reaction pathways are feasible, only the first is well known. In the course of a project involving *dl*-quinine and related synthetic antimalarials, we have studied the epoxidation of several α-amino-α,β-unsaturated ketones and have found some clear-cut[9] examples of the fourth pathway.

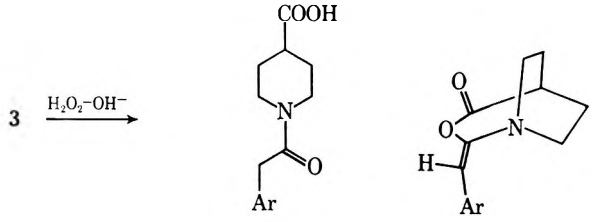
The ketones examined were those with general formula **3**. These compounds are easily prepared by condensing aryl aldehydes with 3-quinuclidinone[10] and could, in principle, be easily converted to antimalarials of the "desvinylquinine type" **5** by epoxidation and reduction with hydrazine.[11]



3 **4** **5**

a, Ar = phenyl
b, Ar = 9-anthryl
c, Ar = 9-phenanthryl
d, Ar = 6-methoxy-4-quinolyl

Although epoxides bearing nitrogen functions on the epoxide ring are known,[12] the epoxidation of α-amino-α,β-unsaturated ketones has not been described previously. β-Amino-α,β-unsaturated ketones respond as vinylogous amides to most reagents and are accordingly inert to alkaline hydrogen peroxide.[13] When the ketones **3a–c** were treated with alkaline hydrogen peroxide in aqueous ethanol, they were smoothly transformed into the *N*-arylacetylisonipecotic acids, **6a–c**, and gave



6a, Ar = phenyl
b, Ar = 9-anthryl
c, Ar = 9-phenanthryl

7

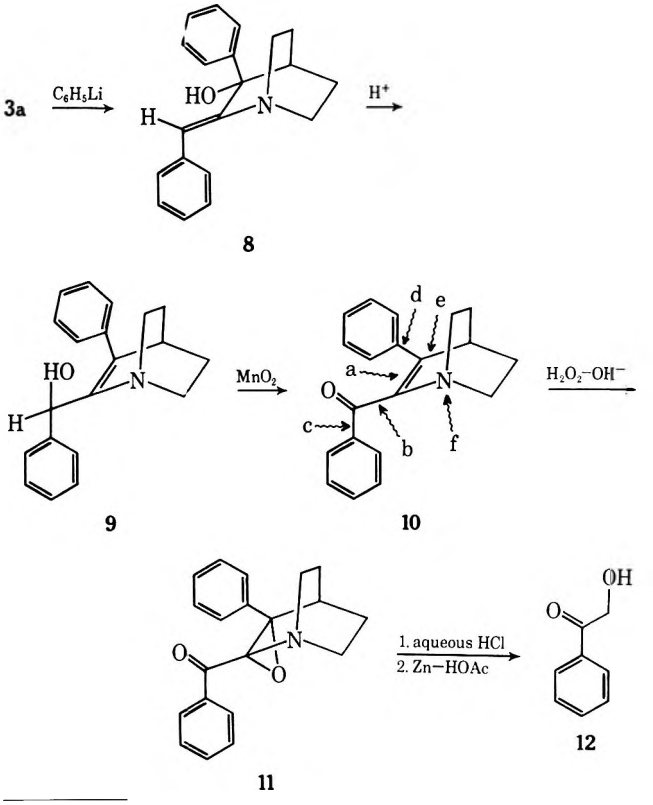
no trace of epoxy ketones **4**. Similar oxidation of **3d** gave only a water-soluble product, presumed to be an amino acid and not isolated. The structures of products **6a–c** were deduced from their analytic and spectroscopic data and were confirmed by synthesizing **6a** and **6b** from isonipecotic acid and the corresponding arylacetyl chlorides.

Thus the hydrogen peroxide anion adds in the direct modes to ketones **3a–c** (and by inference, **d**) giving an intermediate of type **2** which collapses to give the primary products **7** *via* the fourth pathway. Alkaline hydrolysis of the Baeyer–Villiger products **7** yields the isonipecotic acids **6** directly.[14]

The reaction affords an efficient method of transforming aromatic aldehydes into their homologous acids and may, in that respect, have some synthetic utility.

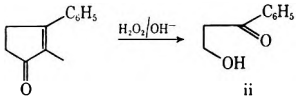
The reaction of the structurally related α-amino-α,β-unsaturated ketone **10** with alkaline hydrogen peroxide was also examined, principally because the fourth pathway would, in this instance, provide ready access to 2-quinuclidinones. 2-Quinuclidinones are rather interesting substances but can only be obtained by a lengthy synthesis.[15] Compound **10** was synthesized from the unsaturated ketone **3a** by sequential treatment of the latter with phenyllithium, hot 10% hydrochloric acid, and manganese dioxide (Scheme II). The allylic rear-

SCHEME II



8 **9** **10** **11** **12**

(9) The alkaline peroxide oxidation of i to ii described by House and Wasson[8] may involve a retrograde aldol reaction before the oxidation step.



ii

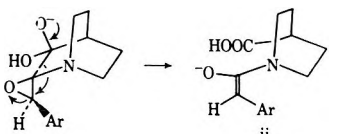
(10) (a) G. R. Clemo and E. Hoggarth, *J. Chem. Soc.*, 1241 (1939); (b) C. A. Grob and A. Kaiser, *Helv. Chim. Acta*, **46**, 2646 (1963); (c) D. R. Bender and D. L. Coffen, *J. Org. Chem.*, **33**, 2504 (1968).

(11) (a) P. S. Wharton and D. H. Bohlen, *ibid.*, **26**, 3615 (1961); (b) Huang-Minlon and Chung-Tungshun, *Tetrahedron Lett.*, 666 (1961).

(12) Aminoepoxide: C. L. Stevens and P. M. Pillai, *J. Amer. Chem. Soc.*, **89**, 3084 (1967). *N*-Acylaminoepoxide: H. Smith, P. Wegfahrt, and H. Rapoport, *ibid.*, **90**, 1668 (1968). Nitroepoxide: H. Newman and R. B. Angier, *Chem. Commun.*, 369 (1969).

(13) For example, 3-amino-5,5-dimethyl-2-cyclohexenone is recovered unchanged after 48-hr exposure to the reagent.

(14) An alternative mechanism involving the epoxy ketones **4** as intermediates was also considered. Attack on the carbonyl group of **4** by a hydroxide ion would produce intermediate i which could fragment to ii in the indicated manner [*cf.* decarboxylation of glycidic acids discussed by E. P. Blanchard and G. Büchi, *J. Amer. Chem. Soc.*, **85**, 955 (1963)]. This mechanism was rejected both because the epoxy ketone **4d**, described later, is inert to alkaline hydrogen peroxide and because, in contradistinction to the rigid stereoelectronic requirements established for such fragmentation processes,[3] the C–C and C–O bonds undergoing cleavage in the process i → ii are virtually orthogonal.



i ii

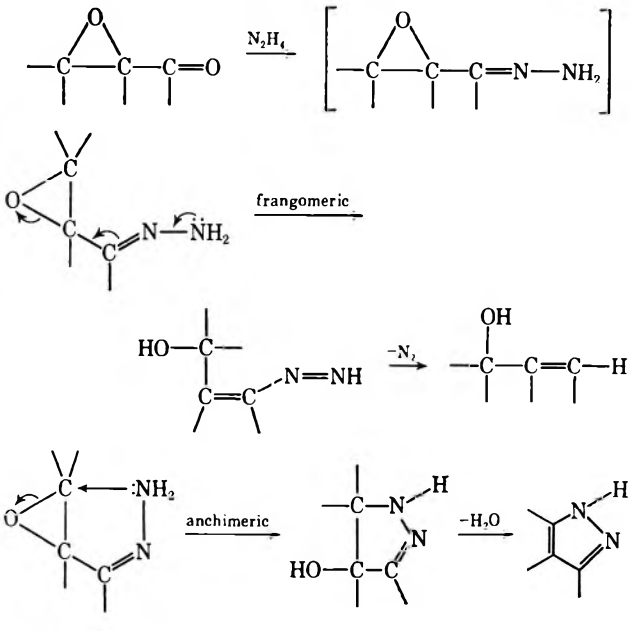
(15) H. Pracejus, *Chem. Ber.*, **92**, 988 (1959); H. Pracejus, M. Kehlen, H. Kehlen, and H. Matschiner, *Tetrahedron*, **21**, 2257 (1965).

rangement of alcohol **8** proceeds readily in high yield and this reaction has subsequently been applied to the synthesis of phenanthrenemethanol antimalarials.[16] Oxidation of ketone **10** proceeded sluggishly but cleanly giving a single product. Analysis and the molecular weight of this product established that the transformation corresponded to the addition of one oxygen atom. This could have been added at any one of the positions indicated with arrows a–f. Acid hydrolysis followed by reduction with zinc in hot acetic acid afforded a low yield of 2-hydroxyacetophenone (**12**). The oxidation product must therefore be the α,β-epoxy ketone **11**.

Since the α-amino-α,β-unsaturated ketone **10** reacts "normally" (first pathway) with alkaline hydrogen peroxide, the preference for the fourth pathway exhibited by the ketones **3** cannot be a consequence of the α-amino group. It is not at present possible to define the structural parameters which determine the choice between these two pathways.

The preference for oxidation *via* the fourth pathway over the first pathway exhibited by ketone **3d** can be reversed by changing (principally the steric bulk) of the oxidizing agent. By using *tert*-butyl hydroperoxide rather than hydrogen peroxide, and acetonitrile and Triton-B as the solvent and base,[17] the oxidation of ketone **3d** proceeded cleanly *via* the first pathway to the epoxy ketone **4d**. Since ketone **3d** is readily available,[10c] a short synthesis of devinylquinine[18] was anticipated at this stage but was thwarted by the subsequent realization that both frangomeric and anchimeric pathways are possible in the reaction of hydrazine with α,β-epoxy ketones (Scheme III). Since the reduction of an

SCHEME III



α,β-epoxy ketone to an allylic alcohol with hydrazine constituted a vital step in our effort to synthesize *dl*-quinine and devinyl analogs, we undertook to establish the structural factors which cause the anchimeric process of Scheme III to prevail in some instances while the frangomeric process prevailed in others.

The results of this investigation permit us to draw the following conclusion. *The anchimeric process leading to a hydroxypyrazoline will prevail with any α,β-epoxy ketone which satisfies both of the following conditions: (a) the ketone and epoxide functions must be cisoidal or have access to the cisoidal conformation; (b) the β-carbon atom must be benzylic. In all other cases the frangomeric process leading to an allylic alcohol will prevail.*

This conclusion was drawn after examination of all available literature[19] on the reactions of hydrazine with α,β-epoxy ketones and after carrying out a series of experiments designed to test it while in the form of a premise. The results with substrates examined during this work and key examples from the literature are presented in Table I.

The reason for the cisoidal conformational requirement is obvious since the anchimeric process is otherwise impossible. Syn–anti isomerism of the hydrazone function could play an important role in this context but there is no evidence that it does. The necessity of having the β-carbon atom benzylic is undoubtedly related to the enhanced S$_N$2 reactivity of groups in a benzylic position.[24] Substituted hydrazines will show different selectivity for the frangomeric and anchimeric processes. Thus, for example, tosylhydrazine gives mainly the anchimeric product with the epoxide of mesityl oxide.[25]

Since both reaction pathways of Scheme III are of synthetic value, the conclusions offered here can con-

(16) Unpublished results.

(17) Conditions described by N. C. Yang and R. A. Finnegan, *J. Amer. Chem. Soc.*, **80**, 5845 (1958).

(18) P. Rabe, *et al.*, *Justus Liebigs Ann. Chem.*, **496**, 151 (1932); *Chem. Ber.*, **74**, 636 (1941); *ibid.*, **76**, 318 (1943). V. Prelog, *et al.*, *ibid.*, **74**, 647 (1941).

(19) The results of reacting hydrazine with epoxy ketones appear to have been first described in 1916.[20] Chalcone oxide and substituted derivatives were observed to give 3,5-diarylpyrazoles *via* diarylhydroxypyrazolines. Several additional examples and analogous reactions were described in subsequent years.[21] In 1961 Wharton and Huang-Minlon[11] independently described the preparation of allylic alcohols by reacting hydrazine with α,β-epoxy ketones. Numerous examples of this reaction have been described since,[22] particularly with steroids and monoterpenes. The frangomeric process delineated in Scheme III was first suggested by Huang-Minlon[11b] as the mechanism leading to allylic alcohols. The manner in which hydrazines react with α-halo ketones[23] makes it highly probable that the epoxyhydrazone is an intermediate and, moreover, vinyl diimides are now known to lose nitrogen spontaneously at room temperature.[23c] Thus this mechanism is probably correct. An alternative reaction pathway, the anchimeric process in Scheme III, is also possible for epoxyhydrazones, this pathway being the one that leads to hydroxypyrazolines and pyrazoles. Since identical reaction conditions can be used, it is reasonable to assume that this same primary intermediate is involved for those substrates which give hydroxypyrazolines and pyrazoles as well. The structures of pyrazoles formed with substituted hydrazines[21] support this assumption.

(20) (a) O. Widman, *ibid.*, **49**, 477 (1916); (b) H. Jörlander, *ibid.*, **49**, 2782 (1916); (c) S. Bodforss, *ibid.*, **49**, 2795 (1916).

(21) W. A. Hutchins, D. C. Motwani, K. D. Mudbhatkal, and T. S. Wheeler, *J. Chem. Soc.*, 1882 (1938); P. P. Dodwadmath and T. S. Wheeler, *Proc. Indian Acad. Sci., Sect. A*, 438 (1935); N. H. Cromwell and R. A. Setterquist, *J. Amer. Chem. Soc.*, **76**, 5752 (1954); A. Padwa, *J. Org. Chem.*, **30**, 1274 (1965).

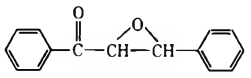
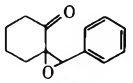
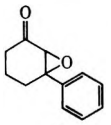
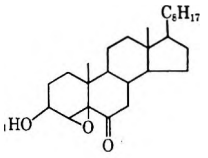
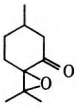
(22) (a) P. S. Wharton, *ibid.*, **26**, 4781 (1961); (b) C. Djerassi, D. H. Williams, and B. Berko, *ibid.*, **27**, 2205 (1962); (c) C. Beard, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, **86**, 269 (1964); (d) K. Klein and G. Ohloff, *Tetrahedron*, **19**, 1091 (1963); (e) W. R. Benn and R. M. Dobson, *J. Org. Chem.*, **29**, 1142 (1964); (f) R. Sciaky and F. Facciano, *Gazz. Chim. Ital.*, **93**, 1014, (1963); (g) S. V. Kessar, Y. P. Gupta, and A. L. Rampal, *Tetrahedron Lett.*, 4319 (1966); (h) G. V. Nair and G. D. Pandit, *ibid.*, 5097 (1966).

(23) (a) P. S. Wharton, S. Dunny, and L. S. Krebs, *J. Org. Chem.*, **29**, 958 (1964); (b) V. R. Mattox and E. C. Kendall, *J. Amer. Chem. Soc.*, **72**, 2290 (1950); (c) B. T. Gillis and J. D. Hagarty, *ibid.*, **87**, 4576 (1965); (d) T. Tsuji and E. M. Kosower, *ibid.*, **91**, 3375 (1969).

(24) A. Streitwieser, "Solvolytic Displacement Reactions," McGraw-Hill, New York, N.Y., 1962, p 13.

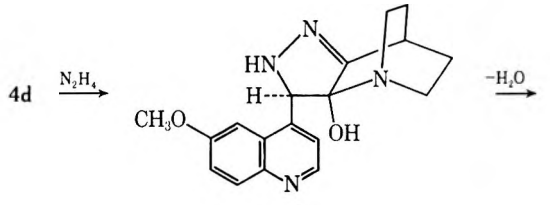
(25) D. P. G. Hamon and L. J. Holding, *Chem. Commun.*, 1330 (1970).

TABLE I
REACTIONS OF SELECTED α,β-EPOXY KETONES WITH HYDRAZINE

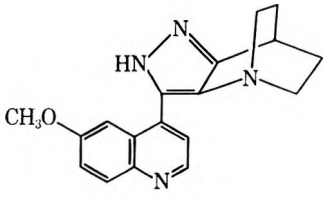
α,β-Epoxy ketone	Cisoidal (accessible)	β carbon benzylic	Product	Yield, %	Ref
	Yes	Yes	Pyrazole		20a
 15	Yes	Yes	Pyrazole (16)	65	This work
 17	No	Yes	Allylic alcohol (18)	92	This work
 19	Yes	No	Allylic alcohol (20)	48	This work
	Yes	No	Allylic alcohol	71.5	22d
	Yes	No	Allylic alcohol	75	22d
	No	No	Allylic alcohol	75	11a

siderably enhance the utility of the reactions of hydrazine with epoxy ketones.[26]

The epoxy ketone **4d**, from which the allylic alcohol was desired, is cleanly transformed into the hydroxypyrazoline **13** with hydrazine in ethanol or into the pyrazole **14**[10c] with hydrazine in hot acetic acid.

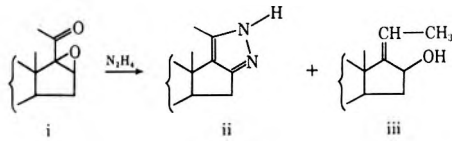


13



14

(26) It should be noted that this, like most generalizations in organic chemistry, has it exceptions. Benzalacetone oxide reacts with hydrazine to give a mixture of allylic alcohol and the expected pyrazole. The steroidal epoxy ketone i gives a small amount of pyrazole ii in addition to the expected allylic alcohol iii.[22e]



i ii iii

Experimental Section[27]

N-**Phenylacetylisonipecotic Acid** (6a). **A. From 2-Phenylmethylene-3-quinuclidinone.**[10b]—Compound **3a** (1.455 g, 6.8 mmol) was placed in 150 ml of ethanol and cooled to 5°. Hydrogen peroxide (4.5 ml, 30%) was added, followed by 10 ml of 5% sodium hydroxide, and the suspension was stirred for 15 hr. Water (30 ml) was then added and the aqueous layer washed with methylene chloride. The aqueous layer was then acidified with dilute hydrochloric acid and extracted three times with methylene chloride. The organic phase was dried over sodium sulfate and evaporated, yielding a clear oil. The pure product (680 mg, 40%) was obtained from ethyl ether as colorless crystals: mp 124–125.5°; ν_{max} (Nujol) 3400, 1705, 1690, 1405, 1300, 1270, 1240, 1210, 1185, 1150, 1030, 945, 925, 723, and 711 cm^{-1}. The nmr spectra of compounds **6a–c** were composed of poorly resolved multiplets which were consistent with the respective structures.

Anal. Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66. Found: C, 67.81; H, 7.02; N, 5.51.

B. From Phenylacetyl Chloride.—The reaction of phenylacetyl chloride with isonipecotic acid using the Schotten–Baumann procedure yielded (41%) material identical (ir, tlc, melting point) with that produced by method A.

2-(9-Anthrylmethylene)-3-quinuclidinone (**3b**).—A slurry of 4.12 g of 9-anthracene carboxaldehyde and 3.23 g of 3-quinuclidinone hydrochloride (20 mmol each) in 50 ml of absolute ethanol was treated with a solution of 1.0 of sodium in 30 ml of absolute ethanol. The mixture was warmed at 50° for 30 min and cooled with resulting formation of yellow crystals. Addition of water and subsequent filtration afforded 5.77 g

(27) Melting points are uncorrected. Nmr spectra were recorded on Varian A-60A and HA-100 instruments using deuteriochloroform as solvent and tetramethylsilane as internal standard. Infrared and mass spectra were recorded on Perkin-Elmer 137 and Atlas CH-5 instruments, respectively. Analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn.

(92%) of yellow powder. Recrystallization from ethanol–chloroform gave yellow needles: mp 284–285°; ν_{max} 1715, 1650, 1325, 1235, 1170, 1100, 993, 887, 850, 842, 812, 783, 738, and 732 cm^{-1}. The nmr spectrum shows quinuclidine proton signals (9 H, multiplet) from 1.9 to 3.1 ppm, aromatic proton signals (9 H, multiplet) from 7.2 to 8.4 ppm, and a vinyl proton signal (1 H, singlet) at 7.52 ppm.

Anal. Calcd for $C_{22}H_{19}NO$: C, 84.31; H, 6.11; N, 4.47. Found: C, 84.40; H, 6.15; N, 4.37.

N-(9-**Anthrylacetyl**)**isonipecotic Acid** (**6b**). **A. From 2-(9-Anthrylmethylene)-3-quinuclidinone** (**3b**).—Compound **3b** (1.00 g) was placed in 150 ml of ethanol and cooled to 5°. Hydrogen peroxide (3 ml, 30%) was added, followed by 5 ml of 5% sodium hydroxide. The suspension was stirred at room temperature for 40 hr with concomitant disappearance of all solid. The ethanol was evaporated and the residue was taken up in a 1:1 water–methylene chloride mixture. The aqueous phase was separated, acidified, and extracted with methylene chloride, which was dried and evaporated. The colorless product (901 mg, 82%) was recrystallized from benzene–methylene chloride: mp 212–214°; ν_{max} 1720, 1595, 1270, 1255, 1195, 1155, 1025, 1015, 925, 895, 870, 732, and 673 cm^{-1}. The product is apparently dimorphic, a form exhibiting a slightly altered infrared spectrum being obtained from some recrystallizations.

Anal. Calcd for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03. Found: C, 76.03; H, 5.86; N, 3.95.

B. From 9-Anthrylacetyl Chloride.—The reaction of 9-anthrylacetyl chloride[28] with isonipecotic acid in *N*-methyl-2-pyrrolidone using triethylamine as the base yielded (64%) material identical (ir, tlc, melting point) with that produced by method A.

2-(9-Phenanthrylmethylene)-3-quinuclidinone (**3c**).—Sodium (0.805 g, 0.035 g-atom) was dissolved in 100 ml of absolute ethanol and was followed by addition of 9-phenanthrene carboxaldehyde (5.15 g, 25 mmol) and 3-quinuclidinone hydrochloride (4.03 g, 25 mmol). The suspension was heated at reflux for 19 hr then cooled and diluted with water. Filtration afforded 7.29 g (92%) of yellow needles: mp 169–171°; ν_{max} 1690, 1615, 1600, 1480, 1320, 1240, 1170, 1095, 928, 885, 850, 764, and 745 cm^{-1}. The nmr spectrum shows quinuclidine proton signals (9 H, multiplet) from 1.9 to 3.3, aromatic proton signals (9 H, multiplet) from 7.3 to 8.8, and a vinyl proton signal (1 H, singlet) at 6.27 ppm.

Anal. Calcd for $C_{22}H_{19}NO$: C, 84.31; H, 6.11; N, 4.47. Found: C, 84.58; H, 6.31; N, 4.56.

N-(9-**Phenanthrylacetyl**)**isonipecotic Acid** (**6c**).—A slurry of compound **3c** (995 mg, 3.2 mmol) in 70 ml of 95% ethanol was cooled to 5°. Hydrogen peroxide (3 ml, 30%) was then added followed by 5 ml of 5% sodium hydroxide, and the mixture was stirred for 15 hr. The residue, after evaporation of the solvent, was taken up in 30 ml of water, acidified with dilute hydrochloric acid, and extracted with methylene chloride. The extract was dried and evaporated, and the resulting solid was recrystallized as colorless prisms (677 mg, 60%) from benzene–methylene chloride: mp 199–201°; ν_{max} 1725, 1595, 1275, 1255, 1195, 1165, 1100, 1025, 948, 927, 810, 747, and 674 cm^{-1}.

Anal. Calcd for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03. Found: C, 76.22; H, 6.16; N, 3.91.

2-Phenylmethylene-3-phenyl-3-hydroxyquinuclidine (**8**).—A suspension of 2-phenylmethylene-3-quinuclidinone[10b] (12.0 g, 0.056 mol) in ether (240 ml) was slowly treated with 1.91 *M* phenyllithium (40 ml, 0.066 mol) in 1:1 ether–benzene. The resulting solution was immediately quenched by the dropwise addition of water (50 ml). The organic layer was separated and combined with three ether extracts of the aqueous layer. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated giving a pale yellow oil. Crystallization from Skellysolve B afforded colorless crystals (8.80 g, 54%): mp 105–106°; ν_{max} 3540, 1650, 1600, 1480, 1225, 1190, 1035, 1015, 973, 896, 881, 858, and 821 cm^{-1}; nmr 1.2–3.3 (9 H, multiplet, quinuclidine H), 6.2 (1 H, singlet, vinyl H), and 7.2–8.0 ppm (10 H, multiplet, aromatic H); mol wt 291 (mass spectrum).

2-Phenylhydroxymethyl-3-phenyl-2-quinuclidinene (**9**).—A suspension of alcohol **8** (8.80 g, 0.03 mol) in 10% hydrochloric acid (90 ml) was heated at reflux for 1 hr and then refrigerated overnight. The hydrochloride of alcohol **9** which crystallized out was filtered and dried giving 9.22 g (96%) of colorless crystals. The free base was obtained by shaking the hydrochloride with saturated sodium bicarbonate solution followed by threefold extraction with methylene chloride. The organic phase was dried and evaporated yielding 8.81 g of colorless solid. A sample recrystallized from ethanol had mp 122–122.5°: ν_{max} 3050, 1600, 1485, 1315, 1295, 1185, 1135, 1118, 1015, 970, 800, 778, and 736 cm^{-1}; nmr 1.5–2.0 and 2.7–3.0 (9 H, multiplets, quinuclidine H), 5.6 (1 H, singlet, secondary alcohol), and 7.3 ppm (10 H, broad singlet, aromatic H); mol wt 291 (mass spectrum).

2-Benzoyl-3-phenyl-2-quinuclidinene (**10**).—A solution of alcohol **9** (3 g, 10.4 mmol) in methylene chloride (200 ml) was treated with activated manganese dioxide (30 g) and stirred vigorously for 3 days. The solid was filtered out and washed with more methylene chloride. The filtrate and washings were evaporated leaving a colorless solid (100%). Recrystallization from ethanol gave colorless crystals: mp 142–143°; ν_{max} 1650, 1600, 1580, 1260, 1240, 1143, 933, 925, 760, and 740 cm^{-1}; nmr 1.6–2.0 and 2.7–3.3 (9 H, multiplets, quinuclidine H), 7.0–7.4 and 7.6–7.8 ppm (10 H, multiplets, aromatic H); mol wt 289 (mass spectrum).

Anal. Calcd for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found: C, 83.30; H, 6.59; N, 4.80.

2-Benzoyl-3-phenyl-2,3-oxidoquinuclidine (**11**).—A solution of ketone **10** (250 mg) in methanol (12 ml) was treated with 30% hydrogen peroxide (0.85 ml). Sodium hydroxide solution (1.2 ml, 4 *N*) was added and the resulting solution heated at reflux for 62 hr. Water was added slowly with swirling until crystallization commenced and 107 mg (40%) of colorless crystals were collected by filtration. An analytical sample recrystallized from ethanol, had mp 137–138°: ν_{max} 1680, 1600, 1575, 1490, 1310, 1265, 1235, 1122, 1010, 924, 873, 854, and 762 cm^{-1}; nmr 1.4–3.6 (9 H, multiplets, quinuclidine H), 7.2–7.6 and 7.9–8.2 ppm (10 H, multiplet, aromatic H); mol wt 305 (mass spectrum).

Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.82; H, 6.41; N, 4.41.

Degradation of Epoxide 11.—A solution of epoxide **11** (2.00 g, 6.6 mmol) in 10% hydrochloric acid (300 ml) was heated at reflux for 1 hr. Overnight refrigeration yielded a light yellow solid which was separated by filtration and washed with water (1.05 g, 44%). A solution of this solid in methanolic silver nitrate (1%) gave a colorless precipitate, indicating an amine hydrochloride. An analytical sample recrystallized from methanol had mp 181–186°: ν_{max} 3300, 1710, 1680, 1620, 1595, 1265, 1140, 942, 910, and 710 cm^{-1}. Neutralization with aqueous sodium bicarbonate gave an oil containing three compounds. This mixture was reconvertible to amine hydrochloride by treatment with 10% hydrochloric acid in the manner described above.

Anal. Calcd for $C_{20}H_{22}NO_3Cl$: C, 66.75; H, 6.16; N, 3.89. Found: C, 66.92; H, 6.23; N, 3.91.

A solution of this amine hydrochloride (320 mg, 0.90 mmol) in glacial acetic acid (30 ml) was cooled in an ice bath and activated zinc (3.0 g, 0.046 g-atom) was added. The resulting suspension was stirred vigorously for 20 hr at room temperature. Most of the acetic acid was evaporated *in vacuo* and 10% hydrochloric acid (30 ml) was added. Threefold extraction was carried out with methylene chloride and the organic phase was dried over anhydrous sodium sulfate and evaporated, yielding a yellow oil (241 mg). Distillation of this oil in a Kugelrohr apparatus [100° (0.1 mm)] gave a colorless solid (6 mg) which was collected on a cooled portion of the glass receiver. The crystals, which had mp 85–87°, exhibited ν_{max} 3400, 1690, 1600, 1580, 1320, 1290, 1235, 1105, 762, 753, and 687 cm^{-1}; the mass spectrum (mol wt 136) exhibited major peaks at *m/e* 136, 122, 105, and 77. All obtainable data agreed with those of an authentic sample of α-hydroxyacetophenone (mp 86–87°). A thin layer chromatographic comparison, using two different solvent systems (1% methanol–chloroform and 5% ether–chloroform), confirmed that the product is α-hydroxyacetophenone.

6′-Methoxy-8,9-oxido-7-ketorubane (**4d**).—To a solution of α,β-unsaturated ketone **3d** (1.00 g, 3.40 mmol) in acetonitrile (50 ml) was added 0.44 ml of *tert*-butyl hydroperoxide and four drops of Triton B (35% methanolic). After 20 hr at room temperature, yellowish crystals (466 mg, 45%) formed, which were separated by filtration. Unoxidized starting material was recrystallized from the mother liquor (367 mg). Small amounts of starting material were removed from the pulverized product by leaching with boiling tetrahydrofuran. The resulting colorless powder had mp 159–161°: ν_{max} 1735, 1615, 1590, 1500,

(28) F. H. C. Stewart, *Aust. J. Chem.*, **13**, 478 (1960).

1225, 1023, 993, 860, 845, 817, and 716 cm^{-1}; nmr[29] 0.75–3.9 (multiplet, quinuclidine H), 4.9 (singlet, methoxy H), 5.27 (singlet, HCO), 6.9–7.8 (3 multiplets, aromatic H); mol wt 310 (mass spectrum).

Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.88; H, 5.92; N, 8.91.

5-(6-Methoxy-4-quinolyl)-3,4-(1,4-piperidylidene)-4-hydroxy-2-pyrazoline (13).—A solution of epoxy ketone **4d** (50 mg, 0.16 mmol) and anhydrous hydrazine (0.1 ml) in absolute ethanol (2 ml) was heated at reflux for 2 hr. The solution was diluted with water (5 ml) and extracted three times with methylene chloride. The extracts gave, when dried and evaporated, 53 mg (100%) of a tan solid. This was recrystallized from benzene to give a sample with mp 173–175°: ν_{max} 3310, 1645, 1625, 1535, 1505, 1345, 1255, 1168, 1110, 1035, 865, and 817 cm^{-1}; nmr 1.5–2.0 and 2.4–3.0 (9 H, multiplets, quinuclidine H), 3.87 (3 H, singlet, methoxy H), 4.05 (1 H, singlet, pyrazoline CH), 7.3 (3 H, multiplet quinoline H), 7.97 and 8.73 ppm (2 H, doublets, quinoline H); mol wt 324 (mass spectrum). Attempts to prepare an analytically pure sample caused partial dehydration to the pyrazole **14**.

5-(6-Methoxy-4-quinolyl)-3,4-(1,4-piperidylidene)pyrazole (14).—A solution of epoxy ketone **4d** (50 mg, 0.161 mmol) and anhydrous hydrazine (0.1 ml) in glacial acetic acid (3 ml) was heated at reflux for 2 hr. The solvent was evaporated *in vacuo* and the colorless residue was treated with saturated sodium carbonate solution. Threefold extraction with methylene chloride followed by drying and evaporation of the extract gave 55 mg (100%) of a light brown solid. Recrystallization from methylene chloride–ether gave brownish-white crystals with mp 230–234° (lit.[10c] mp 239–243°). The infrared spectrum and tlc behavior of this product were identical with those of an authentic sample prepared from ketone **3d** by sequential treatment with hydrazine and mercuric acetate.[10c]

2-Phenylmethylenecyclohexanone Oxide (15).—A solution of 2-phenylmethylenecyclohexanone[30] (2.00 g, 0.01 mol) and 30% hydrogen peroxide (1.5 ml) in ethanol (50 ml) was treated with 20% sodium hydroxide solution (1.0 ml) and kept at room temperature for 6 hr. Water was then added slowly until the solution became cloudy. The mixture was refrigerated overnight then filtered to give 1.19 g (56%) of pale yellow needles. Recrystallization from ethanol gave colorless needles with mp 125–126°: ν_{max} 1710, 1600, 1265, 1152, 1130, 1118, 938, 878, 846, 777, and 750 cm^{-1}; nmr 1.4–2.7 (8 H, multiplet, alicyclic H), 4.1 (1 H, singlet, epoxide H), and 7.3 ppm (5 H, singlet, aromatic H); mol wt 202 (mass spectrum).

Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.45; H, 7.03.

3,4-Tetramethylene-5-phenylpyrazole (16).—Anhydrous hydrazine (0.6 ml) was added to a solution of epoxy ketone **15** (305 mg) in absolute ethanol (12 ml). The solution was heated at reflux for 2 hr and water was then added slowly with swirling causing the product to precipitate. This was filtered out giving 201 mg (65%) of colorless solid. Recrystallization from ethanol afforded a sample with mp 123–126°: ν_{max} 3150, 1600, 1365, 1263, 1145, 1045, 983, 933, and 768 cm^{-1}; nmr 1.5–1.9 (4 H, multiplet), 2.3–2.8 (4 H, multiplet), and 7.1–7.8 ppm (5 H, multiplet, aromatic H); mol wt 198 (mass spectrum).

Anal. Calcd for $C_{13}H_{14}N_2$: C, 78.75; H, 7.12; N, 14.13. Found: C, 78.93; H, 7.19; N, 14.25.

3-Phenyl-2,3-oxidocyclohexanone (17).—A solution of 3-phenyl-2-cyclohexenone[31] (2.00 g, 0.01 mol) in methanol (30 ml) was treated with 30% hydrogen peroxide (4.0 ml), cooled to 5° and treated dropwise with 4 *N* sodium hydroxide solution (4.0 ml). After stirring for 24 hr, the solution was filtered, diluted with water, and extracted three times with ether. The residue from the dried extract was distilled [125° (2 mm)] giving 502 mg (23%) of a colorless oil which crystallized when chilled. The product had mp 49–50°: ν_{max} 1705, 1485, 1320, 1260, 975, 805, 790, and 750 cm^{-1}; nmr 1.7–2.6 (6 H, multiplet, alicyclic H), 3.26 (1 H, singlet, epoxide H), and 7.35 (5 H, singlet, aromatic H); mol wt 188 (mass spectrum).

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43; O, 17.00. Found: C, 76.36; H, 6.54; O, 17.27.

1-Phenyl-2-cyclohexenol (18).—Anhydrous hydrazine (0.5 ml) was added to a solution of epoxy ketone **17** (250 mg, 1.23 mmol) in absolute ethanol (10 ml) and the solution was heated at reflux for 2 hr. Dilution with water (75 ml) followed by threefold extraction with ether afforded 213 mg (92%) of colorless oil. Distillation [110° (1 mm)] gave a product which crystallized. Recrystallization from Skellysolve B gave a sample with mp 42–43°: ν_{max} 3360, 1600, 1485, 1310, 1080, 1045, 1005, 960, 760, and 736 cm^{-1}; nmr 1.3–2.2 (6 H, multiplet, aliphatic H), 5.5–6.1 (2 H, multiplet, vinyl H), and 6.9–7.6 ppm (5 H, multiplet, aromatic H); mol wt 174 (mass spectrum). This material deteriorated rather quickly at room temperature precluding analysis.

3-Hydroxy-4,5-epoxycholestan-6-one (19).—A solution of 3β-acetoxy-Δ^4-cholesten-6-one[32] (500 mg, 1.25 mmol) in methanol (20 ml) was treated with 5% methanolic sodium hydroxide (1.0 ml) and 30% hydrogen peroxide (0.5 ml). The solution was kept at room temperature for 24 hr and then diluted with water (50 ml) and extracted three times with methylene chloride. Evaporation of the dried extract left 467 mg (91%) of colorless oil which solidified on standing. This product showed ν_{max} 3480, 1715, 1262, 1225, 1175, 1070, 975, 898, 867, 818, and 798 cm^{-1}; nmr 0.6–2.3 (39 H, multiplet), 3.2–3.4 (2 H, multiplet), and 3.6–4.2 (2 H, multiplet); mol wt 416 (mass spectrum).

3β,4β-Dihydroxy-Δ^5-cholestene (20).—Anhydrous hydrazine (0.5 ml) was added to a solution of epoxy ketone **19** (300 mg) in absolute ethanol (10 ml) and the resulting solution was heated at reflux for 2 hr. Water was then added gradually to the solution and the product extracted into methylene chloride. Evaporation of the dried extract left 345 mg of pale yellow solid which showed a single spot on tlc. This product was purified by recrystallization from ethanol. The resulting colorless crystals (140 mg, 48%) had mp 175–176° (lit.[33] mp 174–176°): ν_{max} 3400, 1670, 1070, 1040, 965, 916, 903, 855, 838, and 757 cm^{-1}; nmr 0.7–2.4 (41 H, multiplet), 4.0–4.2 (2 H, multiplet), and 5.65 ppm (1 H, multiplet, vinyl H); mol wt 402 (mass spectrum).

Anal. Calcd for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.46; H, 11.63.

Registry No.—**3b**, 26965-30-0; **3c**, 26965-31-1; **4d**, 27006-04-8; **6a**, 26965-32-2; **6b**, 26965-33-3; **6c**, 26965-34-4; **8**, 26965-35-5; **9**, 26965-36-6; **10**, 27005-95-4; **11**, 26965-37-7; **13**, 26965-38-8; **15**, 13243-58-8; **16**, 27005-96-5; **17**, 27005-97-6; **18**, 26965-40-2; **19**, 20951-85-3; **20**, 17320-10-4.

Acknowledgment.—D. G. K. thanks the Continental Oil Company for a predoctoral fellowship in chemistry (1969–1970).

(29) This nmr spectrum was recorded with a CAT because of poor solubility and was not integrated.

(30) D. Vorländer and K. Kurze, *Chem. Ber.*, **59**, 2078 (1926).

(31) G. N. Walker, *J. Amer. Chem. Soc.*, **77**, 3664 (1955).

(32) I. M. Heilbron, E. R. H. Jones, and F. S. Spring, *J. Chem. Soc.*, 801 (1937). We are indebted to Professor A. Hassner for a generous sample of this compound.

(33) O. Rosenheim and W. W. Starling, *ibid.*, 377 (1937).

The Displacement of Nitrite Ion in Nitrobenzenes by Sodium Thiolates[1]

JACOB B. BAUMANN

Department of Chemistry, Pennsylvania State University, Schuylkill Campus, Schuylkill Haven, Pennsylvania 17972

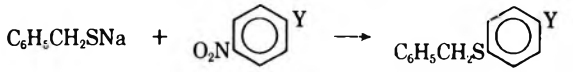
Received June 11, 1970

The reaction of sodium α-toluenethiolate or sodium 1-dodecanethiolate with substituted nitrobenzenes in *N,N*-dimethylformamide led to the production of alkyl aryl sulfides by displacement of the nitro group. The reaction was successful with ethyl *p*-nitrobenzoate and $C_6H_5CH_2S^-$, with methyl *o*-nitrobenzoate, *p*-nitrobenzaldehyde, and *p*-nitrobenzonitrile and $CH_3(CH_2)_{11}S^-$, and with methyl *p*-nitrobenzoate and *p*-nitrobenzophenone with both thiolate salts. The effect of concentration, solvent, and temperature on the yield was investigated.

Recently, we discovered that sodium α-toluenethiolate and methyl *p*-nitrobenzoate react, with loss of nitrite ion, to form methyl *p*-(benzylthio)benzoate (eq 1, compound **1**). The literature contains few examples of the synthesis of aromatic sulfides by nucleophilic substitution upon substrates containing functional groups.[2] There are only a small number of reported cases in which a nitro group has been replaced from disubstituted benzenoid hydrocarbons,[3-10] even though it is one of the most labile substituents.[11,12] This is no doubt due to the fact that it also has a very strong activating effect toward nucleophilic displacement of other substituents on an aromatic nucleus. With two exceptions,[3,4] only dinitro compounds are reported to have undergone loss of nitrite ion. The formation of **1** was thus unusual and an investigation of this reaction as a method of preparing substituted aryl sulfides was undertaken.

Results

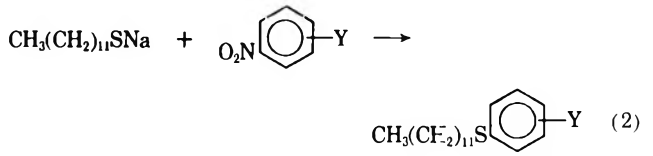
Initial experiments were carried out using the sodium salt of α-toluenethiol (benzyl mercaptan) as the nucleophile and various para-substituted nitrobenzenes as substrates. Successful syntheses are outlined in eq 1. At-



(1)

1, Y = CO_2CH_3
2, Y = $CO_2C_2H_5$
3, Y = $C_6H_5C{=}O$

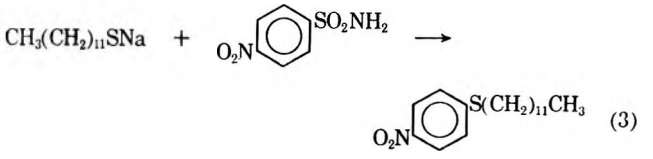
tempts to prepare sulfides from *p*-nitrobenzamide and from *p*-nitrobenzaldehyde using sodium α-toluenethiolate in refluxing DMF (*N,N*-dimethylformamide) failed. It was then assumed that the α-toluenethiolate anion might be susceptible to oxidation at the benzyl carbon, preventing the success of the synthesis with certain substrates. Sodium 1-dodecanethiolate, of comparable nucleophilicity,[13] was therefore chosen for use in further experiments. Syntheses of sulfides which were accomplished with this salt are shown in eq 2.



(2)

4, Y = *p*-CO_2CH_3
5, Y = *p*-$C_6H_5C{=}O$
6, Y = *p*-CN
7, Y = *p*-CHO
8, Y = *o*-CO_2CH_3

The reaction of *p*-nitrobenzenesulfonamide and sodium 1-dodecanethiolate yielded dodecyl *p*-nitrophenyl sulfide (eq 3) *via* replacement of the sulfonamide function.



(3)

Oxidation of the thiolate anion can be the major reaction, as demonstrated by the conversion of sodium 1-dodecanethiolate to dodecyl disulfide when the salt was treated with methyl *m*-nitrobenzoate, or when it reacted with *p*-nitrobenzamide. Products from the reactions of various nitrobenzenes are summarized in Table I.

Relative Reactivity of Nitro Compounds.—An evaluation of the effectiveness of substituents in promoting the displacement of the nitro group may be made from Table I, comparing the formation of compounds **4**, **5**, **6**, and **7**, and of compounds **2** and **3** at the same concentration, temperature, and reaction time. These results, combined with the fact that the formation of the aldehyde **7** was successful at 25° while sodium 1-dodecanethiolate was oxidized to dodecyl disulfide by *p*-nitrobenzamide at 25°, lead to two similar orders of reactivity for para-substituted nitro compounds. These orders are, for $C_6H_5CH_2S^-$, $C_6H_5C{=}O > CO_2C_2H_5$; for $CH_3(CH_2)_{11}S^-$, $CN > C_6H_5C{=}O > CO_2CH_3 > CHO > CONH_2$. It is not unexpected that this does not parallel the established order for aromatic nucleophilic substitution,[14,15] since side reactions such as nucleophilic attack on the functional group or reduction of the nitro substituent are certain to compete effectively. The order given may be regarded as an empiri-

(1) Supported by grants from the Central Fund for Research, Pennsylvania State University.
(2) R. Adams and A. Ferretti, *J. Amer. Chem. Soc.*, **81**, 4927 (1959).
(3) W. Reinders and W. E. Ringer, *Recl. Trav. Chim. Pays-Bas*, **18**, 326 (1899).
(4) W. E. Ringer, *ibid.*, **18**, 330 (1899).
(5) H. H. Hodgson and E. R. Ward, *J. Chem. Soc.*, 2017 (1948).
(6) H. H. Hodgson and E. R. Ward, *ibid.*, 1187 (1949).
(7) H. H. Hodgson and E. R. Ward, *ibid.*, 1316 (1949).
(8) E. R. Ward and L. A. Day, *ibid.*, 398 (1952).
(9) B. A. Bolto and J. Miller, *Aust. J. Chem.*, **9**, 74 (1956).
(10) J. F. Bunnett, E. W. Garbisch, Jr., and K. M. Pruitt, *J. Amer. Chem. Soc.*, **79**, 385 (1957).
(11) J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 273 (1951).
(12) H. Suhr, *Chem. Ber.*, **97**, 3268 (1964).
(13) B. Dmuchovsky, F. B. Zienty, and W. A. Vrendenburgh, *J. Org. Chem.*, **31**, 865 (1966).
(14) R. L. Heppolette and J. Miller, *Chem. Ind. (London)*, 1457 (1954).
(15) J. Miller, *J. Amer. Chem. Soc.*, **76**, 448 (1954).

TABLE I

REACTION CONDITIONS FOR SULFIDE PREPARATIONS IN *N,N*-DIMETHYLFORMAMIDE[a]

Nitrobenzene substituent	Sodium thiolate	Mol of reactants	Time, hr	Yield %	Procedure
p-CO_2CH_3	α-Toluene	0.034	1	36	A[b,c]
p-CO_2CH_3	α-Toluene	0.017	4	39	C[c]
p-$CO_2C_2H_5$	α-Toluene	0.010	2	10	A
p-$C_6H_5C{=}O$	α-Toluene	0.010	2	31	A
p-CO_2CH_3	Dodecyl	0.020	2	31	B
p-CO_2CH_3	Dodecyl	0.010	2	14	A
p-$C_6H_5C{=}O$	Dodecyl	0.010	2	31	A
p-CN	Dodecyl	0.010	2	53	A
p-CHO	Dodecyl	0.010	2	0	A
p-CHO	Dodecyl	0.040	48	53	D[d]
p-$CONH_2$	Dodecyl	0.010	2	0	A
p-$CONH_2$	Dodecyl	0.010	24	0[e]	D[d]
p-SO_2NH_2	Dodecyl	0.010	2	0[f]	A
p-SO_2NH_2	Dodecyl	0.010	48	0[g]	D[d]
o-CO_2CH_3	Dodecyl	0.050	48	23	D[d,h]
m-CO_2CH_3	Dodecyl	0.050	48	0[i]	D[c,d]

[a] All reactions were carried out using 50 ml of DMF unless otherwise noted. [b] Reaction open to air. [c] 100 ml of DMF used. [d] At 25°; other reactions at 155°. [e] 29% yield of dodecyl disulfide, based on moles of thiolate. [f] 30% yield of dodecyl *p*-nitrophenyl sulfide. [g] 33% yield of dodecyl *p*-nitrophenyl sulfide. [h] 75 ml of DMF used. [i] 54% yield of dodecyl disulfide.

cal one which includes side reactions peculiar to each compound.

Effect of Reaction Conditions.—A study of the effect of concentration, temperature, and reaction time is contained in Table II.

TABLE II

FORMATION OF METHYL *p*-(DODECYLTHIO)BENZOATE IN *N,N*-DIMETHYLFORMAMIDE[a]

Expt	Mol of reactants	Time, hr	Yield, %
I	0.010	2	7[b,c]
II	0.010	2	13[c,d]
III	0.010	2	14[c-e]
IV	0.010	48	26[d,f]
V	0.020	2	31[b,c]
VI	0.050	48	12[d,f]

[a] All reactions in 50 ml of solvent except experiment VI which was carried out in 75 ml. [b] Thiolate salt formed *in situ* (procedure B). [c] At 155°. [d] Thiolate salt prepared previously (procedure A). [e] Reaction open to air. [f] At 25°.

Comparison of experiments I and II shows that use of previously prepared thiolate salt results in increased yield, compared to *in situ* formation. Increasing the concentrations of the reactants increased the yield for reactions at 155° (experiments I and V). A similar increase in yield was not obtained in reactions carried out at room temperature (experiments IV and VI). The displacement is favored at low concentrations by a long reaction time at 25° (experiment IV) rather than a few hours at reflux (155°) (experiment II). There was no difference in the yields when the reaction was open to air (experiment III) compared to the same conditions under a nitrogen atmosphere (experiment II). Table I shows that there was only a small reduction in the yield of methyl *p*-(benzylthio)benzoate due to exposure to air. We conclude that oxidation of the thiolate anion by atmospheric oxygen is not an important side reaction, if it occurs at all.

Effect of Solvent.—Table III shows the effect of three solvents upon the reaction of sodium 1-dodecanethiolate and methyl *p*-nitrobenzoate. Dimethyl sulfoxide showed no advantage over *N,N*-dimethylformamide although it is nearly four times as effective in promoting the reaction between *p*-dinitrobenzene and piperidine.[16] Oxidation of the thiolate anion to dodecyl disulfide occurred readily in sulfolane.

TABLE III

PER CENT YIELDS OF PRODUCTS OF THE REACTION OF SODIUM 1-DODECANETHIOLATE AND METHYL *p*-NITROBENZOATE IN VARIOUS SOLVENTS[a]

Products	DMF	DMSO[b]	Sulfolane[c]
Methyl *p*-(dodecylthio)benzoate	14	14	0
Dodecyl disulfide	0	0	43

[a] All data for 140°, reaction time 2 hr, initial concentration 0.20 *M*. [b] Dimethyl sulfoxide. [c] Tetramethylene sulfone.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are corrected. Boiling points are uncorrected. Infrared spectra were measured in a Perkin-Elmer 237B grating spectrophotometer. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Sulfolane used was Sulfolane-W, a gift from Shell Chemical Co. Other solvents were commercial reagent grade products. Preparation of sodium α-toluenethiolate, sodium 1-dodecanethiolate, and *p*-nitrobenzophenone is described below. Other organic compounds used were highly quality commercial products. The boiling point of the petroleum ether used is 30–60°. Baker silica gel was used for column chromatography.

Unless otherwise noted all reactions were carried out under nitrogen. Nitrogen was passed through the apparatus while it was flamed dry and for 10 min thereafter. Following the addition of the solvent and all reactants, nitrogen was passed in for 10 min, maintaining a flow rate sufficient to flush the apparatus thoroughly. Procedures used for the isolation of the crude products from various reactions are outlined below.

Procedure A.—The nitro compound, the thiolate salt, and the solvent were heated and then maintained at an elevated temperature. At the end of the reaction period the solvent was removed *in vacuo*.

Procedure B.—The thiol was dissolved in the solvent and heated with an equimolar amount of sodium metal until the reaction was completed. The solution was cooled, the nitro compound was added, and the mixture was then heated to the desired temperature. After the reaction was completed, the solvent was removed at reduced pressure.

Procedure C.—The thiolate was formed *in situ* as in procedure B. Isolation of the crude product was accomplished by the addition of water (twice the volume of the solvent used).

Procedure D.—The nitro compound, the thiolate salt, and the solvent were stirred at room temperature. Addition of water (twice the volume of the solvent used) resulted in separation of the product mixture.

Methyl *p*-(Dodecylthio)benzoate (4) (Tables II, III).—Extraction of the residue from evaporation using 50 ml of boiling methanol gave the crude ester, typical mp 62–64° after one recrystallization from petroleum ether.

Dodecyl Disulfide (Table III).—The crude residue was boiled with 50 ml of methanol and the hot solution was filtered from an oil, which crystallized upon standing. The product was recrystallized from 1-propanol, mp 32.0–34.0° (lit.[17] mp 34°).

Methyl *p*-(Benzylthio)benzoate (1).—One recrystallization of the impure product from methanol yielded 1.7 g (39%) of the ester, mp 88.4–90.4°, ir (CCl_4) 1725 cm^{-1}. An analytical sample was obtained after three additional recrystallizations, mp 90.4–91.9°.

Anal. Calcd for $C_{15}H_{14}O_2S$: C, 69.74; H, 5.46; S, 12.41. Found: C, 69.63; H, 5.60; S, 12.55.

Ethyl *p*-(Benzylthio)benzoate (2).—The product was dissolved in 50 ml of ether, and the solution was filtered, extracted with

(16) H. Suhr, *Chem. Ber.*, **97**, 3277 (1964).

(17) H. E. Westlake and G. Dougherty, *J. Amer. Chem. Soc.*, **64**, 149 (1942).

water, and dried ($MgSO_4$). Evaporation of the ether yielded an oil which solidified upon standing. The solid was taken up in 10 ml of benzene and chromatographed on 30 g of silica gel, eluting with benzene in fractions of 15 ml. The product was contained in fractions 9, 10, and 11: 0.30 g (10%), mp 54–56°; ir (CCl_4) 1715 cm^{-1}. Two recrystallizations from petroleum ether gave an analytical sample, mp 57.0–57.8° (lit.[18] mp 60°).

Anal. Calcd for $C_{16}H_{16}O_2S$: S, 11.77. Found: S, 11.72.

p-**(Benzylthio)benzophenone (3).**—The crude solid was dissolved in 50 ml of ether and filtered, and the filtrate was evaporated. The residue was recrystallized from methanol to give 0.95 g (31%) of **3**, mp 81.5–84.0°, ir (CCl_4) 1650 cm^{-1}. Four more recrystallizations from methanol afforded the pure ketone, mp 84.5–85.4°.

Anal. Calcd for $C_{20}H_{16}OS$: C, 78.91; H, 5.30; S, 10.53. Found: C, 79.07; H, 5.41; S, 10.74.

Methyl *p*-(Dodecylthio)benzoate (4) (Table I, 0.020 Mol).—The impure product was extracted with 140 ml of boiling methanol and the resulting solid was recrystallized from petroleum ether to give the ester: 2.1 g (31%); mp 62.9–65.4°; ir (CCl_4) 1720 cm^{-1}. Four more recrystallizations from petroleum ether gave pure **4**, mp 63.9–65.4°.

Anal. Calcd for $C_{20}H_{32}O_2S$: C, 71.37; H, 9.59; S, 9.53. Found: C, 71.55; H, 9.55; S, 9.33.

p-**(Dodecylthio)benzophenone (5).**—The residue was boiled with 35 ml of petroleum ether, yielding a crude product which was crystallized from methanol: 1.2 g (31%) of **5**; mp 45.7–46.7°; ir (CCl_4) 1650 cm^{-1}. Two further recrystallizations from methanol yielded pure product, mp 45.7–46.5°.

Anal. Calcd for $C_{25}H_{34}OS$: C, 78.48; H, 8.96; S, 8.38. Found: C, 78.65; H, 8.92; S, 8.31.

p-**Dodecylthiobenzonitrile (6).**—Extraction of the product with 50 ml of boiling methanol gave a solid which after recrystallization, twice from methanol, once from petroleum ether, yielded 1.6 g (53%) of **6**: mp 46.9–48.5°; ir (CCl_4) 2230 cm^{-1}; mp 48.5–49.2° after two more recrystallizations from petroleum ether.

Anal. Calcd for $C_{19}H_{29}NS$: C, 75.19; H, 9.63; N, 4.62; S, 10.57. Found: C, 75.05; H, 9.76; N, 4.60; S, 10.45.

p-**(Dodecylthio)benzaldehyde (7).**—Two recrystallizations of the crude product from methanol gave 6.5 g (53%) of the yellow aldehyde, mp 31.0–33.5°, ir (CCl_4) 1700 cm^{-1}.

A semicarbazone of **7** was prepared which was recrystallized from methanol and then several times from methanol–toluene, mp 185.7–186.9°.

Anal. Calcd for $C_{20}H_{33}N_3OS$: C, 66.06; H, 9.15; N, 11.56; S, 8.82. Found: C, 66.19; H, 9.23; N, 11.50; S, 8.60.

Methyl *o*-(Dodecylthio)benzoate (8).—The residue was dissolved in 100 ml of ether and filtered, and the filtrate was dried ($MgSO_4$) and evaporated. The solid was distilled, yielding 3.9 g (23%) of ester, bp 206–208° (0.65 mm). Three recrystallizations from methanol and three from petroleum ether gave pure product, mp 40.3–41.0°, ir (CCl_4) 1720 cm^{-1}.

Anal. Calcd for $C_{20}H_{32}O_2S$ C, 71.37; H, 9.59; S, 9.53. Found: C, 71.19; H, 9.40; S, 9.68.

***p*-Nitrobenzenesulfonamide and Sodium 1-Dodecanethiolate.**—The residue from the reaction carried out at 155° was extracted with 50 ml of boiling methanol, yielding a solid which was recrystallized from methanol, 0.98 g (30%) of dodecyl *p*-nitrophenyl sulfide, mp 45.0–49.0°. After three recrystallizations from 1-propanol, mp 48.3–49.4° (lit.[19] mp 47°).

Anal. Calcd for $C_{18}H_{29}NO_2S$: C, 66.83; H, 9.04 N, 4.33; S, 9.91. Found: C, 66.81; H, 8.94; N, 4.31; S, 9.92.

***p*-Nitrobenzamide and Sodium 1-Dodecanethiolate.**—The impure product was boiled with 50 ml of methanol and the hot solution was filtered from an oil. The oil solidified readily and was recrystallized from 1-propanol yielding dodecyl disulfide as white flakes, 0.58 g (29%), mp 31.1–33.3° (lit.[17] mp 34°). The identity of the product was confirmed by mixture melting point and by comparison of the infrared spectrum with that of an authentic sample which was prepared by the oxidation of sodium 1-dodecanethiolate with aqueous iodine–potassium iodide.

Methyl *m*-Nitrobenzoate and Sodium 1-Dodecanethiolate.—The mixture of solids obtained was boiled with 40 ml of methanol. The solution was decanted from an insoluble oil which solidified upon standing, 5.5 g (54%) of dodecyl disulfide, mp 31.0–33.0° (lit.[17] mp 34°). The identity of the product was confirmed by mixture melting point and by comparison of its infrared spectrum with that of an authentic sample.

Sodium 1-Dodecanethiolate.—Sodium metal (6.90 g, 0.300 g-atom) was converted to sodium methoxide by reaction with 100 ml of methanol. 1-Dodecanethiol (70.5 g, 0.349 mol) was added to the solution and the thiolate salt was isolated by evaporation of the methanol *in vacuo*. The solid was triturated with 200 ml of absolute ether, suction-filtered, stirred with 100 ml of absolute ether, and suction-filtered again. The salt was dried for 30 min at 30 mm and 100°, 65 g (97%). The product was analyzed by titrating a methanol solution with aqueous iodine. Purity by this method was at least 99%.

Sodium α-toluenethiolate was prepared and analyzed as described for sodium 1-dodecanethiolate. A total of 41 g (93%) of the salt was isolated; purity was at least 99%.

***p*-Nitrobenzophenone.**—Aluminum chloride (16 g, 0.12 mol) was added in portions during 15 min to a refluxing mixture of 18.6 g (0.100 mol) of *p*-nitrobenzoyl chloride and 87.9 g (1.13 mol) of benzene. Refluxing was then continued for 65 min after which the mixture was poured onto 44 g of ice in 70 ml of 45% hydrochloric acid. The crude product was suction-filtered and recrystallized from glacial acetic acid, 11.3 g (50%), mp 136.8–137.7° (lit.[20] mp 135–137°).

Registry No.—Sodium α-toluenethiolate, 3492-64-6; sodium 1-dodecanethiolate, 26960-77-0; **1**, 26960-78-1; **3**, 26960-79-2; **4**, 26960-80-5; **5**, 26960-81-6; **6**, 26960-82-7; **7**, 26960-83-8; **7** semicarbazone, 26960-84-9; **8**, 26960-80-5.

Acknowledgment.—The author wishes to thank Dr. Norman C. Deno for his advice concerning the preparation of the manuscript.

(18) D. F. Elliott and C. Harington, *J. Chem. Soc.*, 1374 (1949).

(19) I. K. Pilgram and F. Korte, *Tetrahedron*, **20**, 177 (1964).

(20) E. H. Charlesworth and P. Charleson, *Can. J. Chem.*, **46**, 1843 (1968).

Neighboring-Group Replacement Reactions of Substituted Phenylcyclohexyl Tosylates

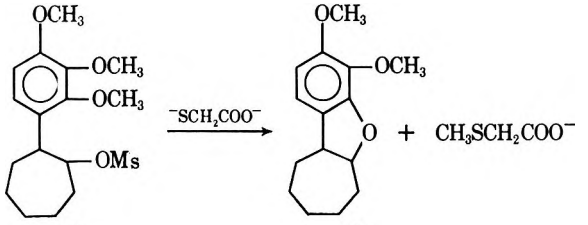
SUE K. CORE* AND F. J. LOTSPEICH

Department of Biochemistry, West Virginia University Medical Center, Morgantown, West Virginia 26506

Received May 27, 1970

Tosylates of *trans*-2-(2′,3′-dimethoxyphenyl)-, (2′,3′,4′-trimethoxyphenyl)-, (2′,5′-dimethoxyphenyl)-, (2′,6′-dimethoxyphenyl)-, (2′,4′-dimethoxyphenyl)-, (3′,4′-dimethoxyphenyl)-, (2′-methoxyphenyl)-, (3′-methoxyphenyl)-, and (4′-methoxyphenyl)cyclohexanols were treated with the dipotassium salt of mercaptoacetic acid in methanol at relative concentrations of 2:1 and 50:1 (anion:tosylate). Neighboring-group replacement of the tosyl group with subsequent formation of the furan derivative predominated in all displacements where an *o*-methoxyl substituent was involved at low anion to tosylate ratios (2:1) with the exception of *trans*-2-(2′,4′-dimethoxyphenyl)cyclohexyl tosylate which favored simple displacement. At high anion to tosylate ratios (50:1), the simple displacement reaction was favored with decreased neighboring-group partcipation and increased elimination. The simple displacement reaction of tosylates with an *o*- or a *p*-methoxyl substituent gave the *trans*-sulfide acid (retention of configuration) at low anion concentration (2:1) while at the higher ratio (50:1) inversion of configuration occurred to give the cis acids. However, those tosylates with an *o*- and a *p*-methoxyl group gave retention of configuration at both ratios. The substituted 3-phenylcyclohexenes were the predominant olefins formed in practically all cases.

The participation of methoxyl groups in numerous solvolysis reactions was summarized by Winstein, *et al.*,[1] in 1958. Methoxyl participation was also shown in the reaction of *trans*-2-(2′,3′,4′-trimethoxyphenyl)cycloheptyl methanesulfonate (I) with the dipotassium salt of mercaptoacetic acid where 5a,7,8,9,10,10a-hexahydro-3,4-dimethoxy-6*H*-benzo[*b*]cyclohepta[*d*]furan (II)[2] was the main product. The above results in the



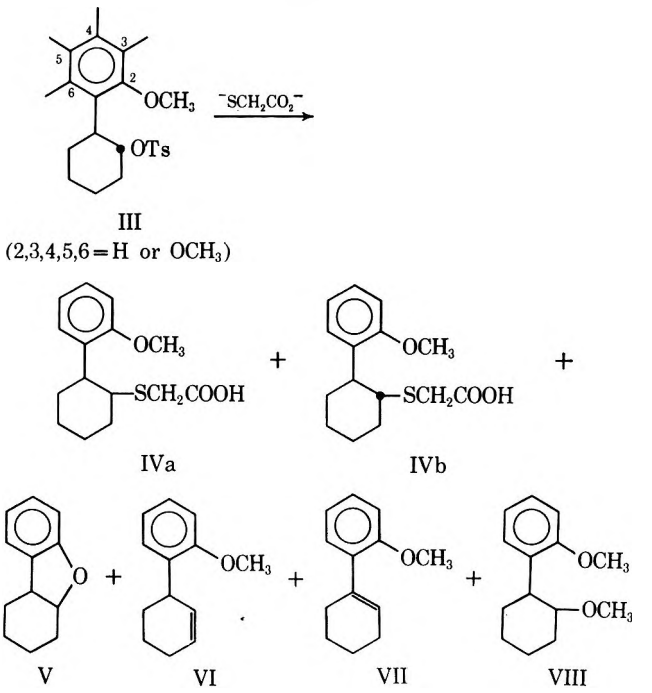
I II

seven-membered-ring system along with the low yield of 2-(2′,3′-dimethoxyphenyl)cyclohexanemercaptoacetic acid resulting from the treatment of 2-(2′,3′-dimethoxyphenyl)cyclohexyl *p*-toluenesulfonate with the dipotassium salt of mercaptoacetic acid led us to investigate the effect of the methoxyl groups on displacement reactions in the substituted phenylcyclohexane system.

Results

The tosylates IX–XVII (Table I) were displaced with the dipotassium salt of mercaptoacetic acid in methanol (56°) for 72 hr at two ratios of anion:tosylate (2:1 and 50:1). The reaction mixtures were separated into two fractions, base-soluble and base-insoluble. Scheme I illustrates the products which were identified. The cis and trans acids (IVa,b) represent the base soluble fractions formed from the reaction of the tosylate with the anion; the cis acid is formed by displacement with inversion of configuration and the trans acid by displacement with retention of configuration. The base-insoluble fraction contains (1) the furan derivative (V) from the neighboring-group replacement by the *o*-methoxyl group, (2) the olefins (VI, VII) by elimination, and (3) the methyl ether (VIII) from solvolysis. The cyclic

SCHEME I



ethers listed in Table II were identified by their nmr absorption spectra. The proton absorption between τ 5.30 and 5.39 was assigned to the proton α to the cyclic ether oxygen.[2-4] Integration of the methoxyl protons indicated that, in the formation of the cyclic compound, one methyl group was lost for each compound. The methylene protons of each compound integrated correctly for eight protons. We were unable to determine the characteristics of the 2,4-dimethoxy derivative because of very low yields of base-insoluble material.

We were unable to obtain pure samples of all methyl ethers. However, in those cases where pure samples were analyzed by nmr, the proton absorption at τ 6.12–6.20 was assigned to the methoxyl group attached to the benzene ring and the absorption at τ 6.85–6.89 to the methoxyl group attached to the cyclohexane ring. The spectra integrated correctly for the methyl ether. We

(1) S. Winstein, E. Allred, R. Heck, and R. Glick, *Tetrahedron*, **3**, 1 (1958).
(2) F. J. Lotspeich, *J. Org. Chem.*, **33**, 3316 (1968).
(3) S. D. Darling and K. D. Wills, *ibid.*, **32**, 2794 (1967).
(4) W. Fulmor, J. E. Lancaster, G. O. Martin, J. J. Brown, C. F. Howell, C. T. Nora, and R. A. Hardy, Jr., *J. Amer. Chem. Soc.*, **89**, 3322 (1967).

TABLE I

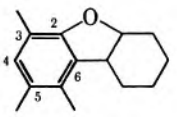
YIELDS OF THE IMPORTANT PRODUCTS FROM THE DISPLACEMENT REACTIONS OF METHOXY-SUBSTITUTED PHENYLCYCLOHEXYL *p*-TOLUENESULFONATES

Compd	Ring substituent	% yield	% IV	% V	% VI	% VII	% VIII	% recovered III	% cis/ % trans acid	Ratio of anion: tosylate
IX	2-OCH_3	102	11.77	47.30	15.66	<1	24.99	0	27/73	2:1
	2-OCH_3	100	42.42	21.03	32.60	0	3.97	0	78/22	50:1
X	2,3-OCH_3	97	6.17	87.50	4.44	2.22	0	0	58/42	2:1
	2,3-OCH_3	101	25.06	45.70	26.28	0	3.13	0	100/0	50:1
XI	2,3,4-OCH_3	107	31.10	48.70	5.69	1.70	12.84	0	0/100	2:1
	2,3,4-OCH_3	96	45.27	27.49	24.00	<1	3.06	0	0/100	50:1
XII	2,5-OCH_3	98	6.07	67.42	8.06	4.92	13.37	0	*a*	2:1
	2,5-OCH_3	100	40.78	30.51	27.29	<1	1.29	0		50:1
XIII	2,6-OCH_3	98	7.30	82.60	7.30	2.79	0	0	*b*	2:1
	2,6-OCH_3	98	0	83.30	12.36	4.34	0	0		50:1
XIV	2,4-OCH_3	85	64.52	8.57	0	3.71	23.00	0	0/100	2:1
	2,4-OCH_3	104	78.20	5.45	15.19	0	1.32	0	0/100	50:1
XV	4-OCH_3	94	23.18	0	0	0	33.03	43.68	18/82	2:1
	4-OCH_3	100	63.94	0	35.09	0	<1	0	85/15	50:1
XVI	3,4-OCH_3	107	22.30	0	0	0	16.02	61.67	31/69	2:1
	3,4-OCH_3	101	64.86	0	33.59	<1	1.24	0	97/3	50:1
XVII	3-OCH_3	85	19.26	0	0	0	0	80.74	100/0	2:1
	3-OCH_3	106	45.58	0	41.84	4.52	8.16	0	100/0	50:1

[a] Isomers could not be separated; nmr showed acid at low concentration to be primarily the trans isomer, at high concentration the cis isomer. [b] Isomers could not be identified due to low yields.

TABLE II

PROTON NMR DATA FOR CYCLIC ETHERS[a]



3, 4, 5, 6 = H or OCH_3

Compd	Registry no.	Proton α to O of cyclic ether
No substitution	13524-79-3	5.30 (1 H)
3-OCH_3	27124-66-9	5.31 (1 H)
3,4-Di-OCH_3	27124-67-0	5.29 (1 H)
5-OCH_3	27124-68-1	5.38 (1 H)
6-OCH_3	27124-69-2	5.39 (1 H)

[a] Expressed as τ values.

were also able to decrease the formation of this product by increasing the concentration of anion.

Characterization of the cis and trans acids was based on their nmr spectra. The *trans*-sulfide acids were identified by a doublet between τ 6.89 and 7.19 representing the methylene hydrogens between the sulfur and carboxy group of the side chain.[5] The corresponding protons for the *cis*-sulfide acids showed a quartet centered between τ 7.40 and 7.58. Nmr data for the cis acids are given in Table III.

To establish the ratio of cis and trans isomers, the methyl esters of all base-soluble products were prepared and analyzed by glc. The cis isomers were identified by comparison with standards prepared by a known procedure and the ratio of cis–trans isomers was determined by peak areas. Although we were unable to separate the isomers of 2-(2′,5′-dimethoxyphenyl)cyclohexanemercaptoacetic acid, the nmr indicated that the trans acid was primarily formed at low-anion concentration and the cis at high-anion concentrations.

(5) F. J. Lotspeich and S. Karickhoff, *J. Org. Chem.*, **31**, 2183 (1966).

Discussion

The products obtained from the displacement reactions reported in Table I can be rationalized by considering Scheme II. Compound IX (2-methoxy) gives a 47% yield of cyclic ether at low-anion concentration and is postulated to react through intermediate C. The formation of this intermediate would require the tosyl and phenyl groups to exist in axial positions.[6] The cyclic ether is formed after displacement of the methoxyl methyl group by the anion 2. Compound XIII (2,6-dimethoxy) with two methoxyl groups available for participation has a greater tendency to form intermediate C and gives an 83% yield of the cyclic ether.

Compounds X (2,3-dimethoxy) and XII (2,5-dimethoxy) form 87 and 67% of the cyclic compound, respectively, at low-anion concentration. The methoxyl groups, which are either ortho or para to the participating methoxyl substituent in these compounds, increase the electron density of the participating methoxyl group and thus facilitate the formation of intermediate C as well as stabilizing the intermediate. The role of the 3-methoxyl group is also evident in the case of compounds XI (2,3,4-trimethoxy) and XIV (2,4-dimethoxy) where the yield of cyclic ether is 49 and 9%, respectively. The relatively low yield of the cyclic ether from compound XI compared to compounds X and XII is undoubtedly due to the presence of the *p*-methoxyl group which facilitates the formation of the "phenonium ion" and results in an increased formation of sulfide acid with a consequent decrease of cyclic ether.

The importance of the "phenonium ion" in these reactions is emphasized by the fact that compounds XI (2,3,4-trimethoxy) and XIV (2,4-dimethoxy) form only *trans*-sulfide acids (retained configuration) at both low- and high-anion concentration, whereas the other tosylates yield increasing amounts of *cis*-sulfide acid at high-anion concentration. The *o*-methoxyl group without

(6) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 229.

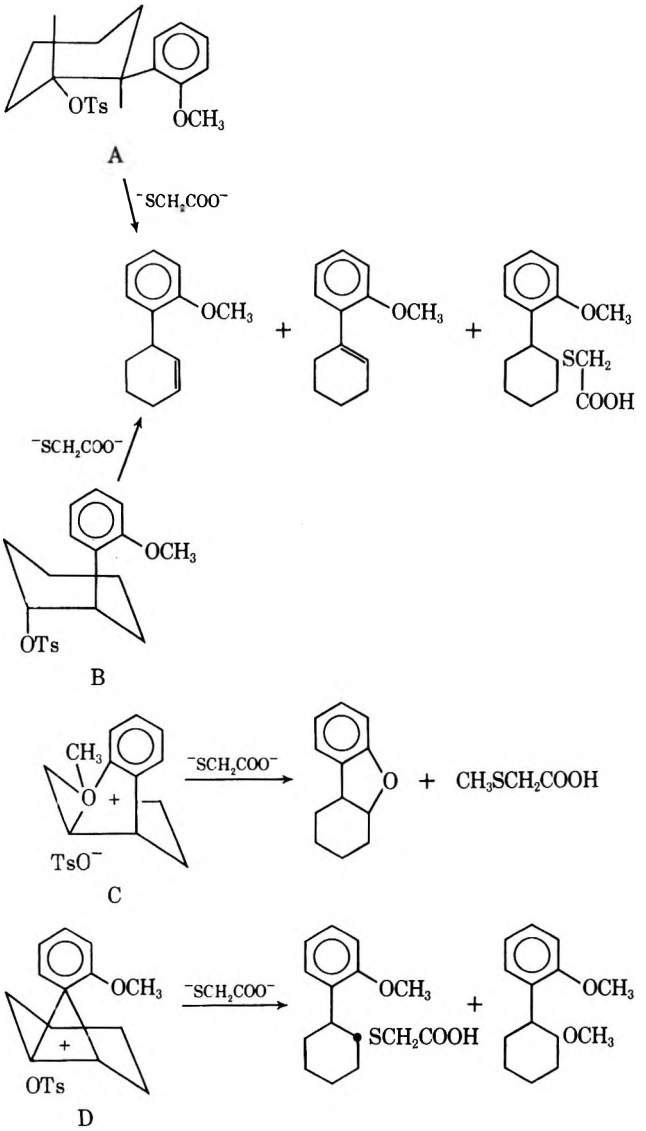
TABLE III

PROTON NMR DATA[a]

Compd[b]	Aromatic	Cyclohexane	Tertiary	$-SCH_2-$	$-OCH_3$
		Substituted *cis*-Sulfide Acids			
2, 3, 4	3.27 (q)	8.05, 8.40	6.60, 6.83	7.44 (q)	6.13, 6.22
3, 4	3.20 (q)	7.80–8.80	6.59, 6.91	7.40 (q)	6.12, 6.15
2, 3	3.13–3.20 (m)[c]	8.05, 8.42	6.58, 6.71	7.46 (q)	6.19, 6.22
2, 5	3.16–3.28 (m)	8.03, 8.38	6.48, 6.73	7.50 (q)	6.21, 6.25
2, 4	2.77–3.58 (m)	8.00, 8.39	6.48, 6.75	7.45 (q)	6.22
4	2.71–3.22 (m)	7.92, 8.32	6.67, 6.95	7.41 (q)	6.23
2	2.82–3.14 (m)	8.00, 8.35	6.47, 6.72	7.58 (q)	6.22
3	2.75–3.15 (m)	7.69–8.80	6.67, 6.95	7.42 (q)	6.22
		Substituted *trans*-Sulfide Acids from Tosylate Displacement			
2, 3, 4	3.23 (q)	7.90–8.90	7.03, 7.73	6.89, 6.98 (d)[c]	6.10, 6.13, 6.17
3, 4	3.18, 3.22 (m)	7.80–8.80		7.11, 7.19 (d)	6.12, 6.16
2, 3	3.03, 3.10 (m)	7.85–8.85		6.93, 7.00 (d)	6.13, 6.15
2, 5	3.16–3.28 (m)	7.80–8.90		6.95, 7.00 (d)	6.19, 6.22
2, 4	3.42–3.57 (m)	7.90–8.80		6.91, 6.97 (d)	6.18
4	2.89–3.23 (m)	7.90–8.82		7.09, 7.18 (d)	6.22
2	2.70–3.19 (m)	7.90–8.86		6.99, 7.05 (d)	6.23

[a] Expressed as τ values. [b] The compound is designated by the methoxyl substitution pattern of the aromatic ring. [c] q = quartet; m = multiplet; d = doublet.

SCHEME II



doubt contributes to the retention of configuration of the sulfide acids in these compounds (XI and XIV) since the *p*-methoxyl group by itself (compound XV) is unable to prevent an inversion in configuration even at low-anion concentration. The *o*-methoxyl substituent probably exerts its influence on the formation of sulfide acid *via* the "phenonium ion" since the 2,6-dimethoxy compound (XIII), which reacts through the "methoxonium ion" C, yields no sulfide acid at high-anion concentration and only 7% sulfide acid at low-anion concentration.

The electron-withdrawing effect of the *m*-methoxyl group is evident when compound XV (4-methoxy), which gives a high yield of *trans*-sulfide acid (retained configuration), is compared to compound XVI (3,4-dimethoxy), which gives a lower yield of *trans*-sulfide acid. The *m*-methoxy compound (XVII) is unable to form intermediate C and gives only *cis*-sulfide acid (inversion of configuration).

The solvolysis reaction at low-anion concentration occurs most readily with those compounds capable of forming intermediate D. The 3-methoxy compound (XVII) gives no solvolysis product and supports the above reasoning. The fact that compound IX (2-methoxy) undergoes solvolysis (25%) further supports the previous contention that the *o*-methoxyl group contributes to the formation of the "phenonium ion" as well as participating directly in anchimeric assistance.

At low-anion concentration trans elimination is favored in the case of compounds IX–XIV and substituted 3-phenylcyclohexenes are formed. These results would be expected from the work of Eliel and Ro,[7] who found that axial tosylates undergo appreciable bimolecular elimination, whereas the equatorial tosylates react more slowly. Cristol and Stermitz[8] also reported that trans elimination was favored over cis elimination in the base-induced elimination of *trans*-phenylcyclohexyl *p*-toluenesulfonate. From these reports and a consideration of Scheme II, it is easy to see that conformer B would not only contribute to the formation of the "phenonium ion" and "methoxonium ion" but would also be the major conformer contributing to the formation of the 3-phenylcyclohexenes. In this conformer, the axial

(7) E. L. Eliel and R. S. Ro, *J. Amer. Chem. Soc.*, **79**, 5995 (1957).
(8) S. J. Cristol and F. R. Stermitz, *ibid.*, **82**, 4692 (1960).

hydrogen on carbon number 6 would be eliminated with the axial sulfonate group.

In general, the results observed at high-anion concentration can be explained on the basis of increased attack by the anion on conformer B. This is supported by the results with the 3-methoxy compound where only 20% of the compound reacted at the low-anion concentration, but a complete reaction was observed at high-anion concentration with 3-(3′-methoxyphenyl)cyclohexene being the main olefin.

Experimental Section

Melting points were taken using a Nalge–Axelrod melting point apparatus and are uncorrected. All elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Nmr spectra were recorded on a Varian A-60 spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. Glc data were recorded on a Microtek 220 with a hydrogen flame detector. All samples were analyzed on two or more columns. All percentages were calculated from peak areas. The following columns were used: 20% silicone oil on 60–80 AW Chromosorb P; 12% Apiezon L–8% tetracyanoethyl pentaerythritol on 100–110 Anakrom ABS; 3% SE-30 on 110–120 Anakrom SD; 3% Apiezon L on 110–120 Anakrom SD; and 3% Carbowax 20M on 110–120 Anakrom SD.

Substituted *trans*-2-Phenylcyclohexanols.—The alcohols were prepared by the addition of the phenyllithium derivative to cyclohexene oxide in diethyl ether according to the procedure of Lotspeich and Karickhoff.[5]

Substituted *trans*-2-Phenylcyclohexyl *p*-Toluenesulfonates.—The tosylates were prepared from the trans alcohols by a procedure reported previously.[5] Elemental analyses are given in Table IV.

TABLE IV

Compd	Mp, °C	C, % Calcd	C, % Found	H, % Calcd	H, % Found
IX	98–99	66.67	66.36	6.67	6.69
X	113–114	64.59	64.79	6.71	6.78
XII[a]	83–85	64.59	64.79	6.71	6.86
XIII	90–93	64.59	64.56	6.71	6.67
XIV	89–92	64.59	64.15	6.71	6.52
XV	116–118	66.67	66.42	6.67	6.72
XVI	92–95	64.59	64.63	6.71	6.71
XVII	96–97	66.67	66.51	6.67	6.67

[a] Compound XI is a known compound.

Tosylate Displacement.—The *trans*-tosylates (0.01 mol) were dissolved in methanol (30 ml) along with the dipotassium salt of mercaptoacetic acid at a molar ratio of potassium mercaptoacetate:tosylate of 2:1 or 50:1. The mixture was flushed with nitrogen and the condenser fitted with an oil trap to exclude air. The reaction was heated at 55–58° for 72 hr, and the solvent was removed by a Rinco evaporator. The resulting oil was taken up in ether and the base-soluble fraction was extracted with 5% NaOH.

The acids (base-soluble fraction) were identified by comparison of glc retention times of their methyl esters and nmr spectra of the acids (Table III) to known compounds.

The base-insoluble fraction was subjected to glc to determine the number of components present. The products were then separated on neutral aluminum oxide (Merck) with successive elutions of 100% pentane, 5% diethyl ether in pentane, 10% diethyl ether in pentane, 30% diethyl ether in pentane, 60% diethyl ether in pentane, and 100% diethyl ether. The fractions were checked for purity by glc. The olefins (100% pentane) were identified by comparison with standards and the cyclic compounds (10% diethyl ether in pentane) were identified by nmr (Table II).

Substituted *trans*-2-Phenylcyclohexanemercaptoacetic Acids.—Solid derivatives were prepared from the displacements of tosylates IX, XI, XIV, XVI, and XVII.

trans-2-(2′-Methoxyphenyl)cyclohexanesulfonylacetic acid, mp 135–138°. *Anal.* Calcd for $C_{15}H_{20}O_5S$: C, 57.69; H, 6.60. Found: C, 58.01; H, 6.42.

trans-2-(2′,3′,4′-Trimethoxyphenyl)cyclohexanemercaptoacetic acid (5) and *trans*-methyl 2-(2′,4′-dimethoxylphenyl)cyclohexanemercaptoacetate, mp 56–58°. *Anal.* Calcd for $C_{17}H_{24}O_4S$: C, 62.93; H, 7.46. Found: C, 62.63; H, 7.40.

Methyl *trans*-2-(3′,4′-dimethoxyphenyl)cyclohexanemercaptoacetate, mp 78–81°. *Anal.* Calcd for $C_{17}H_{24}O_4S$: C, 62.93; H, 7.46. Found: C, 62.76; H, 7.47.

cis-2-(3′-Methoxyphenyl)cyclohexanesulfonylacetic acid, mp 118–120° (lit.[9] mp 119–120°).

We were unable to prepare solid derivatives of the acids from tosylates X, XII, and XV. However, their nmr spectra were consistent with the other trans acids. See Table III.

Substituted *cis*-2-Phenylcyclohexylmercaptoacetic Acid.—The cis acids were prepared by the free-radical addition of mercaptoacetic acid to the substituted 1-phenylcyclohexenes with a catalytic amount of benzoyl peroxide.[10,11] Nmr data are given in Table III.

cis-2-(2′,3′,4′-Trimethoxyphenyl)-,[5] *cis*-2-(2′-methoxyphenyl)-, *cis*-2-(3′-methoxyphenyl)-, and *cis*-2-(4′-methoxyphenyl)-cyclohexanemercaptoacetic acids are known compounds.[9]

cis-2-(2′,4′-Dimethoxyphenyl)cyclohexanemercaptoacetic acid, mp 117°. *Anal.* Calcd for $C_{16}H_{22}O_4S$: C, 61.83; H, 7.20. Found: C, 61.91; H, 7.14.

cis-2-(3′,4′-Dimethoxyphenyl)cyclohexanemercaptoacetic acid, mp 121–124°. *Anal.* Calcd for $C_{16}H_{22}O_4S$: C, 62.11 H, 6.84. Found: C, 61.71; H, 7.12.

We were unable to obtain solid derivatives of *cis*-2-(2′,5′-dimethoxyphenyl)- and *cis*-2-(2′,3′-dimethoxyphenyl)cyclohexanemercaptoacetic acids.

Substituted 1-Phenylcyclohexenes.—The tertiary alcohols were prepared from the addition of the appropriate phenyl-Grignard or lithium derivative to cyclohexanone and dehydrated to the corresponding olefin with oxalic acid in boiling toluene.[5]

1-(2′,5′-Dimethoxyphenyl)cyclohexene. *Anal.* Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.91; H, 8.35

1-(2′,6′-Dimethoxyphenyl)cyclohexene. *Anal.* Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.01; H, 8.41.

1-(2′,4′-Dimethoxyphenyl)cyclohexene. *Anal.* Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.45; H, 8.53.

1-(3′,4′-Dimethoxyphenyl)cyclohexene. *Anal.* Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.71; H, 8.39.

The other olefins are known compounds.[5,9]

Substituted 3-Phenylcyclohexenes.—The appropriate substituted phenyl-Grignard or lithium derivative was allowed to react with 3-bromocyclohexene according to the procedure of Schaeffer and Collins[12] (see Table V). The yields of 3-(2′,3′-dimethoxyphenyl)-, 3-(3′,4′-dimethoxyphenyl)-, and 3-(4′-methoxyphenyl)cyclohexene were very low, and we were unable to obtain pure samples for analysis.

Registry No.—IX, 27124-57-8; X, 27124-59-9; XII, 27124-59-0; XIII, 27124-60-3; XIV, 27124-61-4; XV, 20859-18-1; XVI, 27124-63-6; XVII, 27124-64-7; *trans*-2-(2′-methoxyphenyl)cyclohexanesulfonylacetic acid, 27124-76-1; *trans*-2-(2′,3′,4′-trimethoxyphenyl)-cyclohexanemercaptoacetic acid, 6776-94-9; methyl *trans*-2-(2′,4′-dimethoxyphenyl)cyclohexanemercaptoacetate, 27124-78-3; methyl *trans*-2-(3′,4′-dimethoxyphenyl)cyclohexanemercaptoacetate, 27124-79-4; *trans*-2-(2′,3′-dimethoxyphenyl)cyclohexanemercaptoacetic acid,[13] 27124-80-7; *trans*-2-(2′,5′-dimethoxyphenyl)-cyclohexanemercaptoacetic acid,[13] 27124-81-8; *trans*-2-(4′-methoxyphenyl)cyclohexanemercaptoacetic acid,[13] 27124-82-9; *cis*-2-(2′,3′,4′-trimethoxyphenyl)cyclohexanemercaptoacetic acid, 6776-90-5; *cis*-2-(2′-methoxyphenyl)cyclohexanemercaptoacetic acid, 27124-84-1; *cis*-2-(3′-methoxyphenyl)cyclohexanemercaptoacetic acid, 27124-85-2; *cis*-2-(4′-methoxyphenyl)cyclohexanemercaptoacetic acid, 27124-86-3; *cis*-2-(2′,4′-di-

(9) S. Core and F. J. Lotspeich, *J. Med. Chem.*, **12**, 333 (1969).
(10) H. L. Goering, D. I. Relyea, and D. Larsen, *J. Amer. Chem. Soc.*, **78**, 348 (1956).
(11) F. G. Bordwell and W. A. Hewett, *ibid.*, **79**, 3493 (1957).
(12) H. J. Schaeffer and C. J. Collins, *ibid.*, **78**, 124 (1956).
(13) Compound found in Table III.

TABLE V

Compd	Bp (mm) or mp, °C	Formula	Registry no.	Calcd, % C	Calcd, % H	Found, % C	Found, % H
2-OCH_3	74 (0.05)	$C_{13}H_{16}O$	27124-70-5	82.93	8.57	83.08	8.60
3-OCH_3	83 (0.05)	$C_{13}H_{16}O$	27124-71-6	82.93	8.57	82.82	8.62
2,5-OCH_3	93 (0.07)	$C_{14}H_{18}O_2$	27124-72-7	77.03	8.31	76.76	8.34
2,6-OCH_3	68–69.5	$C_{14}H_{18}O_2$	27124-73-8	77.03	8.31	76.81	8.34
2,3,4-OCH_3	110 (0.05)	$C_{15}H_{20}O_3$	27124-74-9	72.55	8.12	72.54	8.09
2,4-OCH_3	108 (0.1)	$C_{14}H_{18}O_2$	27124-75-0	77.03	8.31	77.17	8.29

methoxyphenyl)cyclohexanemercaptoacetic acid, 27124-87-4; *cis*-2-(3′,4′-dimethoxyphenyl)cyclohexanemercaptoacetic acid, 27124-88-5; *cis*-2-(2′,5′-dimethoxyphenyl)cyclohexanemercaptoacetic acid, 27124-89-6; *cis*-2-(2′,3′-dimethoxyphenyl)cyclohexanemercaptoacetic acid, 27124-90-9; 1-(2′,5′-dimethoxyphenyl)cyclohexene, 1848-14-2; 1-(2′,6′-dimethoxyphenyl)cyclohexene, 27124-92-1; 1-(2′,4′-dimethoxyphenyl)cyclohexene, 27098-25-5; 1-(3′,4′-dimethoxyphenyl)cyclohexene, 27124-93-2; *trans*-2-(2′,4′-dimethoxyphenyl)cyclohexanemercaptoacetic acid,[13] 27124-94-3; *trans*-2-(3′,4′-dimethoxyphenyl)cyclohexanemercaptoacetic acid,[13] 27124-95-4; *trans*-2-(2′-methoxyphenyl)cyclohexanemercaptoacetic acid,[13] 27124-96-5.

Acknowledgments.—This investigation was supported by Public Health Service Research Grant No. CA-10270 from the National Institutes of Health.

Stereochemistry of Displacement Reactions at the Neopentyl Carbon. Further Observations on the Triphenylphosphine–Polyhalomethane–Alcohol Reaction[1]

R. G. WEISS

Department of Chemistry, California Institute of Technology, Pasadena, California 91109

E. I. SNYDER*

Department of Chemistry, East Tennessee State University, Johnson City, Tennessee 37601

Received October 20, 1969

$RMe_3CCHDOH$ was prepared by asymmetric reduction of pivaldehyde-*1*-d_1 with isobornyloxymagnesium bromide. Displacement of the tosyl group in (*R*)-$Me_3CCHDOTs$ by acetate ion occurs with 85 ± 17% inversion. Reaction of (*R*)-$Me_3CCHDOH$ with Ph_3P and CCl_4 affords (+)-$Me_3CCHDCl$, assigned the *S* configuration, of greater optical purity than that resulting from chloride displacement on the tosylate. The analogous reaction using CBr_4 affords bromide which seems to be significantly racemized. The characteristics of the title reaction are summarized to point out major differences between it and an SN2 process.

The sluggishness of neopentyl esters or halides to nucleophilic displacement reactions, both SN1 and SN2, is a well-recognized property of that carbon skeletal system. Yet there are several reactions in which "nucleophilic" substitution does occur fairly readily; these reactions have the common property of employing phosphorus-containing reagents and seem to comprise a mechanistically homogenous set.

$$(PhO)_3P + Me_3CCH_2OH + MeI \longrightarrow Me_3CCH_2I^{2,3}$$
(+6% $EtCMe_2I$)

$$(PhO)_3P + Me_3CCH_2OH + PhCH_2X \longrightarrow Me_3CCH_2X$$
X = I, Br[4]

$$Ph_3PX_2 + Me_3CCH_2OH \longrightarrow Me_3CCH_2X + Ph_3PO + HX$$
X = Br, Cl[5]

Furthermore, there seems to be no case in which the stereochemistry of substitution in the parent neopentyl system has been studied. We report herein the stereochemical course of the neopentyl alcohol–chloride conversion using triphenylphosphine–carbon tetrachloride and the analogous reaction with CBr_4, a study performed with the hope of gaining further insight into the mechanistic process involved. We also determined the stereochemical course of a typical SN2 reaction of neopentyl tosylate to serve as a reference point for the title reaction.

Results

When the reaction of triphenylphosphine, carbon tetrachloride, and neopentyl alcohol at ambient temperature was monitored by nmr, only the characteristic resonances of reactants and neopentyl chloride were observed. Examination by glpc showed no evidence of formation of isomeric C-5 chlorides. These results are similar to those of Downie, *et al.*[6] We prepared chiral neopentyl-*1*-d_1 alcohol by asymmetric reduction (Scheme I). This afforded low yields of alcohol whose acid phthalate showed a specific rotation, after correc-

* To whom correspondence should be addressed: Kraftco Research Laboratories, Glenview, Ill.

(1) This investigation was made possible by grants from the National Science Foundation and Petroleum Research Fund. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their support.

(2) N. Kornblum and P. C. Iffland, *J. Amer. Chem. Soc.*, **77**, 6653 (1955).

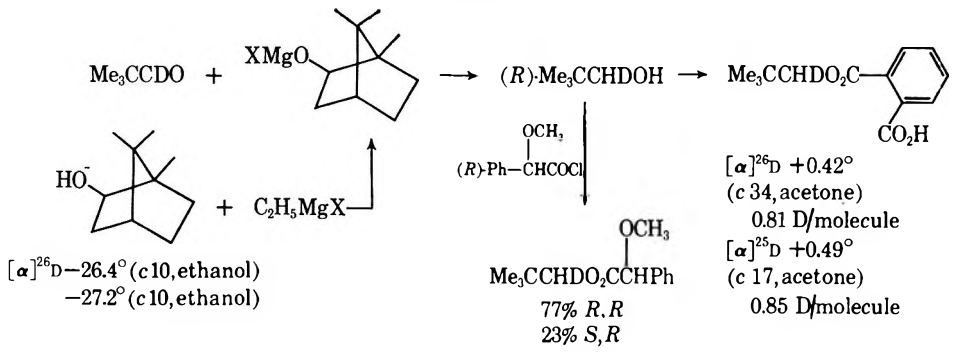
(3) S. R. Landauer and H. N. Rydon, *J. Chem. Soc.*, 2224 (1953).

(4) G. J. Karabatsos, C. E. Orzech, Jr., and S. Meyerson, *J. Amer. Chem. Soc.*, **86**, 1994 (1964). Although the authors obtained only unrearranged iodide and bromide they obtained approximately equal amounts of neopentyl and *tert*-amyl chloride.

(5) G. A. Wiley, R. L. Hershkowitz, B. M. Rein, and B. C. Chung, *ibid.*, **86**, 964 (1964).

(6) I. M. Downie, J. B. Holmes, and J. B. Lee, *Chem. Ind. (London)*, 900 (1966).

SCHEME I[a]

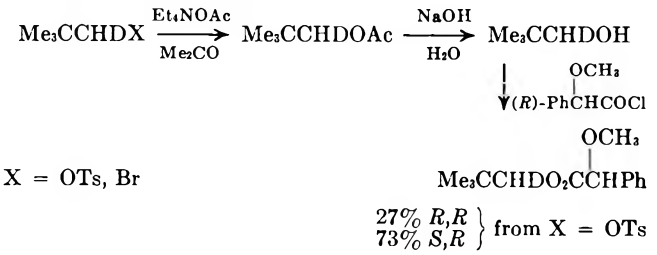


[a] The alcohol was a 10:90 mixture of borneol–isoborneol.

tion to one deuterium per molecule, indicative of about 50% optical purity,[7] and whose dextrorotation showed we had formed the *R* alcohol. (That formed from fermentation[8] is the *S* alcohol[7]). Comparison of the nmr spectrum of the neopentyl ester formed from (*R*)-*O*-methylmandelic acid with that published[9] for the ester from the *S* alcohol confirmed that we had formed predominately the *R* alcohol. Analysis[9] of this spectrum showed the composition of deuterated ester was 77% (*R*)-neopentyl-*1*-d_1 (*R*)-*O*-methylmandelate and 23% (*S*,*R*) ester (with a possible error estimated at ±4%).

The stereochemistry of a typical SN2 reaction was simply determined by acetate displacement on tosylate (Scheme II). The results are clear and unambiguous.

SCHEME II



That *S* alcohol is formed from *R* tosylate means the acetate displacement–hydrolyses sequence occurs with overall inversion (85%, estimated error of 17%).[10] Discounting the unlikely possibility that acetate hydrolysis proceeds with C–O bond cleavage, this shows that a typical SN2 reaction in the neopentyl system occurs with the inversion so characteristic of this reaction class.

Our original hope was to convert neopentyl chloride *via* another typical SN2 reaction (whose stereochemistry presumably would be that of the tosylate–acetate conversion) to neopentyl alcohol or some derivative of it. All such reactions were unsuccessful in our hands (10% or less conversion; see Experimental Section) and in fact led to significant amounts of products lacking the neopentyl skeletal system (as judged from their nmr spectrum), none of which were identified. Consequently, (*R*)-$Me_3CCHDOTs$ was allowed to react with LiCl in DMSO, and the small optical rotation of the resulting $Me_3CCHDCl$ served as a reference for a typical SN2 (inversion) reaction. From Table I one sees that the optical rotation of the chloride prepared from the alcohol *via* Ph_3P–CCl_4 is 50% higher in magnitude and of the same sign as that obtained from the tosylate, thus showing that the former reaction, at least in the neopentyl system, proceeds with greater stereospecificity (inversion) than chloride displacement on the tosylate.

Neopentyl bromide does undergo displacement with acetate, although the reaction is attended by formation of significant amounts of material lacking the neopentyl skeleton (as judged from their nmr spectrum). The bromide prepared from the reaction (*R*)-$Me_3CCHDOH$–Ph_3P–CBr_4 was converted first to the acetate, then to the (*R*)-*O*-methylmandelate ester *via* the alcohol. Examination of the ester by nmr showed the alcohol portion was racemic within experimental error. Because of the possibility that racemization may have occurred in the acetate displacement step the bromide preparation was repeated, and the optical rotation of the product was obtained. A sample of bromide from the LiBr–(*R*)-$Me_3CCHDOTs$ displacement was prepared to serve as a reference point (see Table I). It is clear that the bromide prepared *via* the latter is largely, if not wholly, racemic. Since specific rotations of bromides generally are larger than those of the corresponding chlorides, it seems that bromide prepared directly from the alcohol is also extensively racemized.

Discussion

We have shown that the reaction under discussion yields chlorides with predominant, if not exclusive, inversion in acyclic primary and secondary alcohols,[11] a primary thiol,[11] in 7-norbornanol and *exo*-2-bicyclo[3.2.0]heptanol,[12] and also proceeds with significant, if not predominant, inversion in such systems as *anti*-7-norbornenol and *exo*-2-norbornanol.[11] Our present results show a greater extent of inversion in neopentyl alcohol than the classical chloride displacement on tosylates.

Relatively little seems known about analogous conversions of alcohol to bromide. Downie and Lee have claimed[13] the reaction of 2-octanol with Ph_3P–CBr_4 proceeds with complete inversion. This is contrary to our observations[14] that *threo*-PhCHDCHDOH reacts with CBr_3Cl to afford inverted chloride but equal amounts of

(7) W. Sanderson and H. S. Mosher, *J. Amer. Chem. Soc.*, **88**, 4185 (1966).
(8) V. E. Althouse, K. Ueda, and H. S. Mosher, *ibid.*, **82**, 5938 (1960).
(9) K. Mislow and M. Raban, *Tetrahedron Lett.*, 3961 (1966).
(10) If individual peak areas are measured with an absolute accuracy of 4%, the absolute error in the extent of inversion is $2 \times 4\%/(\%R,R - \%S,R) \cong 17\%$.
(11) R. G. Weiss and E. I. Snyder, *Chem. Commun.*, 1358 (1968).
(12) R. G. Weiss and E. I. Snyder, *J. Org. Chem.*, **35**, 1627 (1970).
(13) D. Brett, I. M. Downie, J. B. Lee, and M. F. S. Matough, *Chem. Ind. (London)*, 1017 (1969).
(14) R. G. Weiss, Ph.D. Thesis, University of Connecticut, 1969.

TABLE I
SPECIFIC ROTATIONS OF Me_3CCHDX

X	Origin[a]	$[\alpha]^{25}D$
Cl	(*R*)-$Me_3CCHDOTs$ + LiCl (DMSO, 90°, 48 hr)	+0.085 ± 0.005[b]
Cl	(*R*)-$Me_3CCHDOH$ + Ph_3P + CCl_4 (rt,[c] 48 hr).	+0.13 ± 0.01[b]
Br	(*R*)-$Me_3CCHDOTs$ + LiBr (DMSO, 90°, 19 hr)	+0.016 ± 0.008
Br	(*R*)-$Me_3CCHDOH$ + Ph_3P + CBr_4 (CH_2Cl_2, rt, 19 hr)	+0.057 ± 0.008

[a] All preparations utilized (*R*)-$Me_3CCHDOH$ containing 0.85 D/molecule, whose acid phthalate showed $[\alpha]^{25}D$ +0.49°. [b] Specific rotations calculated from measured weight percentage of neopentyl chloride in CCl_4 using reported densities for solute and solvent and assuming ideal solution. [c] rt = room temperature.

erythro and threo bromide, which is tantamount to racemization. In this case we were able to demonstrate that erythro–threo isomerization occurred under reaction conditions. The reaction ROH + Ph_3PBr_2 → RBr + Ph_3PO + HBr, which we feel is mechanistically analogous to the title reaction, was shown[15] to proceed with 50% net inversion using 2-butanol. The recent report of Arain and Hargreaves[16] shows the reaction of 3-methyl-2-butanol proceeds with overall inversion. However, the lower specific rotation of the bromide relative to starting alcohol suggests appreciable racemization.[17] It seems that neopentyl alcohol affords bromide with overall inversion accompanied by extensive racemization, but no quantitative statement is possible. It seems significant that the bromide obtained directly from the alcohol is at least partly optically active, whereas that from the tosylate–bromide sequence is effectively racemic.

Any mechanism for the alcohol–polyhalomethane reactions must accommodate the following observations. (1) The alkyl portion of the alkyl halide seems to have little or no cation character at any stage of the reaction coordinate, except for those systems where a highly stabilized cation (*e.g.*, *anti*-7-norbornenyl) may result. That such is the case follows from the lack of skeletal rearrangement in the neopentyl system, exclusive inversion[12] in 7-norbornanol (solvolyses occur with retention[18]), significant inversion in *exo*-2-norbornanol,[11] and significant retention of the cyclopropyl skeleton in reactions of cyclopropanol.[14] Even the observation[11] of some *syn*-chloride from *anti*-7-norbornenol shows that an inversion path can compete with an energetically extraordinary favorable retention (carbonium ion) path. (2) The stereochemical path is typical of SN2 reactions. (3) However, a number of properties are distinctly different from those expected for SN2 reactions. (a) In both the 7-norbornyl and the 2-phenylethyl system it has not been possible for an external nucleophile to compete with chloride.[14] In the latter system we have shown (see Experimental Section) that, in competition for 2-phenylethyl tosylate, cyanide is a far better nucleophile than chloride. Yet the reaction of 2-phenylethanol with triphenylphosphine and carbon tetrachloride in DMSO in the presence of a large excess of cyanide affords *only* 2-phenylethyl chloride. (b) The *absolute* reactviity of the neopentyl system seems qualitatively far too high to be adequately accounted for by a typical SN2 reaction.[19,19a] (c) Decomposition of 7-norbornyloxychlorophosphorane occurs with first-order kinetics.[12]

Because of the reasons enumerated above we have postulated a four-centered, fairly concerted decomposition of a pentacovalent haloalkoxyphosphorane.[12,20]

Experimental Section

Nmr spectra were recorded using an A-60 spectrometer system equipped with an NMR Specialties HD-60A spin decoupler or a Jeolco C-60H with a JNM SD-HC decoupler. Deuterium analyses were performed by Mr. Josef Nemeth, Urbana, Ill. We are indebted to Dr. Robert Fitch of the University of Connecticut for use of his Du Pont Model 310 curve resolver, and to Mr. John Surridge of Esso Research and Engineering Co., Corporate Research Laboratories, for some of the reported polarimetric data obtained with a Perkin-Elmer 141 polarimeter. All observed rotations are for a 1-dm cell length.

(*R*)-**2,2-Dimethylpropanol-d_1.**—A solution of 81 g (0.53 mol) of a 9:1 mixture of isoborneol–borneol, $[\alpha]^{25}D$ −27.2° [from $LiAlH_4$ reduction of (+)-camphor], in 100 ml of THF was added to a solution at 0° of ethylmagnesium bromide (from 0.5 mol of ethyl bromide and 0.5 g-atom of magnesium in 350 ml of THF). Pivaldehyde-d_1[7,21] (30.6 g, 0.35 mol) was added and the mixture was stirred at reflux for 7 hr. The cooled mixture was decomposed with water (75 ml) and filtered, and the solid was washed well with ether. The filtrates were dried ($MgSO_4$) and distilled through a short column virtually to dryness. Because of the volatility of neopentyl alcohol, adequate separation of solvent and other lower boiling components (*e.g.*, unreacted aldehyde) was satisfactorily achieved only by distillation through a Nester-Faust Auto Annular spinning-band column. In this way there was collected 12 g (39%) of crystalline alcohol, mp 53.0–54.2° (lit.[22] mp 52–53°). The acid phthalate, mp 71.0–71.5° (lit.[22] mp 68.5–69.5°), had 5.30 atom % excess deuterium, or 0.85 atom per molecule, and showed $\alpha^{25}D$ +0.083 ±0.002, or $[\alpha]^{25}D$ +0.57 (c 17, acetone, corresponding to 1 deuterium per molecule) [lit.[7] $[\alpha]^{31}D$ −1.15 (*c* 20, acetone), calculated for 100% deuterated (*S*)-$Me_3CCHDOH$], or 50% optical purity (sample 1). An earlier preparation afforded material of $[\alpha]^{26}D$ +0.52° (calculated for 100% deuterium), or 45% optical purity (sample 2).

(*R*)-*O*-**Methylmandelic acid** was prepared as described[23] starting from (*R*)-mandelic acid[24] of $[\alpha]^{26}D$ 151.6° (c 3.3, water) and showed mp 62–67°, $[\alpha]^{25.5}D$ +149.55° [lit. mp 65–66°,[23] $[\alpha]^{17}D$ +150.1° (ethanol)[25]].

(*R*)-**2,2-Dimethylpropyl-d_1** (*R*)-*O*-**Methylmandelate.**[26]—The ester was prepared from 0.178 g (2.00 mmol) of alcohol (sample 2) and acid chloride which was prepared from 0.5 g (3 mmol) of acid; the reaction mixture was distilled (0.05 mm) to give 0.3 g of ester. *Anal.* Calcd for $C_{14}H_{19}DO_3$: C, 70.90; H, 8.81. Found: C, 71.07; H, 8.84. Examination of its nmr spectrum

(15) G. A. Wiley, B. M. Rein, and R. L. Hershkowitz, *Tetrahedron Lett.*, 2509 (1964).

(16) R. A. Arain and M. K. Hargreaves, *J. Chem. Soc. C*, 67 (1970).

(17) It is puzzling that the authors of ref 13 seem to be the only ones who have demonstrated total, or nearly so, inversion using either Ph_3P–CBr_4 or Ph_3PBr_2.

(18) P. G. Gassman and J. M. Hornback, *J. Amer. Chem. Soc.*, **89**, 2487 (1967); F. B. Miles, *ibid.*, **90**, 1265 (1968).

(19) However, the *relative* reactivity of the neopnentyl system, which may be of far greater mechanistic importance, is not yet known, although initial studies indicate *n*-amyl alcohol is at last 20 times more reactive than neopentyl toward Ph_3P and CBr_4.

(19a) NOTE ADDED IN PROOF.—For the reaction with Ph_3P–CCl_4 competition experiments show *n*-amyl alcohol is *only* 14 ± 2 times more reactive than neopentyl alcohol. This ratio in a typical SN2 reaction would be expected to be *ca.* 10^4!

(20) This possibility was suggested initially by Kornblum.[3]

(21) A. Richard, *Ann. Chim. Phys.*, **21**, 323 (1910).

(22) M. Samec, *Justus Liebigs Ann. Chem.*, **351**, 256 (1907).

(23) W. A. Bonner, *J. Amer. Chem. Soc.*, **73**, 3126 (1951).

(24) Norse Chemical Co., Santa Barbara, Calif.

(25) A. McKenzie and H. Wren, *J. Chem. Soc.*, **97**, 484 (1910).

(26) J. A. Dale and H. S. Mosher, *J. Amer. Chem. Soc.*, **90**, 3732 (1968).

failed to show the presence of any material other than the desired ester. Careful examination of the deuterium-decoupled methylene resonances followed by curve resolution showed the composition of deuterated ester was 77% *R,R* and 23% *S,R*.

Acetate Displacement on (*R*)-2,2-Dimethylpropyl-d_1 Tosylate.—The tosylate (from alcohol sample 2) was prepared in the usual way, mp 44–45°. A solution of 3.25 g (13.4 mmol) of tosylate and 3.0 g (16 mmol) of tetraethylammonium acetate in 25 ml of acetone was heated at 100° for 10 days. The reaction mixture was distilled directly to give a fraction of bp >34° (100 mm) which was stirred with 100 ml of 0.75 *N* NaOH at 70° for 44 hr, after which the solution was extracted continuously with 1:1 pentane–ether for 2 days. Solvent was distilled from the dried ($MgSO_4$) extracts through a 12-in. tantalum wire spiral column, and residue was converted to the (*R*)-*O*-methylmandelate ester. Short-path distillation (0.07 mm) afforded 0.125 g of ester, bp 54–56°, which was eluted through 1 g of Florisil with ether. The solvent was evaporated and the nmr spectrum of the ester (CCl_4) showed no observable impurities. Curve resolution of the deuterium-decoupled methylene resonances showed the composition of deuterated ester was 27% *R,R* and 73% *S,R*.

Reaction of (*R*)-$Me_3CCHDOTs$ with LiCl.—A solution of 1.992 g (8.23 mmol) of tosylate (from sample I) and 0.384 g (9.04 mmol) of dried LiCl in 4 ml of DMSO was maintained at 90° for 48 hr. The mixture was diluted with 3 ml of water and distilled (35 mm) to afford 0.55 g (78%) of neopentyl chloride. Examination by nmr showed the resonances of the latter at 57 (s) and 189 (m) Hz, with a small, sharp resonance at 120 Hz (*not* DMSO), whereas the glpc trace (6 ft × 0.25 in. FFAP, 50°) showed the chloride accounted for 96.4% of the total area, with all impurities of quite short retention time, and with no evidence for the presence of other C_5 chlorides or neopentyl alcohol. A solution containing 0.356 g of chloride (assumed 96% pure) in 0.939 g of CCl_4 (weight ratio 0.379:1) showed $\alpha^{25}D$ +0.034 ± 0.002°. Assuming densities of solute and solvent of 0.88 and 1.60, respectively, the concentration is 0.40 g/ml.

Reaction of (*R*)-$Me_3CCHDOH$ with Ph_3P in CCl_4.—A solution of 1.02 g (11.5 mmol) of (*R*)-$Me_3CCHDOH$ (sample 1) and 3.66 g (14.0 mmol) of Ph_3P in 4 ml of CCl_4 remained at ambient temperature for 48 hr. The chilled (0°) solution was diluted with 2 ml of pentane and filtered with the solid being washed with 1:1 pentane–CCl_4. Volatile liquids were collected by a bulb-to-bulb distillation (40 mm), and pentane, chloroform, and most of the carbon tetrachloride were removed by careful distillation through an annular spinning-band column. In our hands it was not possible to satisfactorily separate neopentyl chloride from carbon tetrachloride without significant loss. Using response curves prepared for various solutions of the two chlorides, glpc examination showed in the redistilled pot residue a weight ratio of neopentyl chloride:carbon tetrachloride of 0.3000:1.0, with no other components present (especially neopentyl alcohol). This solution showed $\alpha^{25}D$ +0.046 ± 0.002 (*c* 35.0 calcd).

Reaction of (*R*)-$Me_3CCHDOTs$ with LiBr.—A solution of 1.552 g (6.38 mmol) of tosylate (from alcohol sample 1) and 0.548 g (6.30 mmol) of dried LiBr in 3 ml of DMSO was heated at 90° for 19 hr. The solution was diluted with water and distilled in a sealed system (1 mm) at ambient temperature to afford 0.507 g of bromide (52%). Redistillation through a short-path apparatus afforded 0.253 g of bromide, 98% pure by glpc examination (6 ft × 0.25 in. SE-30, 70°): $\alpha^{25}D$ +0.004 ± 0.002 (*c* 25.3, $CDCl_3$); nmr ($CDCl_3$) 61 (s) and 190 Hz (m).

Reaction of (*R*)-$Me_3CCHDOH$ with Ph_3P and CBr_4.—A solution of 3.23 g (12.3 mmol) of Ph_3P in 5 ml of CH_2Cl_2 was added dropwise to a cooled solution of 0.944 g (10.6 mmol) of alcohol (sample 1) and 4.62 g (14.0 mmol) of freshly recrystallized CBr_4 in 10 ml of CH_2Cl_2. After 19 hr at ambient temperature the mixture was concentrated to *ca.* half its volume by careful fractionation, the residue was chilled and filtered, and the filtrate was distilled bulb to bulb (1 mm) in a sealed system. The distillate so collected was carefully distilled through a short column affording 0.70 g of neopentyl bromide (42%). Redistillation afforded material whose purity according to glpc examination was 95%, the impurities being roughly equally distributed among CH_2Cl_2 and two other unidentified components of shorter retention time than neopentyl bromide; there was no evidence for the presence of neopentyl alcohol. The sample showed $\alpha^{25}D$ +0.014 ± 0.002 (c 24.6, $CDCl_3$).

Reaction of (*R*)-$Me_3CCHDOH$, Ph_3P, and CBr_4.—A solution of alcohol (1.74 g, 20 mmol), Ph_3P (5.24 g, 20 mmol), and CBr_4 (9.96 g, 30 mmol) in 15 ml of CH_2Cl_2 was stirred at ambient temperature for 4 hr. Material was distilled up to bp 57° (80 mm) and then was redistilled through a 6-in. tantalum wire spiral column to afford 1.17 g (38%) of neopentyl bromide. The nmr spectrum showed the presence of some alcohol, but did not have signals expected for rearranged products. Alcohol was removed by elution through 1 g of florisil with 10 ml of acetone. A solution of the bromide in 10 ml of acetone containing 6.8 g of Et_4NOAc was heated at 105° for 6 days; the cooled mixture was filtered and then distilled to afford 0.55 g of distillate, bp >65. (Experiments on undeuterated neopentyl bromide showed, from nmr examination, several acetates lacking the neopentyl skeleton are formed in this displacement.) The distillate was again eluted through Florisil (ether) and then converted to the (*R*)-*O*-methylmandelate as described above. Curve resolution of the deuterium decoupled methylene proton signals showed the *R,R* and *S,R* esters present in equal amounts.

Unsuccessful Attempts to Effect Displacement on Neopentyl Chloride.—Yields of 10% or less (usually the latter) of substitution product were obtained from neopentyl chloride under the following conditions: Et_4NOAc in acetone (120–130°, 9 days) and DMSO (105°, 5 days); KO_2CH in acetone–methanol (120–130°, 4 days); KOAc in DMSO (105°, 4 days); Ac_2O–Ag_2O, (90–95°, 1 day plus 120–130°, 1 day); Et_4NOH in acetone (120–130°, 7.5 days); NaOMe in DMSO (105°, 6 days).

Competition of External Cyanide.—A solution of 1.5 g (12 mmol) of 2-phenylethanol in 8 ml of CCl_4 was added to a solution of 4.32 g (16.5 mmol) of Ph_3P and 1.5 g (30 mmol) of NaCN in 10 ml of DMSO. After being heated at 60–65° for 5.5 hr 150 ml of saturated salt solution was added and the resulting mixture was extracted with three 40-ml portions of pentane. The pentane extract was washed well with water and dried ($MgSO_4$), and the solvent was distilled. The residue was chromatographed on 15 g of Florisil, eluted first with 250 ml of pentane and then with 100 ml of methanol. Concentration of the eluents and examination by vpc (10 ft × 0.25 in. 10% DC550 on 80–100 Chromosorb W at 130°) under conditions permitting facile separation of the alcohol, 2-phenylethyl chloride, and 3-phenylpropionitrile showed the pentane fraction contained only chloride, whereas the methanol eluate contained only unreacted alcohol.

To demonstrate that cyanide competes more effectively than chloride toward a common reagent, a solution of 2-phenylethyl tosylate (4.75 g, 17 mmol), sodium chloride (2.0 g, 34 mmol), and sodium cyanide (1.92 g, 34 mmol) in 25 ml of DMSO was allowed to react for 2 hr at ambient temperature. A saturated salt solution (100 ml) was added and the mixture was extracted with two 50-ml portions of ether. The dried extracts were concentrated, and vpc analysis of the residue showed the ratio of nitrile:chloride was >19:1.

Registry No.—(*R*)-$Me_3CCHDOTs$, 27024-75-5; lithium chloride, 7447-41-8; (*R*)-$Me_3CCHDOH$, 14207-74-0; triphenylphosphine, 603-35-0; lithium bromide, 7550-35-8; CCl_4, 56-23-5; CBr_4, 558-13-4.

Acknowledgment.—Eugene I. Snyder is particularly indebted to East Tennessee State University for its hospitality and the use of its facilities during 1969–1970.

Ionic Peroxide Reactions. The Mechanism of the Reaction of Peroxycarbonates with Trivalent Phosphorus Nucleophiles[1]

WALDEMAR ADAM* AND AGUSTIN RIOS[2]

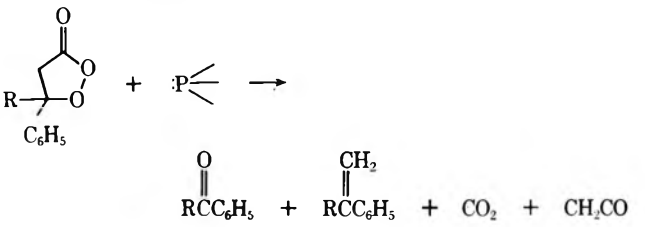
Department of Chemistry, University of Puerto Rico, Rio Piedras, Puerto Rico 00931

Received July 23, 1970

The reaction of diisopropyl peroxydicarbonate with triphenylphosphine in *n*-pentane affords 65% diisopropyl carbonate, 10% diisopropyl pyrocarbonate, and a quantitative yield of triphenylphosphine oxide. The proportion of carbonate to pyrocarbonate is 6.4, 60.0, and ∞ in the solvents *n*-pentane, benzene, and acetonitrile. A crossover experiment indicates statistical crossing in the carbonate but none in the pyrocarbonate. The rates are insensitive to solvent polarity. A mechanism is proposed in which a phosphorane intermediate is formed in a slow step which is subsequently partitioned into carbonate product *via* an ionic route and into pyrocarbonate *via* a molecular path.

Ionic reactions of peroxides are well documented.[3] Among these the heterolysis of the peroxide linkage by nucleophiles such as the hydride ion,[4] carbanions,[5] olefins,[6] amines,[7] phosphines,[8] phosphites,[9] phenols,[10] sulfides,[11] and iodides[12] are typical examples. On the other hand, electrophiles such as aluminum halides,[13] boron halides,[14] and transition metal halides[15] lead to oxygenation of aromatic substrates by heterolysis of peroxides. Examples of intramolecular migration induced by peroxide bond heterolysis are the Criegée rearrangement,[16] the Baeyer–Villiger oxidation,[17] and the carboxy inversion reaction.[18]

Recently we reported[19] an interesting and novel example of a fragmentation reaction when β-peroxylactones are treated with trivalent phosphorus nucleophiles as shown in the equation



In continuation of our work on ionic reactions of peroxides, we decided to investigate the behavior of peroxydicarbonates toward trivalent phosphorus nucleophiles. Our interest in this system was stimulated by the possibility that the pentacovalent phosphorus intermediate, generated between the peroxide and phosphorus compound, might simply form pyrocarbonate or undergo fragmentation into carbonate and carbon dioxide. Both alternatives would be worthy of study since the former would constitute a convenient preparation of pyrocarbonates,[20] while the latter would be a novel fragmentation. In this paper we report on the mechanism of this reaction.

Results

Products.—When equimolar amounts of diisopropyl peroxydicarbonate and triphenylphosphine in hexane are allowed to react at room temperature, instantaneous gas evolution is observed and a white solid precipitates. The white precipitate, formed in quantitative yield, was identified as triphenylphosphine oxide by mixture melting point with an authentic sample. By means of a gas buret it was established that 75–80% carbon dioxide gas was liberated, using *p*-xylene as solvent in order to minimize vapor pressure corrections.

The supernatant liquid was then analyzed for volatile products on a Varian 202-B Aerograph. The major peak was shown to be diisopropyl carbonate and the minor peak diisopropyl pyrocarbonate, identified by retention times and infrared spectra with the authentic materials. From a semimicro scale sample (0.05 mol) were isolated by fractional distillation 53% carbonate and 4% pyrocarbonate.

The quantitative analysis of the volatile products was carried out by means of infrared spectroscopy and by gas chromatography. From the Beer's law plots it was

(1) This work was financed by the National Science Foundation, the A. P. Sloan Foundation, and the Petroleum Research Fund, administered by the American Chemical Society. It was presented at the 5th Caribbean Chemical Symposium, Bridgetown, Barbados, Jan 1969.

(2) Western Fher Fellow, 1967–1970.

(3) A. G. Davies, "Organic Peroxides," Butterworths, London, 1961, Chapters 9 and 10.

(4) H. R. Williams and H. S. Mosher, *J. Amer. Chem. Soc.*, **76**, 3495 (1954); M. Matic and D. A. Sutton, *J. Chem. Soc.*, 2679 (1952); G. A. Russell, *J. Amer. Chem. Soc.*, **75**, 5011 (1953).

(5) S. O. Lawesson and N. C. Yang, *ibid.*, **81**, 4230 (1959).

(6) F. D. Greene, W. Adam, and J. E. Cantrill, *ibid.*, **83**, 3461 (1961); F. D. Greene and W. Adam, *J. Org. Chem.*, **29**, 136 (1964); H. Kwart, P. S. Starcher, and S. W. Tinsley, *Chem. Commun.*, 335 (1967); T. W. Koenig and J. C. Martin, *J. Org. Chem.*, **29**, 1520 (1964).

(7) D. B. Denney and D. Z. Denney, *J. Amer. Chem. Soc.*, **82**, 1389 (1960); W. B. Geiger, *J. Org. Chem.*, **23**, 298 (1958); C. Walling and N. Indictor, *J. Amer. Chem. Soc.*, **80**, 5815 (1958); R. Huisgen and F. Bayerlein, *Justus Liebigs Ann. Chem.*, **630**, 138 (1960).

(8) V. L. Horner and W. Jürgeleit, *ibid.*, **591**, 138 (1955); M. A. Greenbaum, D. B. Denney, and A. K. Hoffmann, *J. Amer. Chem. Soc.*, **78**, 2563 (1956); D. B. Denney and M. A. Greenbaum, *ibid.*, **79**, 979 (1957); D. B. Denney W. F. Goodyear, and B. Goldstein, *ibid.*, **82**, 1393 (1960); A. G. Davies and R. Feld, *J. Chem. Soc.*, 4637 (1958).

(9) C. Walling and R. Rabinowitz, *J. Amer. Chem. Soc.*, **81**, 1243 (1959).

(10) C. Walling and R. B. Hodgdon, Jr., *ibid.*, **80**, 228 (1958); D. B. Denney and D. Z. Denney, *ibid.*, **82**, 1389 (1960).

(11) C. G. Overberger and R. W. Cummins, *ibid.*, **75**, 4250 (1953); D. Swern, L. P. Witnauer, C. R. Eddy, and W. E. Parker, *ibid.*, **77**, 5537 (1955); J. O. Edwards, **78**, 1819 (1956); J. C. Martin, D. L. Tuleen, and W. G. Bentrude, *Tetrahedron Lett.*, 229 (1962).

(12) D. H. Fortmun, C. J. Battaglia, S. R. Cohen, and J. O. Edwards, *J. Amer. Chem. Soc.*, **82**, 778 (1960); J. E. Leffler, R. D. Faulkner, and C. C. Petropoulos, *ibid.*, **80**, 5435 (1958); H. Boardman and G. E. Hulse, *ibid.*, **75**, 4272 (1953).

(13) P. Kovacic and M. E. Kurz, *J. Org. Chem.*, **31**, 2459 (1966).

(14) J. D. McClure and P. H. Williams, *ibid.*, **27**, 24 (1962).

(15) J. T. Edward, H. S. Chang, and S. A. Samad, *Can. J. Chem.*, **40**, 804 (1952); G. A. Razuvaev, N. A. Kartashava, and L. S. Boguslavskaya, *J. Gen. Chem. USSR*, **34**, 2108 (1964).

(16) E. Hedaya and S. Winstein, *J. Amer. Chem. Soc.*, **89**, 1661 (1967); P. D. Bartlett and J. L. Kice, *ibid.*, **75**, 5591 (1953); H. L. Goering and A. C. Olsen, *ibid.*, **75**, 5853 (1953); R. Criegée and R. Kaspar, *Justus Liebigs Ann. Chem.*, **660**, 127 (1948).

(17) C. H. Hassall, *Org. React.*, **9**, 73 (1957); K. Syrkin and I. I. Moiseev, *Russ. Chem. Rev.*, **29**, 193 (1960).

(18) J. E. Leffler and C. C. Petropoulos, *J. Amer. Chem. Soc.*, **79**, 3068 (1957); D. B. Denney and D. Z. Denney, *ibid.*, **79**, 4806 (1957); F. D. Greene, H. P. Stein, C. C. Chiu, and F. M. Vane, *ibid.*, **86**, 2080 (1964).

(19) W. Adam, J. R. Ramírez, and S. C. Tsai, *ibid.*, **91**, 1254 (1969).

(20) W. Thoma and H. Rinke, *Justus Liebigs Ann. Chem.*, **624**, 30 (1959).

extrapolated that 75.3 ± 1.0% carbonate and 6.21 ± 0.45% pyrocarbonate were formed when diisopropyl peroxydicarbonate was treated with triphenylphosphine in chloroform. Using the calibrated internal standard technique, the gas chromatographic analysis showed that 65.0 ± 2.0% carbonate and 10.1 ± 0.8% pyrocarbonate were formed in *n*-pentane, while in benzene a 92% yield of carbonate was obtained under conditions where the pyrocarbonate was decomposed into carbonate. Since the infrared and the gas chromatographic quantitative results were at such variance, we suspected that the carbonate/pyrocarbonate ratio is solvent sensitive. Indeed, gas chromatographic analysis revealed that the carbonate/pyrocarbonate ratio was 6.4, 60.0, and ∞ in pentane, benzene, and acetonitrile.

Since pyrocarbonates are thermally labile,[20] the possibility exists that the carbonate is a secondary product formed from the decomposition of the pyrocarbonate under the reaction conditions. To exclude this possibility, a control experiment was conducted in which a synthetic reaction mixture was simulated consisting of pyrocarbonate and triphenylphosphine in hexane and stirred at room temperature for 6 hr, several times the usual reaction time. Infrared and gas chromatographic analysis showed that no carbonate was formed from the pyrocarbonate under the reaction conditions.

The reaction of diisopropyl peroxydicarbonate with trimethyl phosphite also leads to the formation of carbonate and pyrocarbonate. The interesting finding in this system, however, was that the pyrocarbonate was formed in preference to carbonate. Unfortunately, quantitative product studies were frustrated by the fact that the phosphite and phosphate product severely interfered in the infrared and gas chromatographic work. A number of other trialkyl and triaryl phosphites were tried, but the difficulties persisted.

Kinetics.—Preliminary experiments showed that the phosphines were much too reactive to determine the kinetics by ordinary techniques. Since the trialkyl phosphites and triaryl phosphites led to the same products, and since they are less nucleophilic, the rate studies were carried out for the reaction of tri-*m*-tolyl phosphite with diisopropyl peroxydicarbonate. The reaction was run directly in the thermally equilibrated infrared cell, monitoring the signal output of the decay of the peroxide carbonyl absorption at 1790 cm^{-1} to a Servo-Recorder. Using a 50-fold excess of the phosphite, good pseudo-first-order kinetics through at least three half-lives was observed. The second-order rate constants are 2.78×10^{-4} and 3.76×10^{-4} M^{-1} sec^{-1} at 306.6°K, respectively, in cyclohexane and acetonitrile, at a peroxide concentration of 0.0146 *M* and phosphite concentration of 0.73 *M*.

Crossover Experiment.—In an attempt to capture ionic intermediates by external intervention, diisopropyl peroxydicarbonate was allowed to react with triphenylphosphine in the presence of sodium methyl carbonate. Unfortunately, the peroxydicarbonate reacted vigorously with the carbonate salt, rendering the experiment meaningless. However, when an equimolar mixture of diisopropyl and di-*sec*-butyl peroxydicarbonates was treated with an excess of triphenylphosphine in pentane, gas chromatographic analysis revealed that besides diisopropyl and di-*sec*-butyl carbonate also isopropyl *sec*-butyl carbonate (cross-carbonate) was formed. These carbonates were formed in the proportions 1.00:1.02:1.90, respectively. Therefore, virtually a statistical mixture of carbonates was obtained. Very interesting is the fact that no cross-pyrocarbonate could be detected even at maximum sensitivity, although both the diisopropyl and di-*sec*-butyl pyrocarbonates were formed as minor products.

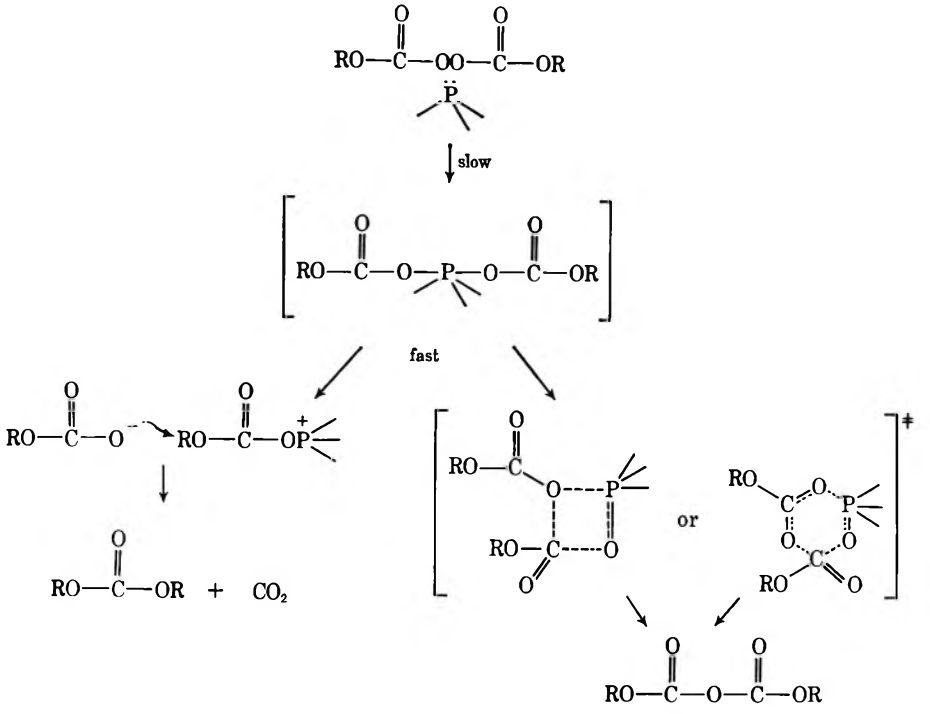
It is possible that triphenylphosphine might have caused statistical interchange of the diisopropyl and di-*sec*-butyl carbonates. However, a control experiment in which a simulated reaction mixture of the two carbonates and triphenylphosphine in benzene was allowed to stand 3 days at room temperature showed no cross-carbonate on gas chromatographic analysis.

Mechanism.—Let us now construct a reasonable mechanism for this reaction from the above experimental data. To facilitate this task we reiterate the important findings together with their mechanistic implications. (a) The second-order kinetics and the absence of a kinetic solvent effect suggest that a pentacovalent phosphorus intermediate is formed in the rate-determining step,[19,21] which subsequently decays *via* a fast step into the carbonate and pyrocarbonate. (b) The stability of the pyrocarbonate under the reaction conditions implies that both the pyrocarbonate as well as the carbonate are primary products, generated by partitioning of the pentacovalent intermediate *via* distinct paths. (c) The solvent effect on the product ratio of carbonate to pyrocarbonate, *i.e.*, with increasing solvent polarity more carbonate is produced, bespeaks the fact that the pyrocarbonate is formed *via* a molecular path, while the carbonate is formed *via* an ionic path from the pentacovalent intermediate. (d) The presence of a product solvent effect but the absence of a kinetic solvent effect presumes that the kinetic and the product steps are separated into two events. (e) The fact that predominantly carbonate is formed with phosphine, but predominantly pyrocarbonate with phosphite, corroborates the above interpretation since the phosphorus of the phosphite is more electron deficient than the phosphorus of the phosphine and thus the pentacovalent intermediate formed from the phosphite prefers to partition *via* the molecular path rather than the ionic path to avoid depositing a positive charge onto an already desparate phosphorus. (f) The absence of cross-pyrocarbonate but the statistical crossover in the carbonates fortifies the conclusion that the pyrocarbonate is formed *via* a molecular process while the carbonate originates from an ionic path, but both are derived from a common pentavalent phosphorus intermediate.

A reasonable mechanism which accommodates these findings is given by Scheme I. This scheme illustrates that a pentacovalent phosphorus intermediate is generated by rate-determining phosphorus insertion into the peroxide bond. Subsequently the phosphorane is partitioned *via* fast steps into the products. As demanded by the experimental data, the kinetic step and the product step are clearly separated into distinct events. The ionic pathway affords the carbonate by attack of the carbonate ion on the alkyl group of the phosphonium ion, displacing carbon dioxide and the phosphine oxide. The most compelling evidence for

(21) D. B. Denney and S. T. D. Gough, *J. Amer. Chem. Soc.*, **87**, 138 (1965).

SCHEME I



R = isopropyl

this interpretation is the statistical crossover in the carbonate product.

The pyrocarbonate, on the other hand, is thought to be produced *via* a molecular route involving either a four- or six-membered cyclic transition state. A more polar solvent would be expected to divert more of the phosphorane *via* the ionic route, while a less nucleophilic phosphorus such as the phosphites compared to the phosphines would channel a greater portion of the intermediate through the molecular path. It is indeed surprising how sensitive the partitioning of the phosphorane into carbonate and pyrocarbonate is toward nucleophilicity and solvent polarity.

It is important to mention that *tert*-butylperoxy isopropyl carbonate behaved normally toward nucleophilic attack by triphenylphosphine. Thus triphenylphosphine oxide was formed quantitatively, but no carbon dioxide gas was evolved. The only volatile product was *tert*-butyl isopropyl carbonate, isolated in 85% yield by distillation.[22] This result suggests that the phosphorane intermediate ROCOOP(≤)O-*tert*-Bu either goes *via* a molecular path to give the carbonate product or that the heterolysis proceeds, as we might have been anticipated, exclusively to give the ions $ROCOO^-$ and *tert*-$BuOP{\leq}^+$ rather than the ions *tert*-BuO^- and $ROCOOP{\leq}^+$. If the latter ions had been formed, some nucleophilic attack by the *tert*-butoxide ion at the alkyl group would have been expected in view of our peroxydicarbonate results. Consequently, alkyl *tert*-butyl ether should have been formed besides the carbonate due to decarboxylation. Alkyl *tert*-butyl carbonates are difficult to make by ordinary methods[23] and we offer this reaction as a convenient synthetic route for these compounds. Similarly the reaction of di-*tert*-butylperoxy carbonate gave di-*tert*-butyl carbonate when treated with excess triphenylphosphine, but no carbon dioxide was liberated.[24]

Related Work.—The existence of pentacovalent phosphorus compounds is well documented.[25] They are conveniently prepared through the reaction of peroxides with trivalent phosphorus nucleophiles.[26] In most cases the pentacovalent adducts are unstable[25] and undergo the oxygen extrusion reaction[8]

$$R{-}OO{-}R + :P{\leq} \longrightarrow R{-}O{-}R + O{=}P{\leq}$$

The novel feature of the reaction of peroxydicarbonates with trivalent phosphorus nucleophiles is that the intermediary phosphorane is partitioned into two products, namely pyrocarbonate and carbonate. A related case of competitive partitioning concerns the cyclic phosphorane produced from β-peroxylactones and trivalent phosphorus compounds,[19] shown in Scheme II. Two possible dipolar ions A and B are produced from the cyclic phosphorane, which subsequently suffer ionic push–pull triggered fragmentation to yield the products. Also in this case solvent polarity, phosphorus nucleophilicity, and β-alkyl group structure control the relative partitioning of the phosphorane into the dipolar ions A and B. In fact, this novel ketene elimination and decarboxylation reactions stimulated us to look for other examples of competitive partitioning of pentacovalent phosphorus intermediates. Indeed, the phosphorane formed from peroxydicarbonates and phosphines undergo competitive partitioning, but, unlike the cyclic phosphorane produced from β-peroxylactones which is partitioned into two distinct dipolar ions, the partitioning competes between a molecular route (pyrocarbonate) and an ionic route (carbonate).

(22) W. Adam and J. Sanabia, unpublished results.

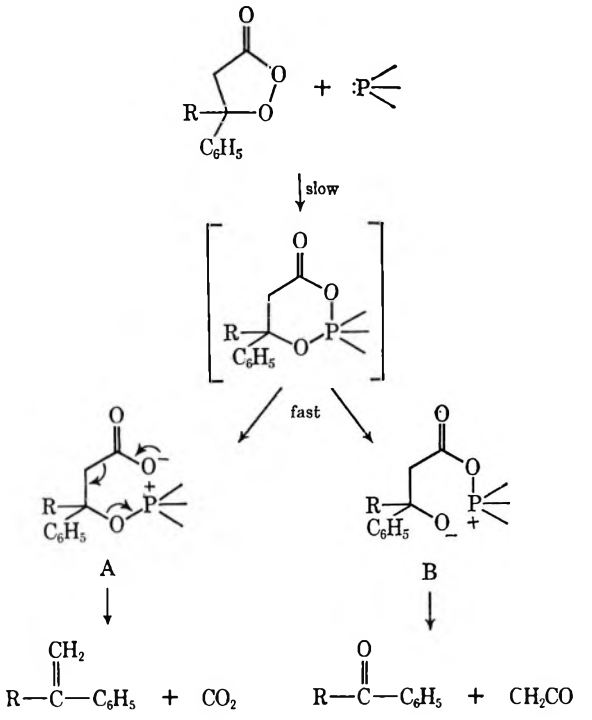
(23) W. Klee and M. Brenner, *Helv. Chim. Acta*, **44**, 2151 (1961); H. A. Staab, *Ber.*, **95**, 1284 (1962).

(24) W. Adam, B. S. Ramaswamy, and P. Rullan, unpublished results.

(25) F. Ramirez, *Accounts Chem. Res.*, **1**, 168 (1968).

(26) D. B. Denny and N. G. Adin, *Tetrahedron Lett.*, 2569 (1966); D. B. Denney and S. T. D. Gough, *J. Amer. Chem. Soc.*, **87**, 138 (1965).

SCHEME II



An alternative mechanistic interpretation of the experimental data of the peroxydicarbonate–triphenylphosphine reaction is to propose that solvent-caged ion pairs are formed. Some of the caged ion pairs collapse to produce the pyrocarbonate; the remainder diffuse apart and finally generate the carbonate and carbon dioxide. For the moment we prefer competitive partitioning between the molecular and ionic paths; however, oxygen-18 labeling experiments and the use of optically active substrates are in progress to provide information on the more subtle aspects of the mechanism of this reaction.

Finally it is worthy to point out that the reaction of tertiary arylamines with diisopropyl peroxydicarbonate has been studied.[27] A free-radical-chain mechanism has been proposed in this case. This contrasting behavior of the tertiary amines compared to the phosphorus nucleophiles has been noted previously.[28]

Experimental Section

Diisopropyl Peroxydicarbonate.[29]—In an open 125-ml erlenmeyer flask were placed 20.6 g (0.17 mol) of isopropyl chloroformate. While the mixture was cooled with an ice bath and stirred magnetically a chilled suspension of 6.63 g (0.085 mol) of sodium peroxide octahydrate, freshly prepared from 9.6 ml of 30% aqueous hydrogen peroxide and 51.8 ml of 11.1% aqueous sodium hydroxide, was added by means of a medicine dropper, keeping the reaction temperature at 5–10°. After the reaction mixture was stirred for 30 min at 5–10°, the organic layer was taken up in ether, washed well with water, and dried over anhydrous magnesium sulfate. Removal of the drying agent and evaporation of the solvent at reduced pressure, keeping the temperature below 5–10°, gave 16.4 g of oily product. Repeated recrystallization from *n*-pentane at −70° afforded 12.4 g (72% yield) of diisopropyl peroxydicarbonate, mp 8–10° (lit.[30] mp 9–10°). Iodometric titration showed that this material had a purity of 98.9%.

Di-*sec*-butyl peroxydicarbonate was prepared in 75% yield as a viscous oil giving a peroxide titer (iodometric) of 90.2%. All attempts to crystallize the oil failed. The infrared spectrum showed a clean double carbonyl band at 1790 and 1815 cm^{-1} similar to that of the diisopropyl peroxycarbonate.

Diisopropyl Pyrocarbonate.—To a mechanically stirred suspension of 35.0 g (0.28 mol) of sodium isopropyl carbonate, freshly prepared by carbonation of sodium isopropoxide in isopropyl alcohol, in 30 ml of methylene chloride was added a solution of 30 g (0.30 mol) of phosgene in 75 ml of methylene chloride over a period of 90 min, maintaining the reaction temperature at 0–5°. During the phosgene addition carbon dioxide gas was evolved spontaneously. After the reaction mixture stirred overnight at room temperature, the reaction flask was flushed with dry nitrogen gas to remove unreacted phosgene. The solids were collected on a Büchner funnel and washed several times with methylene chloride. The solvent was evaporated from the combined filtrates at reduced pressure and the liquid residue vacuum distilled. The fraction collected at 44–45° (0.5 mm), corresponding to 4.1 g (7.7% yield) of diisopropyl pyrocarbonate, had $n^{26}D$ 1.3985 [lit.[31] bp 44–46° (0.3 mm), $n^{25}D$ 1.3982].

Diisopropyl Carbonate.—To a solution of 4.75 g (0.06 mol) of freshly distilled pyridine in 5 ml of isopropyl alcohol was added slowly while stirring magnetically 6.13 g (0.05 mol) of isopropyl chloroformate. After 2-hr total reaction time the solution was diluted with a large excess of water and the organic layer taken up in ether. The organic layer was dried over magnesium sulfate and, on removal of the solvent, the crude product was rectified by distillation. The pure carbonate, 4.2 g (57% yield), was collected at 73° (57 mm), $n^{22}D$ 1.3920 [lit.[32] bp 146–147° (760 mm), $n^{20}D$ 1.3906].

Di-*sec*-butyl carbonate was prepared *via* the above procedure in 53% yield, bp 70–72 (15 mm), $n^{22}D$ 1.4028 [lit.[33] bp 73–74° (18 mm), $n^{22}D$ 1.4039].

Isopropyl *sec*-butyl carbonate was prepared *via* the above procedure in 37% yield, bp 80–82° (40 mm), $n^{22}D$ 1.3960.

Triphenylphosphine was purchased from Matheson Coleman and Bell Co. and recrystallized from ethanol, mp 79–80°.

Tri-*m*-tolyl phosphite was obtained from Mr. S. C. Tsai and fractionated at reduced pressure, bp 182° (0.05 mm) [lit.[34] bp 188° (1.0 mm)].

Solvents were purified according to standard procedures.[35]

The Reaction of Diisopropyl Peroxydicarbonate with Triphenylphosphine.—A 250-ml round-bottom flask, provided with a magnetic stirring bar and a 250-ml pressure-equalized dropping funnel, was charged with 10.25 g (0.0498 mol) of the peroxydicarbonate, dissolved in 40 ml of pentane. While the solution was stirred magnetically, a solution of 15.72 g (0.06 mol) of triphenylphosphine dissolved in 175 ml of pentane was added dropwise from the funnel. Spontaneous gas evolution and precipitation of a white solid was observed. After a total of 14-hr reaction time, the solid was collected on a Büchner funnel and washed several times with pentane, affording 13.7 g (98.9% yield) of triphenylphosphine oxide, mp 156–156.5°, mmp 156–156.5°. The solvent was removed from the combined filtrates and the oily residue fractionated at reduced pressure. The first fraction, identified as diisopropyl carbonate by its carbonyl band at 1735 cm^{-1} and comparison with the authentic material, was collected at 48.2° (18 mm), $n^{26}D$ 1.3900, and weighed 3.85 g (53% yield). The second fraction, identified as diisopropyl pyrocarbonate by its characteristic carbonyl bands at 1825 and 1765 cm^{-1} and comparison with the authentic material, was collected at 64–72° (0.30 mm), $n^{26}D$ 1.3988, and weighed 0.36 g (3.8% yield).

A control experiment was carried out by preparing a solution of 59.9 mg (0.31 mmol) of pyrocarbonate and 79.2 mg (0.31 mmol) of triphenylphosphine in 1.0 ml of benzene and letting it stand 6 hr. No gas was evolved and infrared and gas chromatographic analysis showed the absence of diisopropyl carbonate.

Quantitative Determination of Carbon Dioxide Gas.—A 3-ml round-bottom flask, provided with a magnetic stirring bar and a

(27) J. C. Crano, *J. Org. Chem.*, **31**, 3615 (1966).

(28) R. Huisgen, W. Heydcamp, and F. Bayerlein, *Ber.*, **93**, 363 (1960).

(29) Utmost care should be exercised when working with peroxydicarbonates since a sample allowed to stand at room temperature underwent violent decomposition. All safety measures should be taken.

(30) F. Strain, W. E. Bissinger, W. R. Dial, H. Rudoff, B. T. de Witt, H. C. Stevens, and J. H. Langston, *J. Amer. Chem. Soc.*, **72**, 1254 (1950).

(31) J. H. Howe and L. R. Morris, *J. Org. Chem.*, **27**, 1901 (1962).

(32) K. Sabathy, *Monatsh. Chem.*, **72**, 308 (1939).

(33) R. L. Frank, H. R. Davies, Jr., S. S. Drake, and J. B McPherson, Jr., *J. Amer. Chem. Soc.*, **66**, 1509 (1944).

(34) E. N. Walsh, *ibid.*, **81**, 3023 (1959).

(35) K. B. Wiberg, "Laboratory Techniques in Organic Chemistry," McGraw-Hill, New York, N. Y., 1960.

2-ml pressure-equalized dropping funnel, whose outlet was connected to a 50-ml gas buret, was equilibrated at 29°. The flask was charged with a solution of 377.6 mg (1.83 mmol) of diisopropyl peroxydicarbonate in 0.5 ml of xylene and the dropping funnel with a solution of 602.6 mg (2.30 mmol) of triphenylphosphine in 1.4 ml of xylene. With the mercury level at zero and stirring magnetically the phosphine solution was added dropwise, always maintaining the mercury levels at equal heights in the buret and the leveling bulb. After complete addition (about 15 min) the reaction mixture was stirred until no change in the mercury level was observed (about 30 min). A total volume of 40.6 ml of gas was produced, corrected for xylene vapor pressure,[36] representing 1.42 mmol of carbon dioxide (77.6% yield).

Quantitative Infrared Analysis of Diisopropyl Pyrocarbonate and Carbonate.—Standard solutions of the carbonate (0.01–0.06 M) and pyrocarbonate (0.01–0.03 *M*) were prepared in chloroform. Their absorbances were then determined in 0.2-mm sodium chloride cells at 1735 cm^{-1} for the carbonate and 1820 cm^{-1} for the pyrocarbonate on the Perkin-Elmer 237-B Infracord. For maximum accuracy the above concentrations were chosen so that the absorbance reading were within the range 0.10–0.70. The The Beer's law plots from these data were good straight lines with molar extinction coefficients of 12.96 and 14.58 for the carbonate and pyrocarbonate, respectively. The reaction mixture resulting from 0.386 mmol of proxycarbonate and 0.405 mmol of triphenylphosphine in 3.0 ml of chloroform was transferred to a 10-ml volumetric flask, diluted to the calibration mark, and its absorbance measured at 1735 and 1820 cm^{-1} using the same sodium chloride cells. The respective values were 0.382 and 0.035, which on extrapolation from the Beer's law plots indicated that 76.2% carbonate and 6.5% pyrocarbonate had formed.

Quantitative Gas Chromatographic Analysis of the Volatile Products.—The analyses were performed on a Varian 202-B Aerograph using a 2.5-ft copper column (0.25-in. diameter), packed with 20% SE-30 and 2% NaOH on Chromosorb W, and operated at a helium flow rate of 100 ml/min, an injector temperature of 96°, a detector temperature of 154°, and a column temperature of 83°. Under these conditions, which are extremely critical, the thermally labile pyrocarbonate undergoes less than 1% decomposition, maintaining good base lines, excellent separation, and symmetrical peaks.

A preliminary gas chromatographic run showed that the carbonate/pyrocarbonate ratio was approximately 10. Standard solutions of the products were then prepared in pentane at the ratios 1:8, 1:10, and 1:12 of pyrocarbonate to carbonate, by weighing the respective liquids into appropriate volumetric flasks, the total weight of carbonate and pyrocarbonate being maintained constant. An equal weight of internal standard (*p*-dichlorobenzene) was weighed into the volumetric flask, and the contents were diluted to the calibration mark with pentane. Each standard solution was analyzed by adjusting the injection volume and attenuator setting so that maximum needle deflection was secured. The peak areas were disk integrated, taking in each case an average of three injections. Calibration charts of the peak area ratio of each component to the internal standard against the known concentrations were then prepared, yielding good straight lines with slopes near unity.

A reaction mixture in pentane, prepared at the same concentrations and conditions as the standard solutions, was then analyzed on the above column and the peak area ratio of each component to the internal standard determined. With the help of the calibration charts the percentages of carbonate and pyrocarbonate were found to be 65.0 ± 2% and 10.1 ± 0.8% in pentane. In benzene the total yield was 92%.

Crossover Reaction between Diisopropyl and Di-*sec*-Butyl Peroxydicarbonates with Triphenylphosphine.—In a 10-ml round-bottom flask were placed 103 mg (0.5 mmol) of diisopropyl and 117 mg (0.5 mmol) of di-*sec*-butyl peroxydicarbonate, dissolved in 2 ml of benzene. While the mixture was stirred magnetically and kept at reaction temperature at 25° by means of a water bath, there was added dropwise a solution of 524 mg (2.0 mmol) of triphenylphosphine, dissolved in 2 ml of benzene. After 90 min of reaction time the appropriate amount of internal standard was added; the contents were diluted to the calibration mark and then analyzed for carbonates. The relative proportions of diisopropyl, isopropyl *sec*-butyl, and di-*sec*-butyl carbonates were 1.00:1.90:1.02, respectively.

A control experiment was conducted by allowing an equimolar mixture of diisopropyl and di-*sec*-butyl carbonate in benzene in the presence of excess triphenylphosphine to stand several days. Gas chromatographic analysis of the reaction mixture showed the absence of isopropyl *sec*-butyl carbonate.

Rate Measurements.—The kinetics of the reaction were studied directly in a 0.5-mm sodium chloride cell, using a Perkin-Elmer 237-B Infracord. This instrument was equipped with an ordinate scale accessory which permitted locking the wavelength drive mechanism at the desired wavelength, relaying the signal output to a variable drive Heath Servo-Recorder. The reaction rate was followed automatically as a continuous absorbance–time plot on the recorder. The temperature of the reaction cell was regulated by means of a constant-temperature accessory (Barnes Engineering Co.), situated directly in the sample beam. Temperature control was within ±0.1° during a kinetic run. The reduction of the light intensity of the sample beam was compensated by means of a matched sodium chloride cell and an attenuator.

After the empty sample cell was thermally equilibrated at the desired temperature (usually 30 min), it was externally loaded with the reaction mixture whose kinetics were to be determined. For this purpose the inlet and outlet ports of the sample cell were each extended through the top of the constant-temperature compartment with 22-gauge Teflon tubing, provided with the appropriate Luer lock fittings. The external loading process was accomplished by means of Luer lock syringes. One syringe containing the reaction solution was attached to the inlet port and the empty syringe to the outlet port of the sample cell. Quick and efficient loading without introducing air bubbles into the sample cell was achieved by synchroneous push–pull action of the respective syringes.

The reaction solution was prepared by dissolving quickly about 0.0146 mmol of peroxydicarbonate and 0.73 mmol of phosphite in 2.0 ml of solvent, using a calibrated volumetric flask. This solution was charged into the sample cell, while the solvent cell was charged with a solution of 0.73 mmol of phosphite in 2 ml of solvent. The wavelength drive mechanism was set at 1790 cm^{-1}, the Servo-Recorder set at a convenient rate, and the absorbance of the reaction mixture recorded through three half-lives. The kinetic runs were analyzed in terms of pseudo-first-order kinetics giving good straight-line plots. The second-order rate constants are 2.78×10^{-4} and 3.76×10^{-4} M^{-1} sec^{-1}, respectively, in cyclohexane and acetonitrile.

Registry No.—Diisopropyl peroxydicarbonate, 105-64-6; di-*sec*-butyl peroxydicarbonate, 19910-65-7; diisopropyl pyrocarbonate, 24425-00-1; diisopropyl carbonate, 6482-34-4; di-*sec*-butyl carbonate, 623-63-2; isopropyl *sec*-butyl carbonate, 27040-99-9; triphenylphosphine, 603-35-0; tri-*m*-tolyl phosphite, 620-38-2.

(36) "Handbook of Chemistry and Physics," 46th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, p D-124.

Stereochemical Studies of Monoterpene Compounds. IX.[1] Pinacol-Type Rearrangements of α-Pineneglycol Tosylate[2]

TOSHIFUMI HIRATA AND TAKAYUKI SUGA*[3]

Department of Chemistry, Faculty of Science, Hiroshima University, Hiroshima, Japan

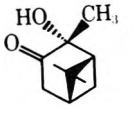
Received May 27, 1970

Treatment of (−)-*cis*-α-pineneglycol monotosylate (**4**) with methanolic potassium hydroxide yielded (+)-2α-acetyl-5,5-dimethylbicyclo[2.1.1]hexane (**5**), (+)-3β-methylnopinone (**6**), (−)-pinocamphone (**7**), and (−)-*cis*-α-pineneglycol (**2**). The formation of ketone **5** is a unique example of the ring contraction of a bicyclo[3.1.1]-heptane skeleton to the highly strained bicyclo[2.1.1]hexane system by a pinacol-type rearrangement. The reaction mechanism is discussed from a stereochemical viewpoint. A preferred conformation for **4**, **5**, and **6** (**4a**, **5a**, and **6a**, respectively) is also proposed.

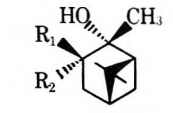
We have previously discussed[4,5] the stereochemistry of (+)-2-hydroxypinocamphone (**1**) and its reduction products **2** and **3**. In order to obtain more chemical evidence for establishing the stereochemistry of **1**, α-pineneglycol monotosylate (**4**) derived from **2** was treated with methanolic potassium hydroxide. We wish to discuss the stereochemical and mechanistic implications of the reaction as well as the stereochemistry of the monotosylate **4** and the reaction products **5** and **6**.

Results and Discussion

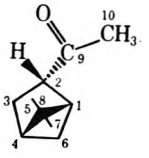
Treatment of (−)-*cis*-α-pineneglycol monotosylate (**4**) with potassium hydroxide in methanol yielded an oily reaction mixture, which was composed of (+)-2α-acetyl-5,5-dimethylbicyclo[2.1.1]hexane (**5**) (50% yield), (−)-*cis*-α-pineneglycol (**2**) (26%), (+)-3β-methylnopinone (**6**) (8.5%), and (−)-pinocamphone



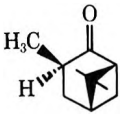
1



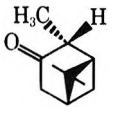
2, $R_1 = H; R_2 = OH$
3, $R_1 = OH; R_2 = H$
4, $R_1 = H; R_2 = OTs$



5



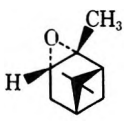
6



7

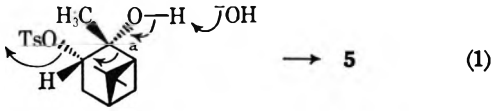
(**7**) (5.6%). These compounds were identified by a combination of spectroscopic and chemical methods.[6] The structure of ketone **5** was further confirmed by its conversion to 5,5-dimethylbicyclo[2.1.1]hexan-2-one (**9**) *via* 5,5-dimethylbicyclo[2.1.1]hexane-2α-carboxylic acid (**8**).

8, $R_1 = COOH; R_2 = H$
9, $R_1, R_2 = O$

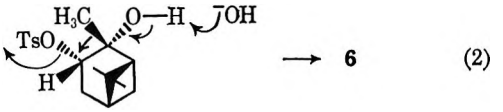


11

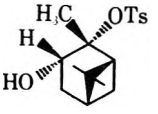
Reaction Mechanism.—Treatment of *cis*-α-pineneglycol (**2**) and 2α,3α-epoxypinane (**11**) with methanolic potassium hydroxide resulted in recovery of starting material. Accordingly, neither **2** nor **11** is an intermediate in the formation of ketones **5**, **6**, and **7** from the tosylate **4**. Glycol **2** is clearly the hydrolyzed product of **4**. Thus, the formation of **5**, **6**, and **7** is best explained by pinacol-type rearrangements as shown below. The driving force for the rearrangements is the base-catalyzed elimination of the tosyloxy group of **4**; concerted migration of bond a then gives ketone **5** (eq 1). On the other hand, migration of the C-2 methyl group instead of bond a forms ketone **6** (eq 2). The formation of **7** from **4** is difficult to explain because it seems quite improbable that the hydroxyl group would ionize to the extent of 5.6% in the presence of a leaving group as good as the tosyloxy group. The admixture of the isomeric monotosylate **12** in **4**, in amounts small enough



4 → **5** (1)



4 → **6** (2)



12

to escape detection by nmr analysis is a possible explanation. This isomer would be expected to give **7** readily by the elimination of the tosyloxy group, followed by concerted migration of the C-3 proton.

Stereochemistry of the Reaction and the Reaction Products.—If the reactive conformation of *cis*-α-

(1) Paper VIII of this series: T. Hirata, T. Suga, and T. Matsuura, *Bull. Chem. Soc. Jap.*, **43**, 2588 (1970).

(2) A part of this paper has been reported in the form of a communication in *Tetrahedron Lett.*, 5553 (1968).

(3) To whom all inquiries regarding this paper should be addressed.

(4) T. Suga, T. Shishibori, T. Hirata, and T. Matsuura, *Bull. Chem. Soc. Jap.*, **41**, 1180 (1968).

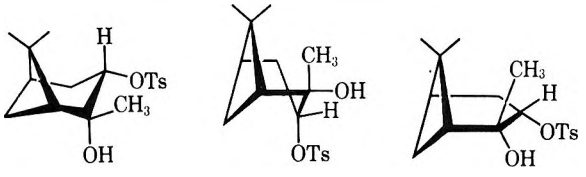
(5) R. G. Carlson, J. K. Pierce, T. Suga, T. Hirata, T. Shishibori, and T. Matsuura, *Tetrahedron Lett.*, 5941 (1968).

(6) The ir spectra of **5** and **9**, and of the 2,4-dinitrophenylhydrazone of **9**, were generously donated by J. Meinwald,[7] ketone **6** was obtained from E. Klein,[8] and pinocamphone (**7**) was prepared in our laboratory.[4]

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

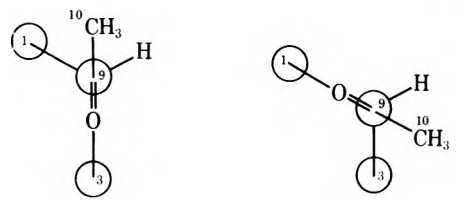
(8) E. Klein and W. Rojahn, *Chem. Ber.*, **100**, 1902 (1967).

pineneglycol monotosylate (**4**) is assumed to be **4a**, the ring-contracted ketone **5** would be expected to form readily, because the migrating moiety would be anti-coplanar to the leaving group. If the tosylate **4** is in conformation **4b**, ketone **6** would be expected to be formed as the main product, because the anti-coplanar migrating group is the methyl group. On the other hand, if the reactive conformation is **4c**, ketones **5** and **6** would be expected to be formed in equal amounts, because both migrating moieties are in equal surroundings with respect to the leaving group. Ketones **5** and **6** were produced in the ratio of 50 to 8.5. Hence it is proposed that the preferred reactive conformation of *cis*-α-pineneglycol monotosylate (**4**) is **4a**. Accordingly, both C-2 and C-3 hydroxyl groups of the starting glycol **2** are trans to the *gem*-dimethyl group.

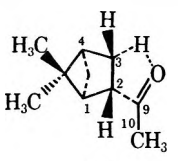


4a **4b** **4c**

We now wish to deal with the conformation of the acetyl group of ketone **5**. Ketone **5** can exist in either of the preferred conformations **5a** and **5b**. According to the octant rule,[9] the Cotton effect should be positive for **5a** and negative for **5b**. The optical rotatory dispersion (ORD) and circular dichroism (CD) curves of ketone **5** showed a positive Cotton effect both in methanol and in isooctane at room temperature. Variable-temperature CD curves in an EPA solvent[10] and in decalin indicated that the positively rotating conformer **5a** is more favored at low temperature and that the amount of the negatively rotating conformer **5b** increases slightly at high temperature, as shown in Figure 1. In addition, the $C_{3\alpha}$ proton is shifted to lower field (δ 2.84 ppm) by the anisotropy of the carbonyl group (*cf.* **5a'**) in the nmr spectrum, because a weak intramolecular interaction as shown in **5a'** may exist in conformer **5a** but not in **5b**. These facts indicate the preferred conformation of ketone **5** to be **5a**.



5a **5b**



5a'

The configuration of the C-3 carbon of dextrorotatory 3β-methylnopinone (**6**) has been assigned[8] as R. The nmr spectrum of the C-3 methyl group showed a small upfield shift ($\Delta\delta_{CDCl_3-C_6H_6}$ = +0.03 ppm) by benzene, and the conformation of the C-3 methyl group of **6** should be equatorial.[11] The preferred conformation of (+)-**6** is therefore **6a**.

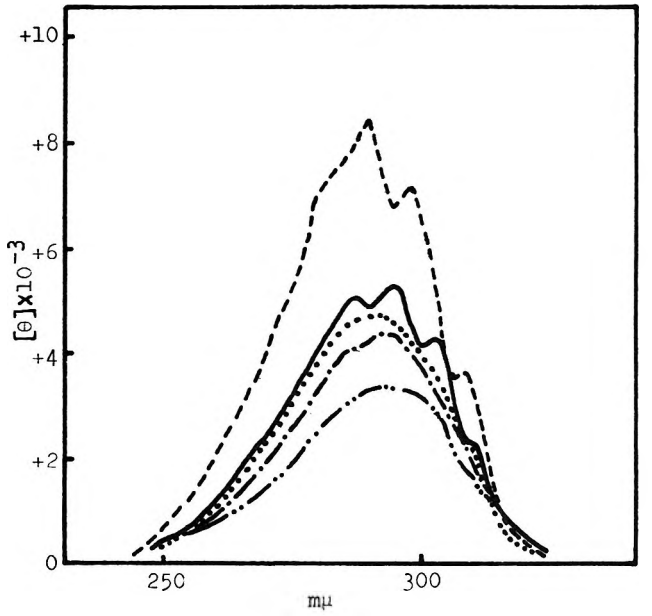
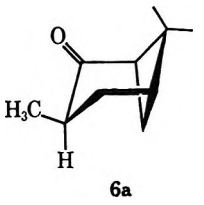


Figure 1.—CD curves of ketone **5** in an EPA solvent at −192° (------), and +19° (· · · · ·) and in decalin at −74° (———), +21° (— · —), and +133° (— · · —).



6a

Experimental Section[12]

***cis*-α-Pineneglycol Monotosylate (4).**—A mixture of 2.2 g of (−)-*cis*-α-pineneglycol (**2**) {$[\alpha]^{25}D$ −0.89° (*c* 7.91, chloroform), derived from (+)-2-hydroxypinocamphone[4]}, 2.7 g of *p*-toluenesulfonyl chloride, and 20 ml of pyridine was left to stand at room temperature for 3 days. The whole reaction mixture was poured into ice water to yield 3.4 g of a crude crystalline mass, which was recrystallized from a mixture of *n*-hexane and ethyl acetate and furnished 3.0 g of *cis*-α-pineneglycol monotosylate (**4**): mp 76–77°; $[\alpha]^{25}D$ −4.4° (*c* 2.6, MeOH); ir (KBr disk) 3536 (OH), 1593 cm^{-1} (C=C).

Anal. Calcd for $C_{17}H_{24}O_4S$: C, 62.94; H, 7.46. Found: C, 62.95; H, 7.75.

Rearrangement of *cis*-α-Pineneglycol Monotosylate (4).—To a solution of 7.0 g of potassium hydroxide in 20 ml of methanol was added 6.2 g of **4**. The solution was heated to 65° for 3 hr and then kept at room temperature overnight. The reaction mixture was diluted with 500 ml of water and extracted with ether. Removal of the solvent from the ether layer yielded 2.5 g of an oily product which was chromatographed on a silica gel column with a mixture of ethyl acetate and *n*-hexane to separate four fractions: fraction 1, 0.29 g; fraction 2, 0.85 g; fraction 3, 0.32 g; fraction 4, 0.55 g.

(9) W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Amer. Chem. Soc.*, **83**, 4013 (1961).

(10) EPA solvent is composed of ether–isopentane–ethanol in the ratio of 5:5:2 by volume.

(11) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1965, p 163.

(12) The ORD and CD spectra were measured at 25° with a Japan Spectroscopic Co., Ltd., Model ORD/UV-5 spectropolarimeter, equipped with a circular dichroism attachment. The nmr spectra were recorded with a Varian Associates HA-100, high-resolution spectrometer using tetramethylsilane as an internal standard. Microanalysis was done at the Microanalytical Center in the Faculty of Pharmacy of Kyoto University. The mass spectral analysis was performed on a Hitachi mass spectrometer, Model RMU-D, ionizing at the order of 70 eV.

Fraction 2 was proved to be 2α-acetyl-5,5-dimethylbicyclo-[2.1.1]hexane (5), which was identified by comparing its infrared spectrum with that of an authentic sample[6] and by its conversion to 8 and 9 as described below. Fraction 4 was identified as (−)-*cis*-α-pineneglycol (2), mp 55–56°. Fraction 1 was further subjected to preparative gas chromatography. This resulted in separation of 0.11 g of (+)-3β-methylnopinone (6) and 0.04 g of ketone 5. Fraction 3 consisted of 5 and two components, which were further subjected to preparative gas chromatography. This resulted in isolation of (−)-pinocamphone (7), $[\alpha]^{25}D$ −15.2° (*c* 0.42, MeOH).

The physical properties of 5 are given as follows: $[\alpha]^{25}D$ +16.0° (*c* 0.86, MeOH); ir (liquid film) 1357 (–$COCH_3$), 1710 (C=O), 1369 and 1386 cm^{-1} (gem-CH_3); uv (MeOH) 280 mμ (ε 35.2); ORD $[\phi]_{400}^{methanol}$ +1650, $[\phi]_{304}$ +1870, $[\phi]_{263}$ −2390, $[\phi]_{230}$ −1730°; ORD $[\phi]_{400}^{isooctane}$ +204, $[\phi]_{316}$ +1970, $[\phi]_{311}$ +1840, $[\phi]_{307}$ +1940, $[\phi]_{268}$ −2450, $[\phi]_{226}$ −1700°; CD $[\theta]_{320}^{methanol}$ 0, $[\theta]_{286}$ +2310, $[\theta]_{235}$ 0°; CD $[\theta]_{325}^{isooctane}$ 0, $[\theta]_{294}$ +2610, $[\theta]_{230}$ 0°; nmr (CCl_4) δ 0.81 (s, C_8 3 H), 1.27 (s, C_7 3 H), 2.09 (s, OAc), and 2.84 (m, $C_{3\alpha}$ H); mass spectrum (70 eV) *m/e* (rel intensity) 152 (8, M^+), 137 (10), 109 (84), 67 (60), 43 (100).

The 2,4-dinitrophenylhydrazone of 5 showed the following properties: mp 113.0–113.5° (from MeOH); uv (MeOH) 364 mμ (ε 9500), 264 (4200), and 228 (6850).

Anal. Calcd for $C_{16}H_{20}O_4N_4$: H, 6.07; C, 57.82; N, 16.86. Found: H, 6.15; C, 58.09; N, 16.86.

The physical properties of 6 are $[\alpha]^{25}D$ +59.7° (*c* 0.64, MeOH); ir (liquid film) 1710 (C=O), 1376 and 1391 cm^{-1} (gem-CH_3); ORD $[\phi]_{400}^{methanol}$ +380, $[\phi]_{301}$ +3550, $[\phi]_{265}$ −3380, $[\phi]_{230}$ −1080°; ORD $[\phi]_{400}^{isooctane}$ +157, $[\phi]_{304}$ +1490, $[\phi]_{268}$ −1530, $[\phi]_{230}$ −315°; CD $[\theta]_{317}^{methano}$ 0, $[\theta]_{285}$ +2740, $[\theta]_{240}$ 0°; CD $[\theta]_{332}^{isooctane}$ 0, $[\theta]_{290}$ +1240, $[\theta]_{238}$ 0°. The nmr signals of the methyl protons appeared at δ 1.35 (s, C_8 3 H), 0.73 (s, C_9 3 H), and 1.17 (d, J = 7.0 Hz, C_{10} 3 H) in 10% deuteriochloroform solution, and δ 1.00 (s, C_8 3 H), 0.57 (s, C_9 3 H) and 1.14 (d, J = 7.0 Hz, C_{10} 3 H) in 10% benzene solution.

5,5-Dimethylbicyclo[2.1.1]hexane-2α-carboxylic Acid (8).—To a sodium hypobromite solution prepared from 1.20 g of sodium hydroxide, 0.5 ml of bromine, and 20 ml of water was added 0.30 g of 5. The reaction mixture was stirred at room temperature for 3 hr. The usual work-up yielded 0.11 g of acid 8: mp 54–55° (lit.[7] mp 55.0–55.5°); ir (KBr disk) 1693 cm^{-1} (C=O).

5,5-Dimethylbicyclo[2.1.1]hexan-2-one (9).—Following the literature method,[7] the permanganate oxidation of 0.34 g of the acid 8 afforded 0.12 g of 9: ir (liquid film) 1750 cm^{-1} (C=O); 2,4-dinitrophenylhydrazone, mp and mmp 155.5–156.0° (lit.[7] mp 155.5–156.0°).

Registry No.—2, 27040-84-2; 4, 22339-18-0; 5, 22339-19-1; 5 2,4-DNP, 27040-87-5; 6, 27040-88-6; 7, 22339-21-5; 8, 27040-90-0; 9, 22339-20-4.

Acknowledgment.—The authors wish to express their gratitude to Professor J. Meinwald of Cornell University for a gift of the 2,4-dinitrophenylhydrazone of ketone 9 and the ir spectra of 5 and 9, to Dr. E. Klein of Dragoco Co. for a gift of ketone 6 and its 2,4-dinitrophenylhydrazone, and to Dr. E. von Rudolloff of the National Research Council of Canada for measuring the nmr spectra on a Varian Associates, HA-100, spectrometer.

The Synthesis of the (3*S*)-Methylcyclopentane-1,2-dicarboxylic Acids (Nepetic Acids Related to the Nepetalactones)[1a]

E. J. EISENBRAUN,* G. H. ADOLPHEN,[1b] K. S. SCHORNO,[1c] AND R. N. MORRIS[1d]

Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma 74074

Received June 15, 1970

The synthesis of the (3*S*)-methylcyclopentane-1,2-dicarboxylic acids [(+)-**3a**, (−)-**3c**, (+)-**3e**, and (+)-**3g**] related to the nepetalactones (**1a** and **1b**) is described. This synthesis starts with (−)-(3*S*)-methylcyclohexanone (**4**) and employs a Favorskii-type rearrangement of γ-bromo β-oxo esters. Also studied was the resolution of intermediates in this synthesis through use of optically active derivatives. This latter technique provides predominately the trans 3*R* or 3*S* nepetic acids and was studied mainly in the more abundant 3*R* series.

Our synthesis of the four (3*R*)-methylcyclopentane-1,2-dicarboxylic acids[2] and their racemic counterparts could not immediately be extended to the 3*S* series since (−)-(3*S*)-methylcyclohexanone (**4**) was not available. These 3*S* acids[3a] [(+)-*t*-3-methyl-*r*-1,*c*-2-cyclopentanedicarboxylic acid (**3a**), (−)-*c*-3-methyl-*r*-1,*t*-2-cyclopentanedicarboxylic acid (**3c**), and (+)-*t*-3-methyl-*r*-1,*t*-2-cyclopentanedicarboxylic acid (**3g**)], except for (+)-*c*-3-methyl-*r*-1,*c*-2-cyclopentanedicarboxylic acid (**3e**), are known as nepetic acids. Their chemical correlation [except (+)-**3e**] with the nepetalactones (**1a** and **1b**)[3a] has been accomplished as shown in Scheme I, and consequently their absolute configurations and stereochemistry are known.[3b-e] It should be noted that the reference position for cis and trans designations of the nepetic acids and the corresponding diols is the carboxyl group or the hydroxymethyl group at the ultimate position from the methyl group.[3a] The rapid expansion of the methylcyclopentane monoterpenoids to many new structural types and their role in biosynthesis place an increased emphasis on the importance of these acids in structure elucidation as well as their absolute configuration and stereochemical assignments.[2,4]

Although the resolution[5a,b] of (±)-**4** to (−)-**4** and its use in the synthesis shown in Scheme II became the suc-

* To whom correspondence should be addressed.

(1) (a) E. J. Eisenbraun, G. H. Adolphen, K. S. Schorno, and R. N. Morris, presented at the 159th National Meeting of the American Chemical Society, Houston, Texas, Feb 22–27, 1970; (b) Research Associate, 1967–1969; (c) Graduate Research Assistant, 1965–1967; (d) National Science Foundation Graduate Trainee, 1969–1970.

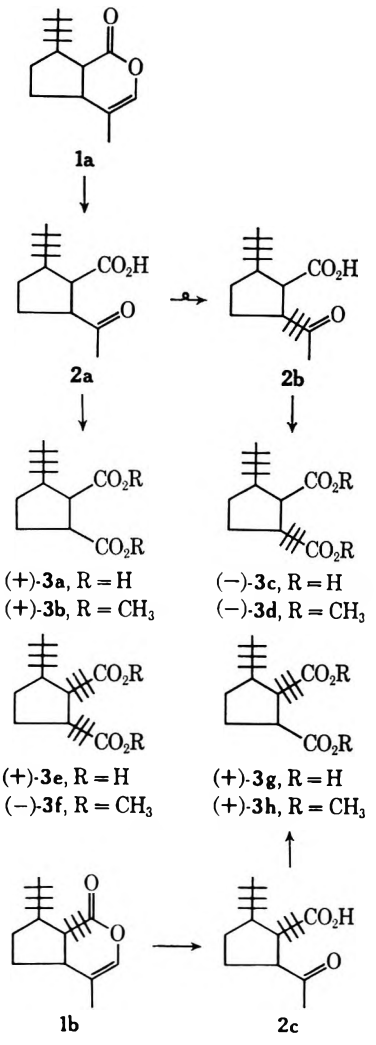
(2) E. J. Eisenbraun, P. G. Hanel, K. S. Schorno, F. Dilgen, and J. Osiecki, *J. Org. Chem.*, **32**, 3010 (1967).

(3) (a) We thank Dr. K. L. Loening for kindly advising us about the systematic nomenclature for this paper and supplying the names for **1a** and **1b** as (4a*S*,7*S*,7a*R*)-5,6,7,7a-tetrahydro-4,7-dimethylcyclopenta[c]pyran-1(4a*H*)-one and (4a*S*,7*S*,7a*S*)-5,6,7,7a-tetrahydro-4,7-dimethylcyclopenta-[c]pyran-1(4a*H*)-one, respectively; *cf.* "International Union of Pure and Applied Chemistry," *J. Org. Chem.*, **35**, 2849 (1970); (b) E. J. Eisenbraun and S. M. McElvain, *J. Amer. Chem. Soc.*, **77**, 3383 (1955); (c) S. M. McElvain and E. J. Eisenbraun, *ibid.*, **77**, 1599 (1955); (d) R. B. Bates, E. J. Eisenbraun, and S. M. McElvain, *ibid.*, **80**, 3413 (1958); (e) *ibid.*, **80**, 3420 (1958).

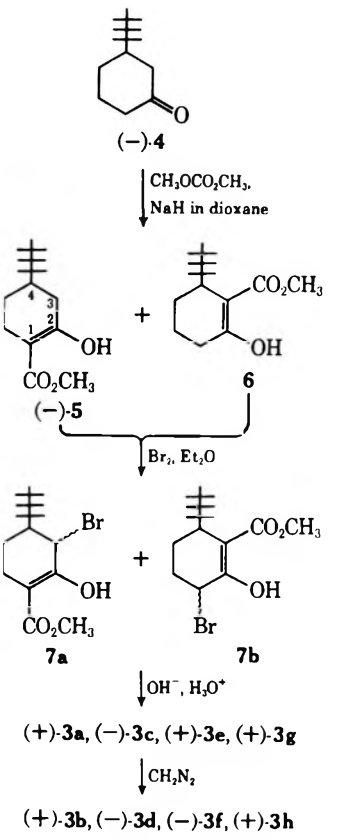
(4) (a) W. I. Taylor and A. R. Battersby, Ed., "Cyclopentanoid Terpene Derivatives," Marcel Dekker, New York, N. Y., 1969; (b) A. G. Horodysky, G. R. Waller, and E. J. Eisenbraun, *J. Biol. Chem.*, **244**, 3110 (1969).

(5) (a) R. Adams and J. D. Garber, *J. Amer. Chem. Soc.*, **71**, 522 (1949); (b) G. Adolphen, E. J. Eisenbraun, G. W. Keen, and P. W. K. Flanagan, *Org. Prep. Proced.*, **2**, 93 (1970); (c) A. W. Ingersoll, *Org. React.*, **2**, 376 (1944).

Scheme I



Scheme II



cessful route to the optically active acids and esters (**3a–h**), we first attempted their synthesis by converting[6] (±)-**5** to the optically active menthyl β-oxo esters shown in Scheme III. Two of the latter were crystalline [(+)-**9a** and (−)-**9a**] and hence permitted resolution. These crystalline, optically active β-oxo esters were used in subsequent steps to prepare resolved nepetic acids. For example, bromination of (−)-**9a** gave the menthyl γ-bromo β-oxo ester (+)-**10** which on successive treatment with alkali and then acid yielded the 3*R trans*-nepetic acids[6b] (+)-**3c** and (−)-**3g**. In a like manner, the less abundant enantiomer, (+)-**9a**, carried through the same sequence, gave the 3*S trans*-nepetic acids[6c] (−)-**3c** and (+)-**3g**. The other menthyl β-oxo esters, (+)-**9b** and (−)-**9b**, remaining in mother liquors from the resolutions failed to crystallize and therefore were not studied except to confirm that the isomer (+)-**9b** is not crystalline, since an independent preparation from (+)-**5** and (+)-**8**[6a,c] gave an oil.

That effective resolution of the C-4 centers of (+)-**9a** and (−)-**9a** had been achieved was established by obtaining the same crystalline menthyl β-oxo ester, (+)-**9a**, from the reaction of (±)-**5** and (+)-**8** as from (−)-**5** and (+)-**8**, and, similarly, (−)-**9a** resulted from either (+)-**5** and (−)-**8** or (±)-**5** and (−)-**8**. A further test of the completeness of the resolution and the reversibility of the ester exchange in the formation of the menthyl β-oxo esters was to heat the menthyl β-oxo ester (+)-**9a** in the presence of a large excess of methanol and recover pure and resolved (−)-**5** from the reaction mixture.

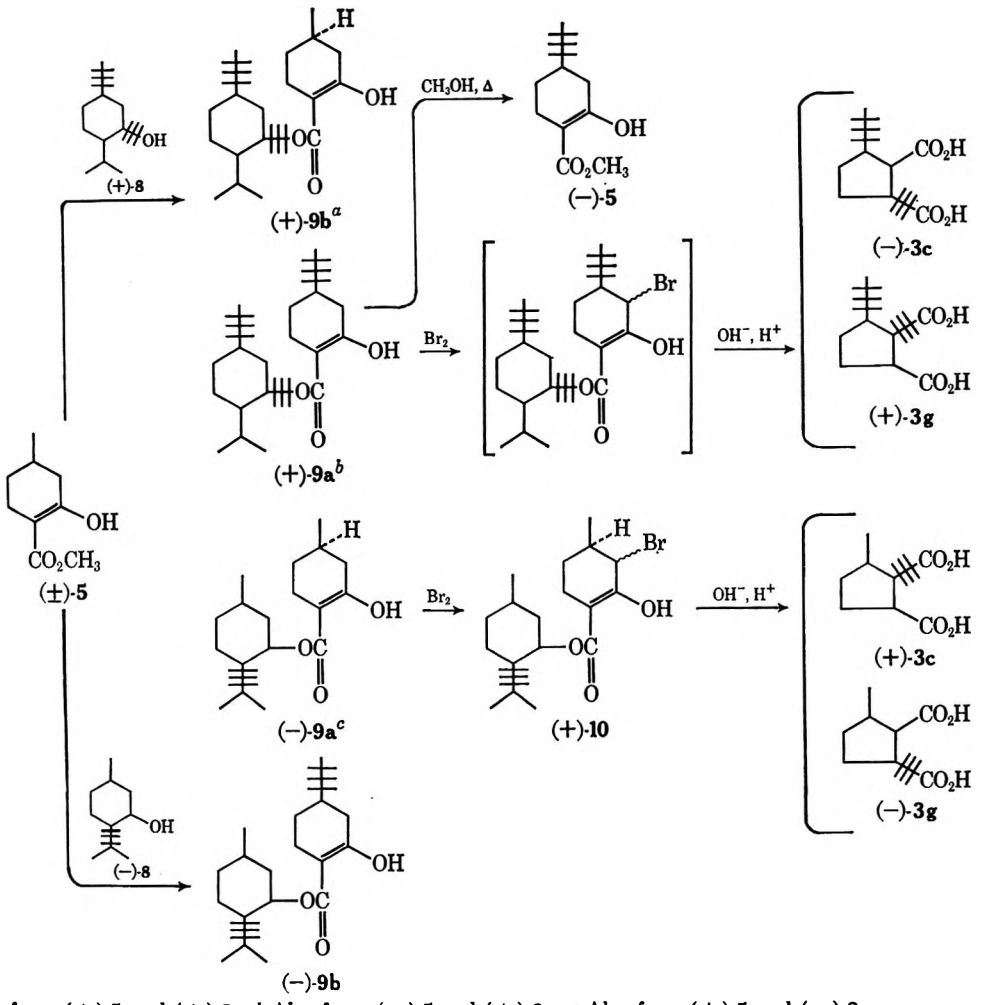
The 3*S* nepetic acids (−)-**3c** and (+)-**3g** having *trans*-carboxyl groups and prepared from (+)-**9a** were shown to be identical with the corresponding nepetic acids derived from **1a** and **b** by comparing optical rotation data,[7] melting points including melting points of appropriate mixtures of pure nepetic acids, and retention times of gas chromatography peaks of their dimethyl esters.

The nepetic acids (+)-**3c** and (−)-**3g** obtained from the menthyl β-oxo ester (−)-**9a** were shown to be identical with the 3*R trans*-nepetic acids previously prepared[2] from (+)-**5**. Thus the reactions shown in Scheme III may be used to prepare nepetic acids of the 3*R* or 3*S* absolute configuration. However, it should be noted that the menthyl β-oxo esters do not provide significant yields of the nepetic acids having *cis*-carboxyl groups unless these esters are reconverted to the methyl β-oxo esters [*e.g.*, (+)-**9a** to (−)-**5** in Scheme III] before bromination and Favorskii-type rearrangement. Unfortunately, the preparation of (+)-**9a** and (−)-**5** at this stage was dependent upon the prior preparation of (+)-menthol (**8**) by resolution.[5c] When it became clear that syntheses of all the 3*S* nepetic acids *via* (+)-**9a**

(6) (a) The exchange of alkoxyl groups is easily accomplished by heating the β-oxo ester in the presence of an excess of the appropriate alcohol; after exchange is complete, the surplus alcohol is removed under partial vacuum. (b) The product from the use of (−)-menthol leads to the (3*R*)-methylcyclopentane-1,2-dicarboxylic acid series (*trans*-carboxyl groups) related to (+)-pulegone. (c) The use of (+)-menthol provides the nepetic acids (*trans*-carboxyl groups) of the 3*S* series derived from the nepetalactones. (d) These studies were carried out on the more abundant compounds derived from (+)-(3*R*)-methylcyclohexanone.

(7) We thank Dr. P. M. Scopes, Chemistry Department, Westfield College, Hampstead, London, NW 3, England, for these determinations.

SCHEME III



[a] Also resulting from (+)-5 and (+)-8. [b] Also from (−)-5 and (+)-8. [c] Also from (+)-5 and (−)-8.

was impractical, we turned to the direct resolution of (±)-4 to optically pure (−)-4, which was accomplished through recrystallization of the amine bisulfite salts obtained from reaction with SO_2 and (+)-α-methylphenethylamine.[5a,b] Once (−)-4 became available, the reactions in Scheme II provided the four nepetic acids (+)-3a, (−)-3c, (+)-3e, and (+)-3g as expected.[2]

This work, particularly the preparation of the unknown and thermodynamically unstable (+)-*cis,cis*-nepetic acid (3e), completes our synthesis of all possible isomeric forms of these acids.[2]

Application of the reactions of Scheme II to pure (±)-5 yielded essentially the same mixture of racemic nepetic acids as obtained from a mixture of (±)-5 and (±)-6. The purity of the methyl β-oxo esters [*e.g.*, (±)-5 or (±)-6] or the composition of a mixture of them was determined by cleavage with alkaline hydrogen peroxide and conversion to (±)-11 or (±)-12 or a mixture of these as shown in Scheme IV. These esters were distinguished by glc studies and were identified by comparison with known standards. This method was also used to show that the ratio of (±)-5 to (±)-6 in the crude β-oxo ester mixture from a typical preparation was 85:15.

An explanation of the inability to obtain *cis* acids from (+)-9a or (−)-9a is desirable. The change of alkyl group (methyl to menthyl) causes a dramatic change in product ratio of nepetic acids in the reactions of Schemes II and III. Whereas the Favorskii-type rearrangement of the methyl γ-bromo β-oxo esters of Scheme II provides a high percentage of the *cis* acids (+)-3a and (+)-3e, under the same conditions the products from (+)-9a or (−)-9a (Scheme III) are mainly *trans* acids 3c and 3g with *none* of the *cis,cis* acids 3e and only *about 2%* of the *cis,trans* acids 3a being observed. These differences may possibly be due to a steric effect of alkyl groups (menthyl *vs.* methyl) imposing an important hindrance to the hydrolysis of the ester function as compared to the epimerization of the carbon–hydrogen bond at the position α to the carbalkoxyl groups of the intermediate half-esters 14 and 15 of Scheme V. This premise would account for the dramatic change in ratio of nepetic acids produced by these competing reactions.

To test this steric concept, Favorskii-type rearrangements of brominated β-oxo esters (Scheme V) as well as hydrolysis of half-esters and diesters were carried out under a variety of conditions. Of these conditions, minimal exposure of (+)-5[6d] to dilute aqueous alkali at room temperature and then acidification provided the highest yield of the thermodynamically less stable cis products, implying that 14 and 15 are formed first and that 16 and 17 are formed by epimerization. The ratios of these products were determined by glc studies of the respective dimethyl esters obtained by reaction with diazomethane.

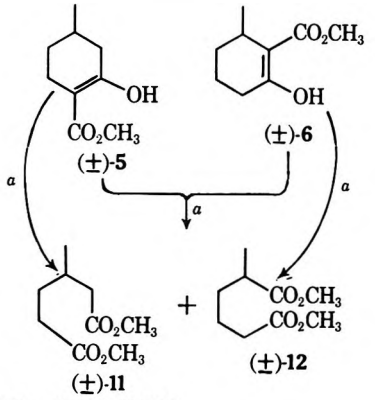
Table I

Glc Ratio of Favorskii-Type Rearrangement Products[a]

β-Oxo ester	Base:solvent ratio[b]	Time at room temp	% [c] t,c 3d	t,t 3h	c,t 3g	c,c 3f
(±)-5	Na_2CO_3:CH_3OH:H_2O = 1:1:5	1 hr	8[d,e]	0	35[d,e]	57[d,e]
			7[d]	0	43[d]	50[d]
(+)-5	NaOH:CH_3OH:H_2O = 2:15:10	4 hr	23	17	20	40
(+)-5	$NaOCH_3$:CH_3OH = 1:4	20 min	73	22	5	0
(+)-5	KOH:CH_3OH = 1:10	3 min	53	22	14	11
(+)-5	KOH:H_2O = 1:5	3 min	18	15	25	42
7a	KOH:CH_3OH:H_2O = 1:6:12	1 hr	10	6	32	52
7a and 7b	KOH:CH_3OH:H_2O = 1:1:5	2 hr	12	8	29	51
(−)-9a	NaOH:CH_3OH:H_2O = 2:15:10	4 hr	64	36	0	0
(−)-9a	NaOH:CH_3OH:H_2O = 2:25:5	3 min	47 (21)[f]	9 (20)[f]	20 (19)[f]	24 (18)[f]
9c[g]	NaOH:CH_3OH:H_2O = 2:25:5	4 hr	34	25	5	36
9d[h]	NaOH:CH_3OH:H_2O = 2:25:5	4 hr	39	27	14	20
9e[i]	NaOH:CH_3OH:H_2O = 2:25:5	4 hr	73	27	0	0
(+)-10	NaOH:CH_3OH:H_2O = 2:10:15	4 hr	72	28	Trace	Trace
(+)-10	NaOH:CH_3OH:H_2O = 2:10:15	1 hr	66	34	Trace	Trace

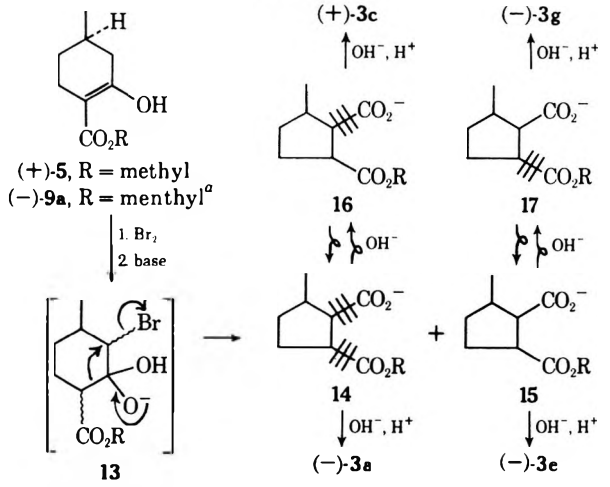
[a] The β-oxo esters except for (+)-10 were brominated and then subjected to base-catalyzed reaction. [b] g:ml:ml. [c] In order of elution (l to r) from LAC 886 column at 210°. [d] Glc curves of racemic dimethyl nepetates from this reaction were compared with those of corresponding esters in the 3S series. [e] Esters obtained by ether extraction of alkaline reaction product. [f] These diols (*cf.* Scheme VI) were analyzed by glc (*cf.* Experimental Section). [g] 2-Methyl-1-butyloxyl group exchanged for methoxyl group of (+)-5. [h] Ethoxyl group exchanged for the methoxyl group of (+)-5. [i] $C_{10}H_{17}O$ group (bornyloxyl) exchanged for the methoxyl group of (+)-5.

Scheme IV



[a] OH^-, H_2O_2; H_3O^+:CH_2N_2.

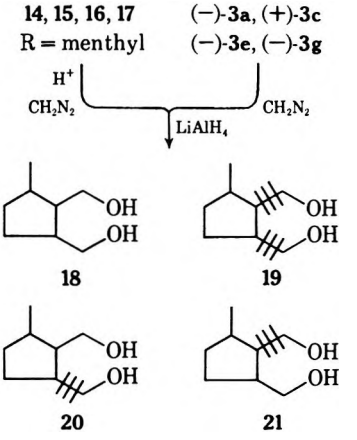
Scheme V



[a] Prepared from (+)-5 and (−)-8.

To establish the composition of the menthyl half-ester products (Scheme V), they were converted to the diols **18**, **19**, **20**, and **21** with $LiAlH_4$ as shown in Scheme VI, and the resulting mixture was analyzed by glc

Scheme VI



through comparison with standards prepared from pure nepetic acids. In the case of mixtures of the menthyl half-esters **14**, **15**, **16**, and **17**, the conversion to and the analysis of the diols showed that the ratio of cis:trans products strongly favored cis if the Favorskii-type reaction was terminated promptly, since products measured as diols then showed the ratio 47:9:20:24 (**21**:**20**:**19**:**18**) as compared to the considerably altered ratio 64:36:0:0 (**3d**:**3h**:**3b**:**3f**) obtained on prolonged hydrolysis. These and other glc data related to the stereochemistry of diols and esters are consolidated in Table I.

It should be pointed out that the Favorskii-type rearrangement of (±)-**5** in aqueous methanolic sodium carbonate gives in low yield a neutral fraction which has been shown to contain dimethyl nepetates (Table I) in the ratio 8:0:35:57 (**3d**:**3h**:**3b**:**3f**) This ratio is particularly remarkable since the isomer (±)-**3f**, the least stable one, is present in greatest abundance. This is comparable to the ratio 7:0:43:50 found for the remaining products following the usual isolation procedure (*cf* Table I).

At this time we prefer the semibenzilic intermediate (**13** of Scheme V) to the cyclopropanone intermediate

as an explanation for the observed Favorskii-type rearrangements.[8]

The behavior of the dimethyl nepetates during acid hydrolysis is of interest. The esters having trans functional groups [(+)-**3d** and (−)-**3h** of the 3*R* series] retain this stereochemistry during hydrolysis to the corresponding *trans* acids. However, the (3*R*)-*cis,cis*-dimethyl ester (+)-**3f** is partially epimerized and yields some of each of the other 3*R* nepetic acids (about 10%), whereas the (3*R*)-*cis,trans* ester (−)-**3b** is hydrolyzed to *cis,trans* acid (−)-**3a** and in low yield (1–2%) to the *trans,cis* acid (+)-**3c**.

Experimental Section[9]

(−)-(3*S*)-Methylcyclohexanone (4).—(+)-α-Methylphenethylamine was used to resolve (±)-**4** to (−)-**4**: bp 70–71° (20 mm); $[\alpha]^{23}D$ −11.8° (neat) [lit.[3c] +11.3° (enantiomer) (neat)].[5b] Optical rotatory dispersion data[7] are reported elsewhere.[5b]

(−)-Methyl (4*S*)-Methyl-2-oxocyclohexanecarboxylate (5).—A 7.4-g sample of (−)-**4** was converted as described[2] to 8.0 g (76%) of a mixture of (−)-**5** and **6**, bp 65° (0.7 mm). This mixture was cooled to −20° and, after solidification, was recrystallized twice from cold petroleum ether, bp 60–70°, to give 4.5 g of pure colorless (−)-**5**: mp 41–42°; $[\alpha]^{23}D$ −105° (*c* 4.4, $CHCl_3$) [lit.[2] $[\alpha]^{23}D$ +101.5° (enantiomer) (*c* 0.5, $CHCl_3$)]; the ir spectra (KBr) of (−)-**5** and (+)-**5** were identical.

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.32; H, 8.24.

Oxidation of (+)-5 and a Mixture of (±)-5 and (±)-6.—A 1.7-g sample of (+)-**5** prepared as described[2] was added to a stirred solution of 1 g of NaOH in 8 ml of H_2O and 4 ml of 30% H_2O_2. Heat was evolved and the stirred reaction mixture foamed. After 30 min, an additional 4 ml of 30% H_2O_2 was added and the mixture was heated with stirring. The reaction mixture was cooled, acidified, and extracted with ether. The ether extracts were washed with acidified ferrous sulfate solution and water and then dried ($MgSO_4$) and concentrated to give a colorless solid which on crystallization from benzene gave 3-methyladipic acid: mp 86–87°; $[\alpha]^{25}D$ +7.24° (*c* 1.3, H_2O) [lit.[3c] mp 85–89°, $[\alpha]^{26}D$ +9.6° (*c* 4.25, $CHCl_3$)]. The melting point of a mixture with authentic (+)-3-methyladipic acid showed no depression. Esterification with CH_2N_2 and gas chromatography on a 0.25 in. × 10 ft column of LAC 886 on acid-washed, DCMS-treated Chromosorb G showed one peak with the same retention time as authentic dimethyl 3-methyladipate.

In a similar manner, a mixture of (±)-**5** and (±)-**6** was oxidized. Gas chromatography analysis of the methyl esters gave two peaks having 5 and 5.7 min retention times, respectively, in the ratio of 15:85, the last peak being due to the dimethyl ester of 3-methyladipic acid. These peaks were identified by successive enrichments with authentic (±)-**11** and (±)-**12**.

(±)-Methyl 6-Methyl-2-oxocyclohexanecarboxylate (6).—A mixture of (±)-**5** and (±)-**6** was refrigerated and crystals of (±)-**5** were cropped by filtration until the residual mixture contained about two-thirds (±)-**5**. Fractional distillation through a 6-in. Vigreux column gave pure (±)-**6** as a last cut: bp 72° (0.7 mm); ir (neat) 834, 1028, 1079, 1155, 1225, 1258, 1285, 1357, 1440, 1615, 1650, 1715, 1745, and 2945 cm^{-1}.

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.69; H, 8.33.

Favorskii-Type Rearrangement of 7a and 7b.—To a stirred mixture of 7.5 g of the oxo esters (−)-**5** and **6** in 25 ml of CCl_4 was added 7.05 g of Br_2 in 10 ml of CCl_4 during 30 min. Ether was added and the mixture was washed with bicarbonate solution and water. After drying ($MgSO_4$), the solution was concentrated *in vacuo* and the residue, dissolved in 10 ml of methanol, was added during 15 min to a stirred and cooled (tap water) mixture of 10 g of KOH in 50 ml of water. After the mixture was stirred for 2 hr, it was extracted with ether (three 25-ml portions) to remove neutral material and then acidified with 20% HCl. To avoid prolonged extraction with ether, the acidified solution was stirred with diazomethane, which rapidly extracts and esterifies the nepetic acids.[10] The mixture was analyzed on the 0.25 in. × 10 ft LAC 886 column at 190° and showed the ratio 12:8:29:51 (**3d**:**3h**:**3b**:**3f**).

Separation, Purification, and Properties of Dimethyl (3*S*)-Methylcyclopentane-1,2-dicarboxylates (3b, 3d, 3f, and 3h).—The crude alkaline reaction product from the Favorskii-type rearrangement of **7a** (Scheme II) was acidified and the aqueous solution was then treated with an ether solution of diazomethane.[10] The ether layer was dried ($MgSO_4$) and concentrated to give a crude mixture of dimethyl nepetates **3b, 3d, 3f, and 3h**. These esters were separated by preparative gas chromatography on a ⅜ in. × 45 ft LAC 886 (30% on acid-washed Chromosorb W) column at 210°. A 5.4-g sample of the mixed esters was injected in 0.2-ml portions. The elution order was **3d**, **3h**, **3b**, and **3f**, and the retention times were 55, 65, 70, and 75 min, respectively.

These esters were evaporatively distilled: bp 110° (0.8 mm); $[\alpha]^{25}D$, for **3b**, +47.2° (*c* 2.2, $CHCl_3$); **3d**, −37.1° (*c* 1.4, $CHCl_3$); **3f**, −27.5° (*c* 1.1, $CHCl_3$); and **3h**, +44.8° (*c* 0.8, $CHCl_3$) [lit.,[2] for (−)-**3b**, −54° (*c* 2.0, $CHCl_3$); (+)-**3d**, +36° (*c* 2.5, $CHCl_3$); (+)-**3f**, +32° (*c* 0.6, $CHCl_3$); and (−)-**3h**, −52° (*c* 2.5, $CHCl_3$)]; **3f**, ir (neat) 1720 s and 1790 w cm^{-1} (ester C=O); the other bands in the spectra of (−)-**3f** and (+)-**3f** were identical.

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98, H, 8.05. Found for **3b**: C, 59.72; H, 7.89. Found for **3f**: C, 59.78; H, 8.12. Found for **3h**: C, 59.75; H, 7.84.

The infrared spectra (cm^{-1}) of **3b, 3d, 3f**, and **3h** were determined as neat liquids (Table II).

(+)-*t*-(3*S*)-Methyl-*r*-1,*c*-2-cyclopentanedicarboxylic Acid (3a).—A 0.402-g sample of (+)-**3b** was saponified by heating 1 hr with 20 ml of barium hydroxide solution saturated at room temperature. The precipitate of the barium salt of the acid which formed was filtered out and washed with distilled water. The salt was treated with dilute hydrochloric acid, and the total mixture was evaporated to dryness under reduced pressure. Ether extraction afforded 0.197 g of **3a**: mp 130–130.5°; $[\alpha]^{24}D$ +62° (*c* 1.15, $CHCl_3$), +59° (*c* 1.7, CH_3OH) (lit.[3c] mp 125–126°, $[\alpha]^{25}D$ +69°). The melting point of a mixture of synthetic and natural **3a** showed no depression.

(−)-*c*-(3*S*)-Methyl-*r*-1,*t*-2-cyclopentanedicarboxylic Acid (3c).—A 0.103-g sample of (−)-**3d** was saponified as described for (+)-**3b** to give 0.064 g of **3c**: mp 119–120°; $[\alpha]^{24}D$ −39.1° (*c* 1.2, $CHCl_3$) [lit.[3c] mp 117–118°, $[\alpha]^{23}D$ −35.4°]. The melting point of a mixture of synthetic and natural **3c** showed no depression.

(+)-*c*-(3*S*)-Methyl-*r*-1,*c*-2-cyclopentanedicarboxylic Acid (3e).—Saponification of 0.345 g of (−)-**3f** yielded 0.068 g of **3e**: mp 140–141°; $[\alpha]^{24}D$ +7.2° (*c* 2.6, $CHCl_3$) and −38.2° (*c* 2.1, CH_3OH) [lit.[2] mp 140–141°, $[\alpha]D$ −4.07° (enantiomer) (*c* 1.0, $CHCl_3$) and +37° (enantiomer) (*c* 0.54, CH_3OH) for 3*R* series].

Anal. Calcd for $C_8H_{12}O_4$: C, 55.80; H, 7.03. Found: 55.94; H, 6.86.

(+)-*t*-(3*S*)-Methyl-*r*-1,*t*-2-cyclopentanedicarboxylic Acid (3g).—Saponification of 0.073 g of (+)-**3h** yielded 0.042 g of **3g**: mp 113–115°; $[\alpha]^{24}D$ +82.6° (*c* 0.9, $CHCl_3$) [lit.[3e] mp 114–115°, $[\alpha]^{21}D$ +85.8° (*c* 5.54, $CHCl_3$)].

Preparation of (+)-9a, (−)-9a, and (+)-9b.—A 17-g sample of (±)-**5** and 20 g of (+)-menthol[5c] (**8**) were dissolved in 40 ml of toluene, and the mixture was heated at reflux for 10 hr.[11] The toluene and excess (+)-**8** were removed *in vacuo*. The product crystallized after 2 days. Recrystallization from hexane gave 9.5 g (65%) of (+)-**9a** as colorless crystals: mp 126–129°; $[\alpha]^{26}D$ +50° (*c* 1.0, $CHCl_3$); ir (KBr) 651, 684, 762, 775, 787, 832, 843, 866, 916, 962, 993, 1015, 1040, 1048, 1110, 1178, 1223, 1260, 1290, 1318, 1373, 1450, 1725, 2890, and 2950 cm^{-1}.

Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.69; H, 10.38.

In a similar manner, a 10-g sample of (+)-**5** and 15 g of (−)-**8** gave 14.1 g (81%) of colorless crystals of (−)-**9a**: mp 128–130°;

(8) E. W. Warnhoff, C. M. Wong, and W. T. Tai, *J. Amer. Chem. Soc.*, **90**, 514 (1968).

(9) Infrared spectra were recorded with a Beckman IR-5A spectrophotometer; C and H analyses were obtained from Galbraith Laboratories, Knoxville, Tenn.; a Varian Associates Model A-60A nuclear magnetic resonance spectrometer was used for nmr spectra; optical rotations were determined using an O. C. Rudolph Model 80 polarimeter. The melting points are corrected and were taken in the stirred bath of a Hoover–Thomas apparatus.

(10) E. J. Eisenbraun, R. N. Morris, and G. Adolphen, *J. Chem. Educ.*, **47**, 710 (1970).

(11) A. R. Bader, L. O. Cummings, and H. A. Vogel, *J. Amer. Chem. Soc.*, **73**, 4195 (1951).

Table II
Infrared Bands of Methyl 3S Nepetates

3b	925		1048		1205	1287	1365		1435	1735	
3d	908	1025	1050	1175	1210	1275	1335	1375	1440	1740	1795 w
3f	915	1020	1050		1205	1285	1340	1395	1435	1735	1790 w
3h	920	1027		1175	1200		1333	1380	1440	1735	

$[\alpha]^{26}D$ −49.5° (*c* 2.5, $CHCl_3$); ir (KBr) was identical with that of (+)-**9a**.

Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.67; H, 10.43.

A 10-g sample of (±)-**5** and 15 g of (−)-**8** were treated as described in the preparation of (+)-**9a**. The crude product (16.7 g) was allowed to crystallize for several days and after filtration was recrystallized twice from hexane to give 7.2 g (84%) of (−)-**9a**: mp 128–130°; $[\alpha]D$ −49.5° (*c* 2.6, $CHCl_3$); ir (KBr) identical with the spectrum described above for (+)-**9a**.

A 1.7-g sample of (+)-**5** was treated with 2.0 g of (+)-**8** as previously described to give 2.4 g (80%) of (+)-**9b** as a colorless oil: $[\alpha]^{23}D$ +104° (*c* 3.9, $CHCl_3$); ir (neat) 827, 959, 983, 1046, 1088, 1163, 1223, 1280, 1365, 1400, 1455, 1625, 1660, 1750, and 2950 cm^{-1}.

Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.37; H, 10.18.

Conversion of (+)-9a to (−)-5 and (−)-9a to (+)-5.—A mixture of 17 g of (+)-**9a** and 90 ml of anhydrous methanol was introduced into a stainless steel autoclave and heated for 13 hr at 110–120°. After cooling, the mixture was distilled to give 7.7 g (78%) of colorless (−)-**5**: bp 63–67° (0.1 mm); mp 42–43°; $[\alpha]^{26}D$ −104° (*c* 2.2, $CHCl_3$).

In a similar manner, (−)-**9a** was converted to (+)-**5** in 73% yield.

(+)-2-Methyl-1-butyl (4*R*)-Methyl-2-oxocyclohexanecarboxylate (9c).—This β-oxo ester was prepared through the exchange of alkoxyl groups by heating (+)-**5** in the presence of excess (+)-2-methyl-1-butanol. The excess alcohol was distilled off to give 70% yield of liquid **9c**: bp 108° (0.3 mm); $\alpha^{24}D$ +79° (neat); ir (neat) 827, 1042, 1088, 1163, 1222, 1280, 1330, 1360, 1405, 1460, 1625, 1660, 1725, and 2950 cm^{-1}.

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.72; H, 9.87.

(+)-1-Methyl 3-Bromo-(4*R*)-methyl-2-oxocyclohexanecarboxylate (10).—A 1.5-g sample of (−)-**9a** was dissolved in 10 ml of anhydrous ether, 0.80 g of Br_2 was added dropwise, and the mixture was stirred for 1 hr at room temperature. The ether was removed and the solid residue was recrystallized from hexane to give 1.6 g (90%) of (+)-**10** as colorless crystals: mp 98–99°; $[\alpha]^{23}D$ −11.4° (*c* 2.2, $CHCl_3$); ir (KBr) 708, 847, 873, 912, 953, 996, 1042, 1088, 1125, 1154, 1197, 1240, 1335, 1375, 1425, 1462, 1730, and 2945 cm^{-1}.

Anal. Calcd for $C_{18}H_{29}BrO_3$: C, 57.91; H, 7.83. Found: C, 58.20; H, 7.68.

Favorskii-Type Rearrangement of (+)-10.—A 0.005-mol sample of (−)-**10** was rearranged by dissolving it in 15 ml of methanol, adding the solution dropwise to 10 ml of 20% NaOH, and stirring for 4 hr at 25°. The resulting mixture of nepetic acids was converted to methyl esters with diazomethane[10] and analyzed (Table I), and the individual esters were separated by preparative glc on a LAC column at 190°. After hydrolysis, the individual acids were shown to be (+)-**3c**, mp 118–119°, and (−)-**3g**, mp 113–115°. These acids showed no depression in melting point on admixture with those previously obtained.[2]

(3*R*)-Diols (18, 19, 20, and 21).—A 1-g sample of (+)-**3c** was esterified with diazomethane, and the resulting solution of methyl esters was dried ($MgSO_4$) and added dropwise to a stirred suspension of 1 g of $LiAlH_4$ in 20 ml of refluxing ether. After 1 hr, water was added, the suspension was filtered, and the filtrate was concentrated to give 0.73 g (100%) of **21**. The diols **18**, **19**, and **20** were prepared in a like manner from the appropriate 3*R* nepetic acid and evaporatively distilled: bp 140° (0.8 mm); $[\alpha]^{24}D$, for **18**, −9.4° (*c* 0.7, $CHCl_3$); **19**, −31.7° (*c* 2.9, $CHCl_3$); **20**, +23.9° (*c* 1.3, $CHCl_3$); **21**, −73.8° (*c* 1.4, $CHCl_3$). The ir spectra (cm^{-1}, neat) were determined (Table III).

Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found for **18**: C, 66.84; H, 11.34. Found for **19**: C, 66.34; H, 11.32. Found for **20**: C, 66.87; H, 11.30. Found for **21**: C, 66.85; H, 11.24.

The gas chromatography curves of these diols on a 0.25 in. × 13 ft column of acid-washed, DMCS-treated Chromosorb G coated with 5% silicone rubber heated to 160° showed 17.6, 19.2, 20.4, and 22.0 min retention times for **21**, **19**, **20**, and **18**, respectively.

Table III
Infrared Bands of Diols from 3*R* Nepetic Acids

18	953	1033	1074	1375	1450		2940	3300
19		1032	1065	1375	1455	2875	2945	3275
20		1035	1072	1380	1455		2930	3290
21	953	1025	1058	1375	1455	2880	2945	3295

The Conversion of (−)-9a to the Diols 18, 19, 20, and 21.—A 2.94-g sample of (−)-**9a** was brominated to (+)-**10** as previously described, the latter was dissolved in 10 ml of methanol, and the solution was added to a vigorously stirred mixture of 2 g of NaOH dissolved in 5 ml of water and 25 ml of methanol at 0°. After 3 min, the reaction was quenched by acidifying to pH 5 with 20% hydrochloric acid. The mixture was extracted with three portions of ether, dried ($MgSO_4$), and concentrated. A 1.0-g sample of the crude mixture was reduced with $LiAlH_4$ to a mixture of **18**, **19**, **20**, and **21**, as described for the preparation of **21**. The mixture of diols was analyzed by glc as described, which showed the ratio 47:9:20:24 (**21**:**20**:**19**:**18**); *cf.* Table I.

Favorskii-Type Rearrangement of (±)-5 in Aqueous Methanolic Sodium Carbonate.—A 1.7-g sample of (±)-**5** was treated with 0.8 g of bromine in ether solution. The bromo derivative was stirred for 1 hr at room temperature with a solution of 5.7 g of Na_2CO_3 in 50 ml of H_2O and 10 ml of methanol. The reaction mixture was extracted with ether to remove neutral products. Analysis of this neutral fraction on the LAC 886 glc column at 190° showed the ratio 8:0:35:57 (**3d**:**3h**:**3b**:**3f**);[12] *cf.* Table I. The dimethyl esters obtained from the alkaline layer showed the corresponding ratio 0:7:50:43.

Acid Hydrolysis of Dimethyl Nepetates.—About 100 mg of each of the dimethyl esters of (−)-**3b**, (+)-**3d**, (−)-**3f**, and (−)-**3h** were heated at reflux in 20 ml of 10% sulfuric acid for 9 hr. The reaction mixture was cooled, made basic with 30% NaOH, and extracted with ether to remove neutral material. Sulfuric acid was added and the acidic solution was extracted 8–10 times with ether. The ether extracts were dried ($MgSO_4$) and treated with CH_2N_2. Glc analyses of each run were made and these showed no change in isomer composition for the *trans* acids (−)-**3g** and (+)-**3c**, respectively. The *cis,cis*-dimethyl ester (+)-**3f** was accompanied by about 10% of the dimethyl esters (−)-**3b**, (+)-**3d**, and (−)-**3h**, whereas the *cis,trans*-dimethyl ester (−)-**3b** was accompanied by 1–2% of the (+)-*trans,cis*-dimethyl ester **3d**.

Registry No.—(+)-**3a**, 13368-64-4; (+)-**3b**, 27040-65-9; (−)-**3c**, 13350-94-2; (−)-**3d**, 27040-67-1; (+)-**3e**, 27040-68-2; (−)-**3f**, 27040-69-3; (+)-**3g**, 13368-63-3; (+)-**3h**, 27040-71-7; (−)-**5**, 27040-72-8; (+)-**5**, 27040-83-1; (±)-**6**, 27040-73-9; (+)-**9a**, 27040-74-0; (−)-**9a**, 27040-75-1; (+)-**9b**, 27040-76-2; (+)-**9c**, 27040-77-3; (+)-**10**, 27040-78-4; (−)-**18**, 27040-79-5; (−)-**19**, 27040-80-8; (+)-**20**, 27040-81-9; (−)-**21**, 27040-82-0.

Acknowledgment.—Support of this work by the National Science Foundation (Grant GB-5607) and the American Petroleum Institute through Research Project 58A is gratefully acknowledged. We thank Dr. E. W. Warnhoff for his interest in this work and for stimulating discussions. We also thank Dr. O. C. Dermer for reading the manuscript.

(12) Dimethyl esters (−)-**3b**, (+)-**3d**, (+)-**3f**, and (−)-**3h** were used to obtain these comparisons.

Relative Leaving Abilities and Isotope Effects in Electrophilic Aromatic Substitution

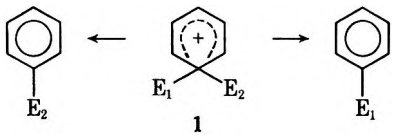
CHARLES L. PERRIN[1]

Department of Chemistry, University of California, San Diego, La Jolla, California 92037

Received August 18, 1970

In acetic acid–acetic anhydride containing HCl, 1-ehloro-1-nitro-2-keto-1,2-dihydronaphthalene (2, X = Cl) undergoes both migration and loss of NO_2^+, rather than Cl^+. In contrast, the bromo analog (2, X = Br) loses Br^+. We therefore conclude that the leaving abilities of these electrophiles increase in the order $Cl^+ < NO_2^+ < Br^+$. An order of relative leaving abilities for most of the common electrophiles is presented and justified. The factors that govern relative leaving abilities are considered. The implications of these relative leaving abilities for isotope effects and other aspects of electrophilic aromatic substitution are discussed.

For some time we have been interested in relative leaving abilities of electrophiles in electrophilic aromatic substitution. We may state the general question as follows. In the intermediate **1**, which of the two electrophiles, E_1^+ or E_2^+, is cleaved more rapidly (or migrates more readily), and why? Notice that this question concerns the leaving abilities of cationic species, rather than the anionic ones that are involved in nucleophilic substitutions at saturated carbon.



1

For the special case that one of the electrophiles is H^+, hydrogen isotope effects[2-7] provide the answer to this question. In the reaction

$$E^+ + ArH \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} EArH^+ \xrightarrow{k_2} ArE + H^+$$

ArD will be observed to react at nearly the same rate as ArH if $k_2 \gg k_{-1}$. If this condition is not met, then loss of H^+ must compete with loss of E^+ and the second step becomes partly or completely rate limiting. We may thus conclude that the electrophile E^+ is more rapidly lost than H^+ if and only if electrophilic substitution by E^+ shows an isotope effect appreciably greater than 1. For example, since iodinations, nitrosations, and mercurations all proceed with appreciable isotope effects, we may conclude that I^+, NO^+, and Hg^{2+} are all lost at least as readily as H^+. In contrast, NO_2^+, Cl^+, and R^+ must be lost much less readily than H^+, since nitrations, chlorinations, and alkylations rarely show appreciable isotope effects. (The alternative explanation for the small isotope effects in these reactions is considered in the Discussion.) Aromatic substitutions by still other electrophiles, such as ArN_2^+, Br^+, SO_3, and RCO^+, which are usually lost less readily than H^+, show higher isotope effects under special circumstances, usually when steric effects hinder swinging the substituent into the plane of the aromatic and thus decrease k_2.

Of course, these relative leaving abilities are not intrinsic properties of the electrophiles. For example, we must keep in mind that proton loss is an SN2 displacement on hydrogen, whereas loss of NO_2^+ or NO^+ is an SN1 process. Here we are invoking the principle of microscopic reversibility to conclude that, since nitration and nitrosation proceed *via* attack by NO_2^+ and NO^+, loss of NO_2^+ or NO^+ from the intermediate does not occur *via* SN2 attack on nitrogen. Whether loss of some other electrophile is an SN1 or SN2 process may likewise be determined on the basis of the mechanism of attack by that electrophile. Thus we may conclude that I^+, Br^+, and Cl^+ are never lost as such, but are removed by nucleophiles, among which halides seem to be especially effective, and the isotope effect in mercuration varies from 3.2 to 6.8, depending on the state of the water that must discriminate between H^+ or Hg^{2+}. Therefore it is necessary to recognize that the reaction conditions can have a considerable effect on leaving abilities of species that react by an SN2 process. An excellent example of this phenomenon was furnished by Zollinger,[4] who demonstrated that under some conditions a diazonium ion is more readily lost than H^+, but that this order is reversed by bases. Finally, we must keep in mind that leaving ability is also affected by substitution: *tert*-Bu^+ is clearly a better leaving group than *i*-Pr^+, and *p*-$MeOC_5H_4N_2^+$ is better than *p*-$O_2NC_6H_4N_2^+$.

If we take the magnitude of the hydrogen isotope effect[8] (or the extent to which steric effects must be introduced in order to produce an appreciable isotope effect) as a quantitative reflection of the ratio k_{-1}/k_2, we may list the substituents in approximate order of increasing leaving ability: $Cl^+ \sim NO_2^+ \sim R^+ < Br^+ < D^+ \sim ArN_2^+ \sim SO_3 \sim RCO^+ < NO^+ \sim H^+ \sim I^+ < Hg^{2+}$. Furthermore, we shall assume transitivity. If E_1ArH^+ loses E_1^+ much less readily than it loses H^+, and if E_2ArH^+ loses E_2^+ about as readily as it loses H^+, then intermediate **1** loses E_1^+ much less readily than it loses E_2^+, etc. Then we may also take the above sequence as a list of electrophiles in order of increasing leaving ability relative to each other (subject to the qualifying statements of the previous paragraph).

We consider the order for those electrophiles that are lost readily to be rather secure, since it is based on isotope effects (k_H/k_D) ranging from 3 to 7. On the other hand, we cannot be so certain about the relative leaving abilities of those electrophiles that are lost much less readily than protons, since substitutions with these electrophiles generally show isotope effects $k_H/k_D < 2$.

(1) Alfred P. Sloan Research Fellow, 1967–1969.

(2) L. Melander, "Isotope Effects on Reaction Rates," The Ronald Press, New York, N. Y., 1960, Chapter 6.

(3) E. Berliner, *Progr. Phys. Org. Chem.*, **2**, 253 (1964).

(4) H. Zollinger, *Advan. Phys. Org. Chem.*, **2**, 163 (1964); *Ann. Rev. Phys. Chem.*, **13**, 400 (1962).

(5) H. Cerfontain, H. J. Hofmann, and A. Telder, *Recl. Trav. Chim. Pays-Bas*, **83**, 493 (1964).

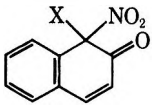
(6) G. A. Olah, *J. Tenn. Acad. Sci.*, **40**, 77 (1965).

(7) R. O. C. Norman and R. Taylor, "Electrophilic Substitution in Benzenoid Compounds," Elsevier, Amsterdam, 1965.

(8) These have been tabulated in ref 5 and 6, and citations of the original references may be found there.

Even the observation of an isotope effect that is produced by steric effects does not necessarily bear upon relative leaving abilities. For example, we have inferred that Br^+ and ArN_2^+ are inherently better leaving groups than Cl^+ and NO_2^+ because brominations and diazo couplings of sterically hindered aromatics more often show isotope effects. However, it is possible (though unlikely) that Br^+ and ArN_2^+ are ordinarily the poorer leaving groups, but that they are more sensitive to steric effects.

Therefore we decided that direct comparison of the relative leaving abilities of these poorer leaving groups is necessary, rather than inferences based on isotope effects. In particular, we have been especially interested in the relative leaving abilities of Cl^+, Br^+, and NO_2^+ in acetic acid–acetic anhydride mixtures. As a *model* for an intermediate **1** having two of these substituents, we chose the conjugate acids of the 1-halo-1-nitro-2-keto-1,2-dihydronaphthalenes (**2**, X = Cl, Br),

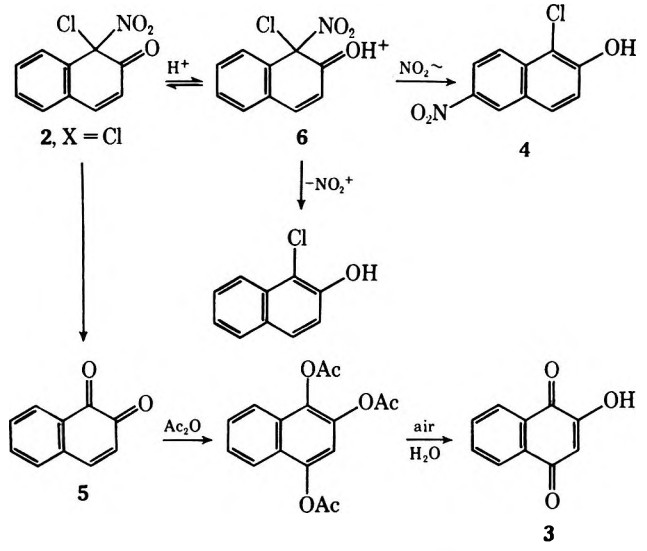


2

and we have investigated their behavior both in the presence and in the absence of chloride. Also, since it is known[9] that these ketones readily decompose to 1,2-naphthoquinone, with liberation of nitrous fumes, we have included urea in the reaction mixture, in an attempt to prevent nitration through nitrosation. (1,6-Dinitro-2-naphthol has been isolated[9] from solutions of the bromonitro ketone in acetic acid.)

Results

A solution of 1-chloro-1-nitro-2-keto-1,2-dihydronaphthalene (**2**, X = Cl) in chloroform was prepared according to Fries.[9] This very sensitive material was not isolated or purified, but its solution was added immediately to an acetic acid–acetic anhydride mixture containing HCl and urea. On work-up, both 2-hydroxy-1,4-naphthoquinone (**3**) and 1-chloro-6-nitro-2-naphthol (**4**), mp 197.5–198°, were obtained, the latter as its acetate. The former presumably arises *via* 1,2-naphthoquinone (**5**), which is formed on heating **2** in inert solvents, and which we have found to be converted to **3** under the conditions employed. The latter arises from the conjugate acid **6** (or its acetate) by migration of NO_2^+, and not by an intermolecular process, since under the reaction conditions 1-chloro-2-naphthol is not nitrated by 1 equiv of acetyl nitrate.



The 1-chloro-6-nitro-2-naphthol (**4**) is an unknown compound, although it may be the same as the chloronitronaphthol, mp 192°, of Gaess[10] and the chloronitronaphthol, mp 190–191°, of Kaneko.[11] Our structure proof rests on elemental analysis, a consistent infrared spectrum, inertness to nitrosation, monobromination to a ketone, and oxidation by alkaline permanganate to 4-nitrophthalic acid. Thus we conclude that this is another example of the rare migration of a nitro group.[12]

A small amount of 1-chloro-2-naphthol was also detected among the products. This arises through competing loss of NO_2^+ from **6**. The alternative possibility, that this represents material that did not undergo the initial nitration, is excluded, since appreciable 1-chloro-2-naphthol was also detected by tlc in the products from **6** prepared by chlorination of 1-nitro-2-naphthol in base.

No 1-nitro-2-naphthol or 1,6-dinitro-2-naphthol was detected. Therefore, we conclude that even in the presence of HCl and acetic acid the loss of Cl^+ does not compete with loss and migration of NO_2^+.

In contrast, the bromo analog, 1-bromo-1-nitro-2-keto-1,2-dihydronaphthalene (**2**, X = Br), undergoes loss of Br^+ and forms 1-nitro-2-naphthol, even in the absence of HCl. Therefore we conclude that loss or migration of NO_2^+ does not compete with S_N2 displacement on bromine by acetic acid or chloride.

Discussion

Relative Leaving Abilities of the Poor Leaving Groups Br^+, Cl^+, and NO_2^+.—From the experiments here reported, we may conclude that the leaving abilities of these electrophiles increase in the order, $Cl^+ < NO_2^+ < Br^+$. In particular, we may now conclude that a species like **1** (E_1 = Cl, E_2 = NO_2) is more likely to react by loss or migration of NO_2^+ rather than Cl^+. Also, we have substantiated the expectation based on isotope effects that a species like **1** (E_1 = Br, E_2 = NO_2) is more likely to lose Br^+ than NO_2^+, and, if our assumption of transitivity is valid, then we would expect a species like **1** (E_1 = Br, E_2 = Cl) to lose (or migrate) Br^+ rather than Cl^+. Of course, this result has already been obtained[13] for 1-bromo-1-chloro-2-keto-1,2-dihydronaphthalene, which with HCl or HBr gives 1-chloro-6-bromo-2-naphthol and 1-chloro-2-naphthol. Indeed, the preferential loss and migration of Br^+ is just what chemical intuition would lead one to expect. Also, we note that, with HBr in acetic acid, 1-chloro-1-methyl-2-keto-1,2-dihydronaphthalene was found to undergo halogen migration, rather than loss or migration of methyl;[13] so we may further conclude that methyl is a poorer leaving group than even chlorine.

Berliner[3] has suggested that under the proper condi-

(9) K. Fries, *Justus Liebigs Ann. Chem.*, **389**, 315 (1912).

(10) F. Gaess, *J. Prakt. Chem.*, **45**, [2] 616 (1892); through Elsevier's "Encyclopaedia of Organic Chemistry," 1950, Vol. 12B, p 1565.

(11) T. Kaneko, *Yakugaku Zasshi*, **68**, 179 (1948).

(12) P. H. Gore, *J. Chem. Soc.*, **1957**, 1437.

(13) K. Fries and K. Schimmelschmidt, *Justus Liebigs Ann. Chem.*, **484**, 245 (1930).

tions practically all substitutions except nitration may proceed with an appreciable isotope effect, and he has expected that even chlorination should do so. On the basis of our results, we conclude that nitration is more likely than chlorination (or methylation) to proceed with an appreciable isotope effect. Myhre[14] has tentatively reached this same conclusion.

General Considerations of Leaving Abilities of Electrophiles.—First we must demonstrate that kinetic isotope effects observed in electrophilic aromatic substitution really do reflect relative leaving abilities. It seems to be generally accepted that "the most important factor which determines the occurrence of an isotope effect is the relative magnitude of k_{-1} and k_2, and hence the heights of the transition state barriers leading from the intermediate to reactants and products."[3] However, there have also been suggestions[3,6,15,16] that a small isotope effect does not necessarily mean that $k_2 \gg k_{-1}$, but that it may be due to an asymmetry in the transition state, which is quite likely for these very exothermic proton transfers. Despite the general validity of this argument and its widespread acceptance, we reject it as the explanation for the low isotope effects sometimes observed in electrophilic aromatic substitution. Although the isotope effect on proton loss from the intermediate does vary[16,17] with the acidity of $EArH^+$, the range seems to be only from 3 to 7. Indeed, observations of $k_H/k_D > 6$ in diazo couplings and hydrogen isotope exchanges where $EArH^+$ is a relatively weak acid and in mercurations where $EArH^+$ is probably a strong acid suggest that the isotope effect on proton transfer from $EArH^+$ can approach and even surpass the limiting value of *ca.* 7. Also, calculations[18] show that, even when the transition state is so asymmetric that the proton is bound seven times as strongly to the carbon atom as it is to the base, k_H/k_D drops only to 3.3. Such extreme asymmetry seems quite unlikely in these reactions. Therefore we contend that the isotope effect *is* determined almost entirely by the ratio k_{-1}/k_2, that values of $k_H/k_D \sim 1$ do correspond to reactions with $k_2 \gg k_{-1}$, and that we are justified in estimating relative leaving abilities from magnitudes of k_H/k_D.

Next we consider the factors that govern relative leaving abilities of electrophiles. Both Berliner[3] and Olah[6] have stated, "It is by no means always clear why in some reactions the proton loss becomes part of the rate-determining step and in others not. Many factors seems to contribute to where exactly the transition state for the rate-controlling step occurs." On the contrary, we feel that the above order of relative leaving abilities is not so baffling but is in fact a reasonable one for the relative rates of breaking the carbon-electrophile bond. It seems to parallel what might be expected for the order of stability[19] (lack of reactivity and electrophilicity, "happiness") of the various electrophiles. For example, NO_2^+ is an especially powerful electrophile; it forms a strong C–N bond that is quite difficult to cleave. Likewise, ionization of R^+ (data are for benzhydryl and isopropyl) from the intermediate would not be expected to be a fast reaction unless R^+ is an extremely stable carbonium ion. Species of intermediate leaving ability, such as SO_3, RCO^+, and ArN_2^+, are also species of greater ease of formation through routes other than from **1**, and the good leaving groups, such as Hg^{2+}, H^+, and NO^+, are particularly stable species, of low electrophilicity; it is therefore understandable that C–Hg^+, C–H, and C–NO bonds are readily cleaved. Similarly, iodine is not very electrophilic; so it is not surprising that C–I bonds are also readily cleaved. Of course, species such as Cl^+, Br^+, I^+, H^+, Hg^{2+}, and some R^+ (*e.g.*, methyl) do not ionize from the intermediate in an SN1 process, but are removed in an SN2 process. Therefore the relative leaving abilities of these species depend on the nature and concentration of the nucleophiles present, so that comparisons involving such species cannot be absolute but are applicable only under whatever conditions are specified. Nevertheless, it is obvious that the rate of nucleophilic attack by either oxygen or halogen nucleophiles must increase in the order $CH_3 < Cl < Br < I$, inasmuch as this is the order of increasing polarizability.

Alternative Explanations for Leaving Abilities of Electrophiles.—It is instructive to consider other factors that have been suggested as important in determining leaving abilities.

Several researchers[20] have suggested that the strength of the carbon–electrophile bond is important. For example, C–Hg and C–I bonds are especially weak; so they are readily cleaved. This explanation is quite close to ours, except that considerations of bond strengths are more relevant to homolytic cleavages, rather than the heterolytic ones that are involved here. (For SN1 processes this suggestion may be made equivalent to ours if the electron affinity of the electrophile is also included as an important factor. We prefer to focus on the "heterolytic" bond strength.) Besides, for those substituents that are removed in an SN2 process, it is necessary to consider the strengths of both the bond to be broken and the bond to be made (just as for free radicals, which prefer to abstract hydrogen atoms, rather than halogen atoms, even though the C–H bond is stronger than the C–X bond).

We have already mentioned that steric effects are important, as has long been recognized.[4] Clearly, large groups flanking the reaction center will hinder the approach of a bulky electrophile into the plane of the aromatic and thus decrease k_2. (Many previous interpretations of these steric effects stressed an increase in k_{-1}, but it seems quite likely that bulky substituents may even decrease this rate in some cases.) As the leaving ability of protons is thus decreased relative to that of the electrophile, reversal of the electrophilic attack can compete with loss of proton, thereby leading to a hydrogen isotope effect.

It has also been suggested[3,6] that the selectivity of the reaction is important, with reactions involving powerful electrophiles showing no isotope effect. In some respects this approach is quite similar to ours, in that a powerful electrophile will be one whose leaving ability

(14) P. C. Myhre, M. Beug, and L. L. James, *J. Amer. Chem. Soc.*, **90**, 2105 (1968); P. C. Myhre and J. W. Tilley, Abstracts, 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968, Organic Division No. 107; P. C. Myhre, personal communication.

(15) G. S. Hammond, *J. Amer. Chem. Soc.*, **77**, 334 (1955); F. H. Westheimer, *Chem. Rev.*, **61**, 265 (1961).

(16) R. P. Bell and D. M. Goodall, *Proc. Roy. Soc., Ser. A*, **294**, 273 (1966).

(17) J. L. Longridge and F. A. Long, *J. Amer. Chem. Soc.*, **89**, 1292 (1967); A. J. Kresge, D. S. Sagatys, and H. L. Chen, *ibid.*, **90**, 4174 (1968).

(18) R. A. More O'Ferrall and J. Kouba, *J. Chem. Soc. B*, 985 (1967).

(19) A. V. Willi, *Chimia*, **15**, 239 (1961).

(20) L. G. Cannell, *J. Amer. Chem. Soc.*, **79**, 2932 (1957); H. G. Kuivila and K. V. Nahabedian, *ibid.*, **83**, 2164 (1961); A. J. Kresge and J. F. Brennan, *Proc. Chem. Soc.*, 215 (1963).

is quite poor, so that proton loss is always favored and no isotope effect is observed. Nevertheless, there does not seem to be a very good correlation between selectivity and isotope effect, mercuration being a rather unselective reaction that shows a large isotope effect. It has also been suggested[3,6] as a corollary that reactions involving reactive aromatics should also show no isotope effects. However, we would expect that the reactivity of the aromatic cannot affect the *relative* leaving abilities (except insofar as a reactive intermediate formed from an unreactive aromatic should be less selective as to which electrophile is lost). Thus we reject the suggestions[4,21] that formation of a stable quinonoid intermediate is somehow associated with the occurrence of an isotope effect.

We also reject the suggestions[2,22] that iodinations and sulfonations show isotope effects because the intermediate (1, E_1 = H, E_2 = SO_3^-, or one resulting from iodination of a phenoxide) is neutral and therefore a weaker acid. What is important in determining whether there is an isotope effect is the ratio k_{-1}/k_2; thus, even though k_2 is smaller for a neutral species, so is k_{-1}.

It has long been recognized that reactants and reaction conditions affect the isotope effect. Now we may readily understand these observations in terms of relative leaving abilities. For example, bromination of anisole-*m*-sulfonate with $BrOH_2^+$ or BrOH shows no isotope effect whereas bromination with Br_2 shows $k_H/k_D = 2.6$. Of course, this is not really due to the change in brominating agent, but to the change in reaction conditions; attack by H_2O on Br^+ does not compete with attack by H_2O on H^+, but attack of Br^- on Br^+ can compete. Another example is the remarkable k_H/k_D = 6.1 for nitration of anthracene in acetonitrile;[23] in so weakly basic a solvent, the proton becomes a very poor leaving group, in this case even poorer than NO_2^+, which needs no nucleophile to remove it. Notice that this result demonstrates that the product-forming step must be proton transfer from the σ-complex intermediate, and *not* formation of an NO_2BF_4 π complex or separation of an HBF_4 π complex.[6]

Further Aspects of Leaving Abilities.—We may include some other electrophiles whose relative leaving abilities may be gauged. From kinetic studies and/or isotope effects in protodecarboxylation,[24] protodeboronation,[25] and protodesilylation,[26] we may conclude that H^+ is a poorer leaving group than CO_2, $B(OH)_3$ (or Ph_3B), and Me_3Si^+. By transitivity we conclude that I^+ and Br^+ are also poorer leaving groups than these. This conclusion is consistent with the kinetics of bromodecarboxylation[27] and halodeboronation.[28] We also note that the kinetics of bromodesulfonation[29] show that loss of Br^+ is also competitive with cleavage of SO_3, as suggested above by isotope effects and the assumption of transitivity. Likewise, in the presence of Br^-, loss of Br^+ has been found[30] to be competitive with cleavage of $ArCHOH^+$. The well-known occurrences of nitrodealkylation,[31] halode-*tert*-butylation,[32] and diazodehydroxyalkylation[33] suggest further relative leaving abilities, as indicated below.

Finally, we indicate how simple considerations of leaving abilities can clarify some previously puzzling features of aromatic reactivity.

Whereas bromination of dianisylcarbinol leads to considerable cleavage and formation of *p*-bromoanisole, bromination of dianisylmethane produces very little cleavage product.[34] This result is readily understood in terms of the poorer leaving ability to be expected for p-$MeOC_6H_4CH_2^-$, relative to p-$MeOC_6H_4CHOH^+$.

Whereas nitration of phenylmercuric ion leads primarily to nitrophenylmercuric ions,[35] nitrosation leads to nitrosobenzene, *via* nitrosodemercuration.[36] This contrast may be attributed to the reversibility of NO^+ attack, which is perhaps faster than proton loss, but slower than loss of Hg^{2+} from 1 (E_1 = Hg^+, E_2 = NO).

The variations in the mechanism of protodecarboxylation[24] are readily understood in terms of the variations in the relative leaving abilities of H^+ and CO_2. In dilute acid, intermediate 1 (E_1 = H, E_2 = CO_2^-) loses CO_2 more readily than H_2O removes H^+. In buffer solutions, general base catalysis increases the rate of proton removal, but does not affect the rate of CO_2 loss. In strong acid, there is very little such intermediate, since it is present almost entirely as a species protonated on carboxyl oxygen, which readily loses H^+ but cannot lose CO_2. Similar phenomena are apparently involved in protodecarbonylation,[37] protodeformylation,[38] and protodesulfonation.[39]

Finally, for a test of our understanding of relative leaving abilities, we wish to make the following prediction. Since $ArCHOH^+$ (and possibly CH_2OH^+) have leaving abilities comparable with that of Br^+, steric effects should create a situation in which they also have a leaving ability comparable with that of H^+. Therefore we predict that hydroxyalkylation and chloromethylation[40] of tri-*tert*-butylbenzene (or perhaps even mesitylene) should show a hydrogen isotope effect, $k_H/k_D > 3$.

Conclusions

Thus we have demonstrated that considerations of the relative leaving abilities of electrophiles are sufficient

(21) E. Grovenstein, Jr., and D. C. Kilby, *J. Amer. Chem. Soc.*, **79**, 2972 (1957).

(22) E. S. Lewis and M. C. R. Symons, *Quart. Rev. (London)*, **12**, 230 (1958).

(23) H. Cerfontain and A. Telder, *Recl. Trav. Chim. Pays-Bas*, **86**, 371 (1967).

(24) A. V. Willi, *Trans. Faraday Soc.*, **55**, 433 (1959); K. R. Lynn and A. V. Willi, *Chem. Ind. (London)*, 782 (1963); J. L. Longridge and F. A. Long *J. Amer. Chem. Soc.*, **90**, 3092 (1968); H. H. Huang and F. A. Long, *ibid.*, **91**, 2872 (1969).

(25) H. G. Kuivila and K. V. Nahabedian, *ibid.*, **83**, 2159, 2164 (1961); J. N. Cooper and R. E. Powell, *ibid.*, **85**, 1590 (1963).

(26) C. Eaborn, P. M. Jackson, and R. Taylor, *J. Chem. Soc. B*, 613 (1966).

(27) E. Grovenstein, Jr., and U. V. Henderson, Jr., *J. Amer. Chem. Soc.*, **78**, 569 (1956); E. Grovenstein, Jr., and G. A. Ropp, *ibid.*, **78**, 2560 (1956).

(28) H. G. Kuivila and E. J. Soboczenski, *ibid.*, **76**, 2675 (1954); H. G. Kuivila and R. M. Williams, *ibid.*, **76**, 2679 (1954).

(29) L. G. Cannell, *ibid.*, **79**, 2927, 2932 (1957); B. T. Baliga and A. N. Bourns, *Can. J. Chem.*, **44**, 363 (1966).

(30) E. M. Arnett and G. B. Klingensmith, *J. Amer. Chem. Soc.*, **87**, 1038 (1965).

(31) D. V. Nightingale, *Chem. Rev.*, **40**, 117 (1947); G. A. Olah and S. J. Kuhn, *J. Amer. Chem. Soc.*, **86**, 1067 (1964).

(32) P. D. Bartlett, M. Roha, and R. M. Stiles, *ibid.*, **76**, 2349 (1954); P. B. D. de la Mare, J. T. Harvey, M. Hassan, and S. Varma, *J. Chem. Soc.*, 2756 (1956).

(33) M. Stiles and A. J. Sisti, *J. Org. Chem.*, **25**, 1691 (1960).

(34) E. M. Arnett and G. B. Klingensmith, *J. Amer. Chem. Soc.*, **87**, 1023 (1965).

(35) F. Challenger and E. Rothstein, *J. Chem. Soc.*, 1258 (1934).

(36) F. H. Westheimer, E. Segel, and R. Schramm, *J. Amer. Chem. Soc.*, **69**, 773 (1947).

(37) W. M. Schubert and P. C. Myhre, *ibid.*, **80**, 1755 (1958).

(38) H. Burkett, W. M. Schubert, F. Schultz, R. B. Murphy, and R. Talbott, *ibid.*, **81**, 3923 (1959).

(39) V. Gold and D. P. N. Satchell, *J. Chem. Soc.*, 1635 (1956).

(40) Y. Ogata and M. Okano, *J. Amer. Chem. Soc.*, **78**, 5423 (1956).

to provide a simple basis for understanding why some reactions proceed with an isotope effect and others do not, and we have shown how this approach is applicable to understanding why a particular step in a general aromatic substitution is rate limiting.

In summary, we may list the electrophiles here considered in order of increasing leaving ability, as judged from isotope effects, from reactions of model compounds, and from other kinetic studies. We list those that ionize in an SN1 process separately from those that are cleaved in an SN2 process.

$$NO_2^+ < i\text{-}Pr^+ \sim SO_3 < tert\text{-}Bu^+ \sim ArN_2^+ < ArCHOH^+ < NO^+ < CO_2 < B(OH)_3$$

$$CH_3^+ < Cl^+ < Br^+ < D^+ \sim RCO^+ > H^+ \sim I^+ < Hg^{2+} < Me_3Si^+$$

It is possible to compare SN1 and SN2 processes, but they vary more strongly with conditions. For example, we have demonstrated that a frequent order is $Cl^+ < NO_2^+ < Br^+$. We suggest that these relative leaving abilities can provide a useful basis for considering any electrophilic substitution. Furthermore we maintain that these sequences of leaving abilities are reasonable ones to be expected for the relative rates of heterolysis of a carbon–electrophile bond. And variations in leaving ability are readily understood in terms of steric effects and effects of reaction conditions. Finally, we suggest that study of the reactions of an appropriate 2-keto-1,2-dihydronaphthalene system can provide a general method for determining more relative leaving abilities and for further testing of the applicability of the above sequences.

Experimental Section

Melting points were determined on a Fisher–Johns block and are uncorrected. Microanalysis was by Galbraith Laboratories, Inc. Thin layer chromatography on Eastman chromagram sheets (silica) with chloroform, methanol, or absolute ethanol eluent, followed by development with NH_3 vapor, was found suitable for separating the compounds of interest.

Materials.—1-Chloro-2-naphthol was prepared according to Franzen and Stäuble[41] and recrystallized from ligroin, mp 66.5–67.5 (lit.[42] 70–71°). 1,6-Dinitro-2-naphthol was prepared according to published methods,[43] mp 195.5–197.5° (lit.[44] 195 dec). 1-Bromo-2-naphthol (Aldrich) was recrystallized from ligroin, mp 81–82° (lit.[45] 84°).

Preparation of 1-Bromo-1-nitro-2-keto-1,2-dihydronaphthalene (2, X = Br).[9]—To a cooled, stirred solution of 1.00 g of 1-bromo-2-naphthol in 5 ml of $HCCl_3$ was added 1 ml of chilled 90% HNO_3. After 2 min, ice was added and the lower layer was removed, washed with cold water, and dried with Na_2SO_4. Hexane was added to the chilled solution until crystals appeared. The mixture was immediately filtered and the filtrate was cooled to −78° and then allowed to warm to *ca.* −20°. The yellow crystals were collected and dried to obtain 525 mg of product: mp 60–62.5° (lit.[9] 74°); ir ($HCCl_3$) prominent bands at 5.92 (C=O), 6.35 (NO_2), 7.50 (NO_2), and 12.3 μ (CH); nmr ($DCCl_3$) τ 2.50 (d) + 2.57 (m) (5 H total), 3.68 (d, J = 10 Hz, 1 H). On standing at room temperature this material slowly decomposed with evolution of nitrous fumes and formation of 1,2-naphthoquinone: ir ($HCCl_3$) 5.99 μ (C=O) [lit.[46] 1678 cm^{-1} (CCl_4)]. Therefore, this ketone was not generally isolated, but its freshly prepared $HCCl_3$ solution was immediately reacted. This solution showed the same ir and nmr (prepared in $DCCl_3$) peaks as did the solution of the crystalline material, and no OH, $ArNO_2$, or quinone peaks could be detected.

A $HCCl_3$ solution showing these same ir peaks could also be prepared by rapidly adding a solution of 83 mg of Br_2 in 1 ml of $HCCl_3$ to a cooled stirred solution of 95 mg of 1-nitro-2-naphthol in 25 ml of 0.1 M Na_2CO_3 containing 0.1 g of NaBr, removing the $HCCl_3$ layer after 2 min, and washing with water.

Preparation of 1-Chloro-1-nitro-2-keto-1,2-dihydronaphthalene (2, X = Cl).[9]—To a cold solution of 80 mg of 1-chloro-2-naphthol in 500 μl of $HCCl_3$ was added 100 μl of chilled 90% HNO_3, and the mixture was swirled vigorously. After 2 min, ice was added and the $HCCl_3$ was washed with cold water and dried with Na_2SO_4. The ir spectrum of this solution was quite similar to that of the bromo analog (2, X = Br), with prominent bands at 5.91, 6.34, 7.50, and 12.2 μ. A solution of this product in $DCCl_3$ was also prepared: nmr τ 2.50 (d) + 2.57 (m), (5 H total), 3.72 (d, J = 9 Hz, 1 H). However, as Fries[6] also found, no pure ketone could be isolated from these solutions. Indeed, the solution of this material readily evolved nitrous fumes even at room temperature, and formed 1,2-naphthoquinone. Therefore this ketone was never isolated or purified, but its freshly prepared solution was immediately reacted.

A $HCCl_3$ solution showing these same ir peaks could also be prepared by rapidly adding 1 ml of 0.7 M NaOCl to a cooled stirred solution of 95 mg of 1-nitro-2-naphthol in 25 ml of 0.1 M Na_2CO_3 containing 0.35 ml of 10% H_2SO_4, removing the $HCCl_3$ layer after 2 min, and washing with water.

Reaction of 1-Chloro-1-nitro-2-keto-1,2-dihydronaphthalene (2, X = Cl) with Acid.—A fresh $HCCl_3$ solution of this material, prepared from 3.20 g of 1-chloro-2-naphthol, was filtered through Na_2SO_4 into a cooled, stirred solution of 1.20 of g of urea and 3.0 ml of concentrated HCl in 40 ml of redistilled Ac_2O plus 20 ml of AcOH. The mixture was allowed to stand for 2.5 hr at 25° and then for 2.5 hr at 60°; 1 ml of concentrated H_2SO_4 was then added; and the mixture was held 0.5 hr more at 60°. The mixture was then poured into 600 ml of H_2O and stirred gently overnight to hydrolyze the Ac_2O.

The mixture was extracted with ether and the ether layer washed with H_2O and 1 N NaOH. Evaporation of the ether gave 1.80 g of yellowish solid whose nmr and ir were characteristic of a nitronaphthyl acetate. Recrystallization of this material from 95% EtOH furnished a tan powder, mp 152–153.5°. The crude acetate was hydrolyzed in refluxing aqueous methanolic NaOH; work-up led to 1.20 g of crude 1-chloro-6-nitro-2-naphthol (4) as a brown solid. Thin layer chromatography indicated that the crude 1-chloro-6-nitro-2-naphthol contained a small amount of 1-chloro-2-naphthol (also detected by odor), but no 1-nitro-2-naphthol or 1,6-dinitro-2-naphthol.

Acidification and extraction of the NaOH washings of the original reaction mixture led to 700 mg of dark red powder, whose principal component was identified as 2-hydroxy-1,4-naphthoquinone by tlc, by ir (6.04 μ), and by melting point (195–197 dec) and mixture melting point of a sublimed sample. Formation of 2-hydroxy-1,4-naphthoquinone was also indicated by the uv spectrum of the aqueous washings of the original reaction mixture. No 1-nitro-2-naphthol or 1,6-dinitro-2-naphthol could be detected by tlc or ir. It was also found that under the conditions employed, both 1,2-naphthoquinone and 1,2,4-triacetoxynaphthalene are partially converted to 2-hydroxy-1,4-naphthoquinone. Also, treating the original ether extract with *o*-phenylenediamine gave the characteristic uv spectrum of benzo[*c*]phenazine, so that some 1,2-naphthoquinone does survive.

Reaction of 1-chloro-1-nitro-2-keto-1,2-dihydronaphthalene (2, X = Cl) prepared by chlorination of 1-nitro-2-naphthol gave the same products, as evidenced by tlc. Also these same products were detected from decomposition in aqueous HOAc.

Characterization of 1-Chloro-6-nitro-2-naphthol (4).—The crude product from the reaction of 2 (X = Cl) was purified by precipitating it from alkali with HOAc and repeated recrystallization from 50% EtOH, to give orange needles: mp 197.5–198°; ir 2.72 m, 2.81 m, 6.15 m, 6.52 m, 7.47 μ s.

Anal. Calcd for $C_{10}H_6ClNO_3$: C, 53.71; H, 2.705; Cl, 15.85. Found: C, 53.81; H, 2.75; Cl, 16.05.

With benzoyl chloride in dry THF, the lithium salt of 4 could be converted to a benzoate, mp 221–222°. Under conditions[47]

(41) H. Franzen and G. Stäuble, *J. Prakt. Chem.*, **103** [2], 379 (1921–1922).
(42) T. Zincke, *Ber.*, **21**, 3378 (1888).
(43) C. Graebe, *Justus Liebigs Ann. Chem.*, **335**, 1239 (1904).
(44) O. Wallach and H. Wichelhaus, *Ber.*, **3**, 846 (1870).
(45) A. J. Smith, *J. Chem. Soc.*, **35**, 789 (1879).
(46) M.-L. Josien, N. Fuson, J.-M. Lebas, and T. M. Gregory, *J. Chem. Phys.*, **21**, 331 (1953).
(47) R. Henriques and M. Ilinski, *Ber.*, **18**, 704 (1885).

such that 1-naphthol, 2-naphthol, or 6-bromo-2-naphthol was readily nitrosated, **4** was unreactive, just as 1-chloro-2-naphthol or 1-bromo-2-naphthol. Also, with 1 equiv of Br_2 in HOAc containing NaOAc, followed by quenching with ice and extraction with $HCCl_3$, **4** gave a solution that exhibited strong absorption at 5.89 μ and that liberated iodine from aqueous KI. This behavior was the same as that of 1-chloro-2-naphthol or 1-bromo-2-naphthol, and quite different from that of 2-naphthol. Oxidation of **4** with alkaline $KMnO_4$ led to 4-nitrophthalic acid, identified by melting point and mixture melting point.

Intramolecularity of the Rearrangement.—1-Chloro-2-naphthol (320 mg) in 3 ml of $HCCl_3$ was added to a solution of 120 mg of urea, 0.2 ml of H_2SO_4, and 0.11 ml of 70% HNO_3 in 4 ml of Ac_2O and 2 ml of AcOH. The mixture was allowed to stand at 60° for 3 hr and was then treated as above. Tlc of the hydrolyzate showed only 1-chloro-2-naphthol.

Reaction of 1-Bromo-1-nitro-2-keto-1,2-dihydronaphthalene (2, X = Br).—A fresh $HCCl_3$ solution of this material, prepared by nitration of 1.00 g of 1-bromo-2-naphthol, was filtered through Na_2SO_4 into a cooled, stirred solution of 0.6 g of urea, 1 ml of concentrated H_2SO_4, 10 ml of redistilled Ac_2O, and 5 ml of AcOH. Work-up as for the chloro analog gave 480 mg of crude acetate, which was hydrolyzed to 320 mg of brown solid. Recrystallization of this material from $HCCl_3$ gave orange crystals of 1-nitro-2-naphthol, identified by melting point and mixture melting point. Tlc of the crude material indicated that 1-nitro-2-naphthol was the principal product. No 1-bromo-2-naphthol could be detected, but tlc indicated the presence of a small amount of another substance, presumably 6-bromo-1-nitro-2-naphthol, which was not investigated. Acidification of the NaOH extract led to 130 mg of brown solid containing chiefly 2-hydroxy-1,4-naphthoquinone.

Registry No.—2, X = Br, 26885-81-4; 2, X = Cl, 26885-82-5; **4**, 26885-83-6.

Acknowledgments.—We are indebted to Dr. F. Thomas Bond for helpful suggestions and to Mr. Jerome F. Keeton for some preliminary experiments.

Substituent Effects on Solvolyses of 1,4-Ethano-1,2,3,4-tetrahydronaphthalen-2(*exo* and *endo*)-yl (Benzobicyclo[2.2.2]octen-2(*exo* and *endo*)-yl) Derivatives[1,2]

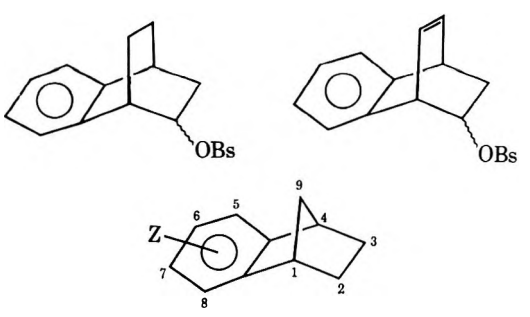
HIROSHI TANIDA* AND SADAO MIYAZAKI

Shionogi Research Laboratory, Shionogi and Company, Ltd., Fukushima-ku, Osaka, Japan

Received September 3, 1970

Series of aromatic-substituted 1,4-ethano-1,2,3,4-tetrahydronaphthalen-2(*exo*)-yl *p*-bromobenzenesulfonates (Z-A-OBs) or chlorides and the corresponding endo epimers (Z-B-OBs) were prepared and the solvolysis reactions studied. In the exo series, the relative rates of acetolysis of 6-CH_3O, H, 7-CH_3O, 7-NO_2, 6-NO_2, and 6,7-$(NO_2)_2$ derivatives at 77.6° were 224, 1, 0.58, 3.4×10^{-3}, 2.4×10^{-3}, and 2.1×10^{-4}, respectively. The solvolyses of 6-CH_3O, H, and 7-CH_3O lead to products entirely controlled by the neighboring aryl group, **A** alcohols (or esters) of retained configuration, and 1,5-methanobenzocyclohepten-2(ax)-ols (or esters) (Z-C-X) by rearrangement. In contrast, the acetolysis of deactivated 7-NO_2-**A**-OBs gave, besides **A** and **C** derivatives, the inverted 7-NO_2-**B**-OAc, 7-nitro-1,4-methanobenzocyclohepten-5(ax and eq)-yl acetates (7-NO_2-**D**-OAc), and minor hydrocarbons. Also, the **A**-OAc:**C**-OAc product ratio for the 7-NO_2 compound was different from the constant ratio obtained from the 6-CH_3O, H, and 7-CH_3O compounds. From the 6,7-$(NO_2)_2$ brosylate, **B** and **D** derivatives and hydrocarbons were obtained, but not **A** and **C** derivatives. The results from the 7-NO_2 compound are interpreted in terms of concurrence of the aryl-assisted path (k_Δ) and the solvent-assisted path (k_s); those from the 6,7-$(NO_2)_2$ compound suggest no participation and the products are explained in terms of a k_s process and its leakage. The rates of the 6-CH_3O, H, 7-CH_3O, 7-NO_2, and 6-NO_2 brosylates are well correlated with σ^+ constants, yielding a ρ of −3.25, but that of the 6,7-$(NO_2)_2$ brosylate is not. The relative rates in acetolysis of the endo brosylates were 0.34 for H, 2.7×10^{-2} for 7-NO_2, 2.4×10^{-2} for 6-NO_2, and 2.0×10^{-3} for 6,7-$(NO_2)_2$. No notable substituent effect on the distribution of products was observed. The predominant products in these cases were **D** acetates. The ρ–σ treatment of the endo rates yields a straight line with a ρ of −1.50. The apparent exo:endo rate ratios decrease from 2.9 for the H compounds to 0.13 for the 7-NO_2 compounds, but those for the 7-NO_2, 6-NO_2, and 6,7-$(NO_2)_2$ compounds are essentially constant at ~0.1.

In a previous paper solvolyses of the parent 1,4-ethano-1,2,3,4-tetrahydronaphthalen-2(*exo* and *endo*)-yl brosylates and of 1,4-ethano-1,4-dihydronaphthalen-9-(*exo* and *endo*)-yl (benzobicyclo[2.2.2]octadien-2(*exo* and *endo*)-yl) brosylates were reported.[3] Since our initial work on the benzonorbornen-9-yl system,[4] interest in substituent effects on the solvolysis of this ring system has remained at a high level.[5-8] The study of cationic intermediates of bicyclo[2.2.2]octyl



(1) The terms endo and exo are defined as follows: substituents on the side of the benzene ring are endo and those on the other side are exo. Axial and equatorial indicate the configuration of a substituent on the cyclohexane moiety and are abridged as ax and eq, respectively.

(2) The numbering used in this paper is shown in the charts.

(3) H. Tanida, K. Tori, and K. Kitahonoki, *J. Amer. Chem. Soc.*, **89**, 3212 (1967).

(4) H. Tanida, *ibid.*, **85**, 1703 (1963); H. Tanida, Y. Hata, S. Ikegami, and H. Ishitobi, *ibid.*, **89**, 2928 (1967), and a series of our papers cited therein.

(5) (a) H. C. Brown and G. L. Tritle, *ibid.*, **88**, 1320 (1966); (b) **90**, 2689 (1968); (c) H. C. Brown and K.-T. Liu, *ibid.*, **91**, 5909 (1969); (d) H. C. Brown, S. Ikegami, and K.-T. Liu, *ibid.*, **91**, 5911 (1969).

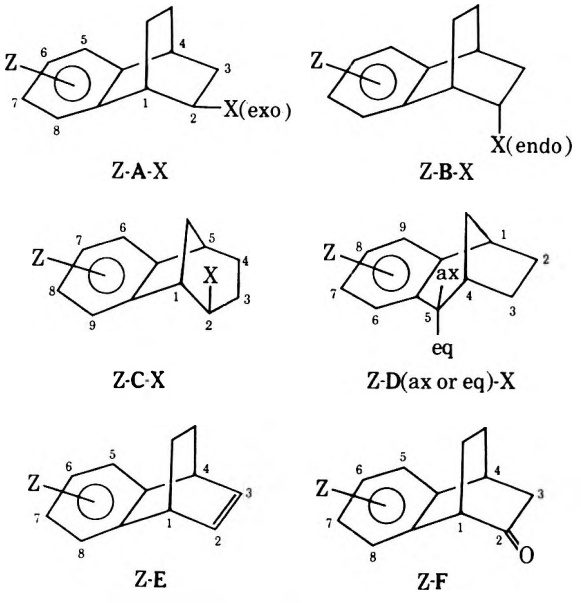
(6) (a) D. V. Braddon, G. A. Wiley, J. Dirlam, and S. Winstein, *ibid.*, **90**, 1901 (1968); (b) J. P. Dirlam and S. Winstein, *ibid.*, **91**, 5905 (1969); (c) *ibid.*, **91**, 5907 (1969).

(7) (a) H. Tanida, H. Ishitobi, T. Irie, and T. Tsushima, *ibid.*, **91**, 4512 (1969); (b) H. Tanida, T. Irie, and T. Tsushima, *ibid.*, **92**, 3404 (1970), and a series of our papers cited therein.

(8) A systematic study on the solvolysis of benzonorbornenyl derivatives was recently reported by J. W. Witt and P. J. Chenier, *J. Org. Chem.*, **35**, 1562, 1571 (1970).

and its unsaturated derivatives is also very active.[9-15] This is perhaps because the structural types available with the [2.2.2] carbon skeleton provide good opportunity for investigation of σ *vs.* π (homoallylic or homobenzylic) participation. Considering these situations, we undertook a study of substituent effects on the solvolysis of 1,4-ethano-1.2,3,4-tetrahydronaphthalen-2(*exo* and *endo*)-yl systems, which was based principally on the same ideas as applied to the benzonorbornenyl system.[7] The results are discussed in comparison with those from the benzonorbornenyl system.

To economically describe the compounds used, the following symbols are used: for 1,4-ethano-1,2,3,4-tetrahydronaphthalen-2(*exo*)-yl derivatives and their endo epimers, **A** and **B**; for 1,5-methanobenzocyclohepten-2(ax)-yl (benzo[6,7]bicyclo[3.2.1]octen-2(ax)-yl) derivatives, **C**; 1,4-methanobenzocyclohepten-5(ax and eq)-yl [benzo[3,4]bicyclo[3.2.1]octen-2(ax and eq)-yl] derivatives, **D** (ax and eq); for 1,4-ethano-1,4-dihydronaphthalene (benzobicyclo[2.2.2]octadiene) derivatives, **E**; and for 1,4-ethano-2-oxo-1,2,3,4-tetrahydronaphthalene (benzobicyclo[2.2.2]octen-2-one) derivatives, **F**.



Z-A-X Z-B-X

Z-C-X Z-D(ax or eq)-X

Z-E Z-F

Z = CH_3O, H, NO_2, $(NO_2)_2$; X = OH, OAc, OBs, Cl

Results

Preparations.—A facile synthetic method for the parent aromatic-unsubstituted **E** was recently reported,[16a] and the exo and endo alcohols **A**-OH and **B**-OH are already known.[16b] In this study these alcohols were prepared by the addition of diborane to **E** followed by oxidation with alkaline hydrogen peroxide, which gave a mixture showing an **A**:**B** ratio of 3:7 (separable by elution chromatography). Intramolecular hydrogen bonding between the hydroxyl group and the benzene ring is detected in **B**-OH, but not in **A**-OH. Nmr signals of the proton α to the hydroxy group (or its ester, or the chloro group) in the **A** system appear as a complicated multiplet, while those in **B** appear simply as a doublet of triplets. Nmr data of these protons and the bridgehead protons characteristic of the ring systems **A**–**D** are summarized in Table IV in the Experimental Section. On the basis of one or both of the ir and nmr spectral features, the orientation (exo or endo) of substituents at C_2 was determined in all [2.2.2] derivatives prepared in the present study. Electrophilic aromatic substitution reactions of the [2.2.2] system show an unusually strong β orientation.[17] Thus, nitration of a mixture of the acetates, **A**-OAc and **B**-OAc, with fuming nitric acid in acetic anhydride yields almost exclusively the 6- or 7-mononitro acetates (in total, four kinds of isomers), which were hydrolyzed into alcohols and oxidized with chromic anhydride–pyridine complex to a mixture of the nitro ketones, 6-NO_2**F** and 7-NO_2**F**, and separated by preparative layer chromatography (eq 1). Similarly to previous cases,[7] the analysis of nmr patterns of aromatic protons in the nitro ketones (AMX type, in acetone-d_6 at 100 MHz) produces evidence for the homo-para and homo-meta assignments. Lithium borohydride reductions of these ketones followed by separation of exo and endo epimers gave pure samples of 6-NO_2-**A**-OH, 6-NO_2-**B**-OH, 7-NO_2-**A**-OH, and 7-NO_2-**B**-OH.

Further nitration of the mononitro mixture, NO_2-**A**-OAc plus NO_2-**B**-OAc, with fuming nitric acid and concentrated sulfuric acid yielded predominantly a mixture of the 6,7-dinitro derivatives, $(NO_2)_2$-**A**-OAc and $(NO_2)_2$-**B**-OAc (eq 2). After hydrolysis, $(NO_2)_2$-**A**-OH and $(NO_2)_2$-**B**-OH were isolated by elution chromatography. Esterification with *p*-bromobenzenesulfonyl chloride in pyridine gave brosylates for solvolytic studies from the endo and exo epimers of the parent, the homo-para nitro, the homo-meta nitro, and the dinitro alcohols.

Oxidation of dicyclohexadiene (**1**)[16a,18] at the secondary allylic carbon by allowing it to stand with chromic anhydride in pyridine afforded the enone **2**, but not the isomer **3**, accompanying a double-bond migration. The structure of **2** was assigned by nmr. Treatment of **2** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in anhydrous dioxane containing 1% hydrochloric acid yielded the phenol HO-**E** in a crude state, the product to be expected from the dienone–phenol rearrangement of the cross dienone **4**. This phenol was, without purification, methylated to give 6-methoxy-1,4-ethano-1,4-dihydronaphthalene (CH_3O-**E**, homogeneous on vpc) in 20% yield from **2** (eq 3), the structure of which was confirmed by an independent synthesis which is shown in eq 3. The Friedel–Crafts acylation of 1,4-ethano-1,2,3,4-tetrahydronaphthalene afforded the β-acyl derivative **5**.[17] Oxidation of **5** with *m*-chloroperbenzoic acid to the

(9) H. M. Walborsky, J. Webb, and C. C. Pitt, *J. Org. Chem.*, **28**, 3214 (1963), and other papers by this group.

(10) H. L. Goering and G. N. Fickes, *J. Amer. Chem. Soc.*, **90**, 2848, 2856, 2862 (1968), and other papers in that series.

(11) (a) N. A. LeBel and J. E. Huber, *ibid.*, **85**, 3193 (1963); (b) N. A. LeBel and R. J. Maxwell, *ibid.*, **91**, 2307 (1969).

(12) J. A. Berson, J. J. Gajewski, and D. S. Donald, *ibid.*, **91**, 5550 (1969), and references cited therein.

(13) H. Kwart and J. L. Irvine, *ibid.*, **91**, 5541 (1969).

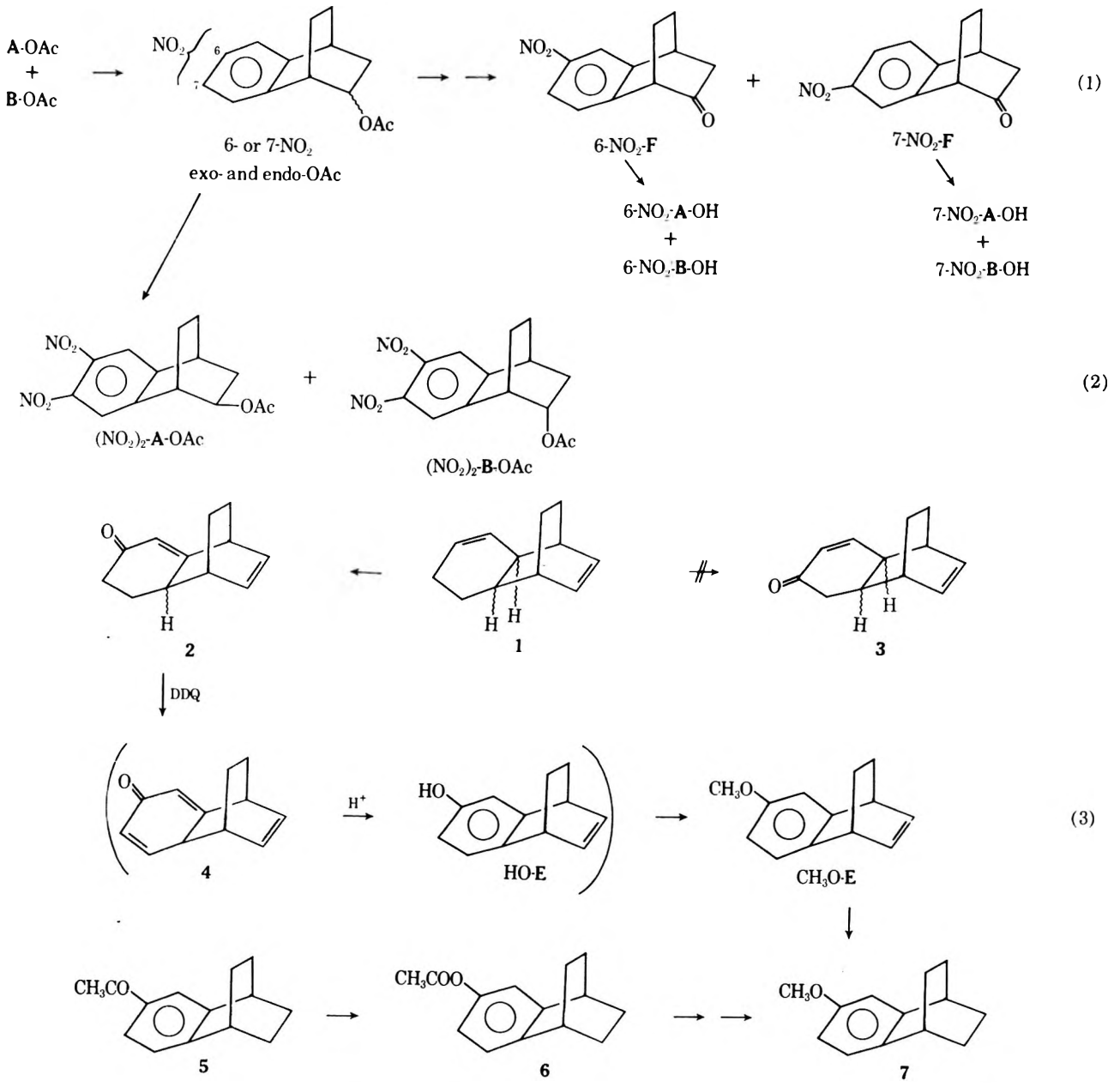
(14) S. J. Cristol, F. P. Parungo, D. E. Plorde, and K. Schwarzenbach, *ibid.*, **87**, 2879 (1965).

(15) E. Ciorănescu, A. Mihai, G. Mihai, M. Elian, and C. D. Nenitzescu, *Rev. Roum. Chim.*, **10**, 149 (1965).

(16) (a) K. Kitahonoki and Y. Takano, *Tetrahedron*, **25**, 2417 (1969); (b) *Tetrahedron Lett.*, 1597 (1963).

(17) H. Tanida and R. Muneyuki, *J. Amer. Chem. Soc.*, **87**, 4794 (1965).

(18) D. Valentine, N. J. Turro, Jr., and G. S. Hammond, *ibid.*, **86**, 5202 (1964).



β-acetoxy derivative **6**, followed by hydrolysis and methylation, yielded the methoxy compound **7**, identical with the hydrogenation product of CH_3O-**E**. Hydroboration of CH_3O-**E** gave a mixture of the four isomeric alcohols, 6-CH_3O-**A**-OH, 6-CH_3O-**B**-OH, 7-CH_3O-**A**-OH, and 7-CH_3O-**B**-OH, in which the ratio of the pair of **A** to the pair of **B** was 3:7 by vpc.[19] Isolation of the desired 6-CH_3O-**A** derivative is, in principle, based on the following findings. (a) The **A** and **B** alcohols are easily separated by elution chromatography on alumina. (b) The reaction of 6-CH_3O-**A**-OH with thionyl chloride in ether gives very predominantly 6-CH_3O-**A**-Cl with retention, whereas those of 7-CH_3O-**A**-OH as well as **A**-OH produce the **C** chlorides with rearrangement and the **A** chlorides with retention (for **A**-OH, the C:A ratio was 6:4). No formation of inverted chlorides was observed in any these chlorinations. (c) The homo-para 6-CH_3O-**A**-Cl is much more reactive in solvolysis than the chlorides derived from 7-CH_3O-**A**-OH. Thus, the exo alcohol fraction, 6-CH_3O-**A**-OH plus 7-CH_3O-**A**-OH, was separated, converted into a mixture of chlorides, and then subjected to partial hydrolysis to transform only the reactive homo-para chloride into a mixture of the alcohols, 6-CH_3O-**A**-OH and a rearranged alcohol (7-CH_3O-C-OH), in the ratio 79:21. This mixture was isolated from the less reactive chlorides and recrystallized to obtain the main 6-CH_3O-**A**-OH as pure crystals. Action of thionyl chloride upon these crystals yielded predominantly one chloride, 6-CH_3O-**A**-Cl. In contrast, the same reaction with **A**-OH gave two chlorides in the ratio 59:41, which were separated by preparative vpc. Conceivable ring structures for these chlorides are **A** of retention and **C** of rearrangement. Nmr spectra of the chloride from 6-CH_3O-**A**-OH and the minor chloride from **A**-OH are consistent with the **A** structure, but not the **C** structure.[20] As shown in Figure 1, the **A** acetates and chlorides exhibit bridge-

(19) The methoxy substituent showed no important directing effect on this hydroboration, because this alcohol mixture was converted by treatment with chromic anhydride–pyridine into a mixture of 6-CH_3OF and 7-CH_3OF in the ratio 55:45.

(20) From the present results, an activated aryl group rearranges less than a deactivate done. Participation and rearrangement of the β-aryl group in the thionyl chloride reaction would be an interesting problem which requires further studies.

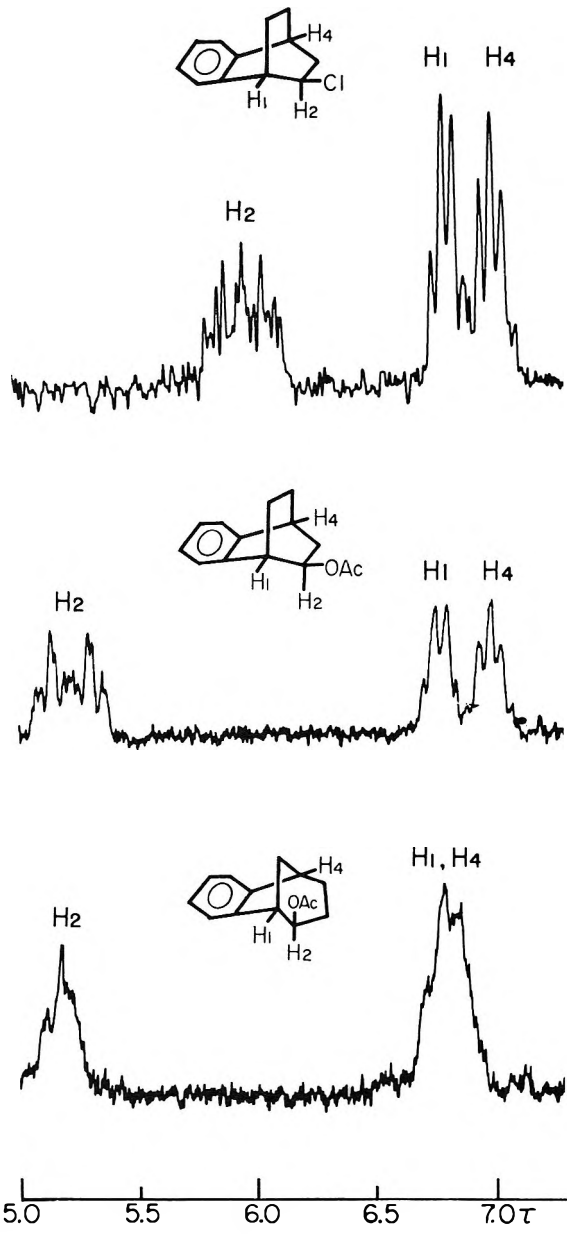


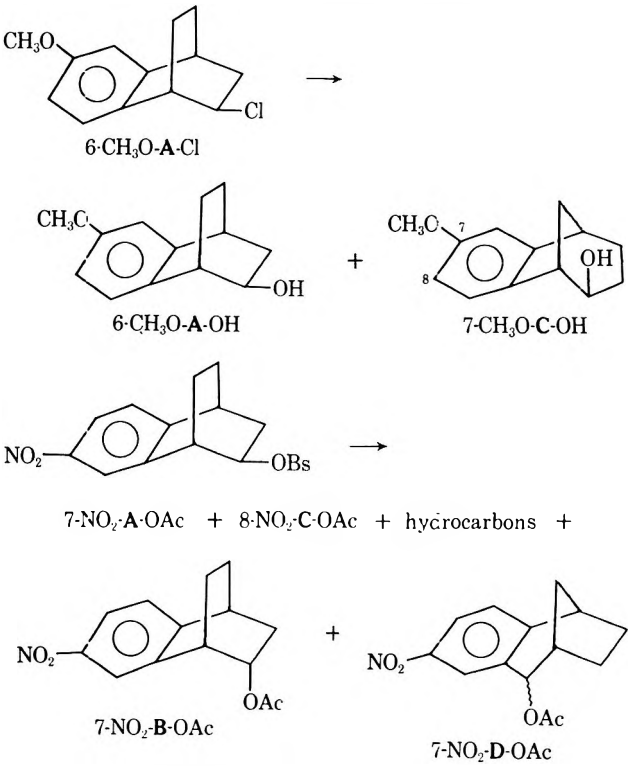
Figure 1.—Protons at bridgeheads and C_2 in the 60-MHz nmr spectra of the [2.2.2] and [3.2.1] derivatives.

head protons as a quartet (C_1 H) and a quintet (C_4 H), while bridgehead protons in the corresponding **C** derivatives appear as a broad signal which is a result of two overlapping multiplets; the structure for **C**-OAc used for comparison has been established.[3] In addition, half-height width, $W_{1/2}$, of the proton signals at C_2 bearing substituents is much larger for the **A** derivatives than for the **C** derivatives. The absence of formation of the **D** derivatives in solvolyses confirmed these **A** chlorides to be free from the **B** chlorides.

Purification of the chloride fraction, separated from the above-mentioned partial hydrolysis mixture, yielded 7-CH_3O-**A**-Cl.

Solvolysis Rates.—Rates for the brosylates were determined in glacial acetic acid containing equivalent sodium acetate by the standard procedure.[3,21] Good first-order kinetics were observed and the infinity titers corresponded to theory. Because of great reactivities of the homo-para exo system, the rate of solvolysis of 6-CH_3O-**A**-Cl in 70% aqueous acetone was determined by titration of the liberated hydrochloric acid and compared with those of 7-CH_3O-**A**-Cl and **A**-Cl. The rates are summarized in Table I. For comparison, the rate constants at 25 and 77.6° were calculated together with activation parameters. Relative reactivities are recorded at 77.6° because of convenience for comparison with reported data in the benzonorbornenyl system.

Solvolysis Products.—For product determination, the acetolyses and hydrolyses were carried out under the same conditions as used for the rate studies. Table II summarizes the substituent effects on the product composition in the exo and endo systems. The acetolysis of **A**-OBs has been reported to produce 83% the retained **A**-OAc and 17% the rearranged **C**-OAc. The hydrolysis of **A**-Cl was found to produce the same compounds in the ratio 75:23, not greatly different from the above. The vpc pattern of the hydrolysis products from 6-CH_3O-**A**-Cl was very similar and showed two important peaks in the ratio 77:20, together with a very minor peak of 3% ratio. The first product of 77 was proven to be the retained 6-CH_3O-**A**-OH. In these connections, the structure of the second important product was assigned as the rearranged 7-CH_3O-**C**-OH, although we had not sufficient amounts of the material to allow identification upon an isolated sample.

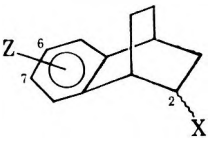


As the substituents become more electronegative, the products from the exo brosylates become more complex. However, since the products from 7-NO_2-**A**-OBs and $(NO_2)_2$-**A**-OBs [also, from 7-NO_2-**B**-OBs and $(NO_2)_2$-**B**-OBs] crystallized well, their separation into pure states was not difficult by preparative layer chromatography. Formation of the acetates of retention was detected from 7-NO_2-**A**-OBs, but not from $(NO_2)_2$-**A**-OBs. Acetates of inversion were produced

(21) S. Winstein, C. Hanson, and E. Grunwald, *J. Amer. Chem. Soc.*, **70**, 812 (1948); S. Winstein, E. Grunwald, and L. L. Ingraham, *ibid.*, **70**, 821 (1948).

TABLE I

RATE OF SOLVOLYSIS OF 6- AND 7-SUBSTITUTED 1,4-ETHANO-1,2,3,4-TETRAHYDRONAPHTHALEN-2-YL (A AND B) DERIVATIVES



Substituent[a]							
Z	X	Solvent[b]	Temp, °C	k_1, sec^{-1}	$\Delta H^{\ddagger}$, kcal	$\Delta S^{\ddagger}$, cal/deg	Rel rate, 77.6°
H	*exo*-OBs[c]	AcOH	25.0	2.37×10^{-5}[d]	23.7	−0.2	
			77.6	1.11×10^{-2}[c]	23.6	−0.5	1
H	*exo*-Cl	70% Me_2CO	89.98	1.76×10^{-5}			
			120.02	2.50×10^{-4}			
			25.0	9.09×10^{-9}[c]	24.5	−13.3	
			77.6	5.17×10^{-6}[a]	24.4	−13.6	1
6-CH_3O	*exo*-Cl	70% Me_2CO	25.02	2.25×10^{-6}			
			59.03	1.66×10^{-4}			
			64.89[e]	2.99×10^{-4}			
			25.0	2.25×10^{-6}[a]	24.1	−3.6	
			77.6	1.16×10^{-3}[a]	24.0	−3.9	224
7-CH_3O	*exo*-Cl	70% Me_2CO	89.98	1.05×10^{-5}			
			120.02	1.61×10^{-4}			
			25.0	4.36×10^{-9}[c]	25.2	−12.3	
			77.6	2.98×10^{-6}[a]	25.1	−12.6	0.58
7-NO_2	*exo*-OBs	AcOH	54.90	2.26×10^{-6}			
			77.88	3.88×10^{-5}			
			25.0	2.89×10^{-8}[d]	27.7	−0.01	
			77.6	3.76×10^{-5}	27.6	−0.34	3.4×10^{-3}
6-NO_2	*exo*-OBs	AcOH	54.90	1.79×10^{-6}			
			77.80	2.76×10^{-5}			
			25.0	2.67×10^{-8}[c]	26.7	−3.5	
			77.6	2.70×10^{-5}[c]	26.6	−3.8	2.4×10^{-3}
6,7-$(NO_2)_2$	*exo*-OBs	AcOH	79.98	3.07×10^{-6}			
			120.55	2.15×10^{-4}			
			121.30	2.18×10^{-4}			
			121.30	2.24×10^{-4}			
			140.12	1.11×10^{-3}			
			25.0	1.74×10^{-9}[d]	27.9	−5.0	
			77.6	2.37×10^{-6}[c]	27.8	−5.3	2.1×10^{-4}
H	*endo*-OBs[c]	AcOH	25.0	8.33×10^{-6}[c]	23.6	−2.7	
			77.6	3.79×10^{-3}[d]	23.5	−3.0	0.34
7-NO_2	*endo*-OBs	AcOH	54.90	2.39×10^{-5}			
			77.88	3.04×10^{-4}			
			25.0	4.85×10^{-7}[d]	24.7	−4.4	
			77.6	2.95×10^{-4}[d]	24.6	−4.8	2.7×10^{-2}
6-NO_2	*endo*-OBs	AcOH	54.90	2.05×10^{-5}			
			77.80	2.71×10^{-4}			
			25.0	3.88×10^{-7}[d]	25.2	−3.3	
			77.6	2.65×10^{-4}[d]	25.1	−3.7	2.4×10^{-2}
6,7-$(NO_2)_2$	*endo*-OBs	AcOH	79.98	2.64×10^{-5}			
			100.08	2.35×10^{-4}			
			120.01	1.12×10^{-3}			
			120.05	1.28×10^{-3}			
			120.45	1.35×10^{-3}			
			25.0	2.83×10^{-8}[d]	25.6	−7.1	
			77.6	2.16×10^{-5}[d]	25.5	−7.4	2.0×10^{-3}

[a] The concentrations of brosylates and chlorides were 0.02 *M*. Only in the cases of the dinitro compounds, the concentration was 0.01 *M*. [b] The aqueous acetone is expressed as volume per cent at 24° and the acetic acid contained equivalent amounts of AcONa and 1% acetic anhydride. [c] Calculated by Arrhenius plots of the data in ref 3. [d] Calculated by Arrhenius plots. [e] Determined by conductivity measurements.

from both the brosylates. The acetates of rearrangement, 7-NO_2-**D**-(ax and eq)-OAc and $(NO_2)_2$-**D**-(ax and eq)-OAc, were proven to be identical with the major products from the corresponding epimers, the endo brosylates. Convincing evidence for the structures of these acetates as well as for 7-NO_2-**C**-OAc is obtained from the 60- and 100-MHz nmr spectra, because data for pertinent compounds, for example, the parent **C** and **D** acetates[3] and bicyclo[3.2.1]oct-2-enes,[22] are available (Table IV). Appreciable amounts of hydrocarbons, formed by elimination, were found from 7-NO_2-**A**-OBs and $(NO_2)_2$-**A**-OBs. Those from $(NO_2)_2$-**A**-OBs were composed of an unsaturated compound and a saturated compound. The structure of

(22) C. W. Jefford, S. Mahajan, J. Waslyn, and B. Waegell, *J. Amer. Chem. Soc.*, **87**, 2183 (1965); C. W. Jefford and K. C. Ramsey, *Tetrahedron*, **24**, 2927 (1968); R. C. DeSelms and C. M. Combs, *J. Org. Chem.*, **28**, 2206 (1963); also, A. R. Katrisky and B. Wallis, *Chem. Ind. (London)*, 2025 (1964).

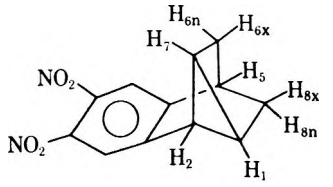
TABLE II

PRODUCTS[a] AND YIELDS[b] IN SOLVOLYSES[c] OF THE A AND B SYSTEMS

Substituent in material		Temp, °C	A-OAc	B-OAc	C-OAc[d]	D-OAc	E	Unknown
6-CH_3O	*exo*-Cl	25	77 ± 1		20 ± 1		0	3 ± 1[e]
H	*exo*-OBs[f]	50	83 ± 2	0	17 ± 2	0	0	
H	*exo*-Cl	120	75 ± 1	0	23 ± 1	0	0	2 ± 1[e]
7-CH_3O	*exo*-Cl	120	82 ± 1		15 ± 1		0	3 ± 1[e]
7-NO_2	*exo*-OBs	75	27 ± 2	15 ± 4	20 ± 2	ax 22 ± 4 eq 7 ± 4		9 ± 4[g]
6,7-$(NO_2)_2$	*exo*-OBs	100	0	49 ± 2	0	ax 27 ± 1 eq 0	6 ± 1	15 ± 3[g,h]
H	*endo*-OBs[f]	50	0	0	0	ax 98 ± 2 eq 2 ± 2	0	
7-NO_2	*endo*-OBs	75	0	0	0	ax 93 ± 2 eq 4 ± 3		
6,7-$(NO_2)_2$	*endo*-OBs	100	0	9 ± 3	0	ax 73 ± 2 eq 6 ± 1	4 ± 1	5 ± 3[g,h]

[a] The symbols A–D indicate the ring systems, as described in the introduction. [b] Per cents of theory. 0% means <1%. Vacancies mean the absence of any peak on vpc assignable to the compounds, though authentic samples are not available at hand. [c] Acetolysis of brosylates. Hydrolysis of chlorides in 70% aqueous acetone. [d] The ax configuration of OAc was proven in the H compound,[f] but presumed in the CH_3O and NO_2 compounds. [e] Vpc appears in the alcohol region. [f] Reference 3. [g] Vpc appears in the hydrocarbon region. [h] The major component is **12**.

the unsaturated one was assigned by nmr as $(NO_2)_2$-**E** (6% yield in Table II). Comparison of the 100-MHz nmr spectrum of the saturated one (Experimental Section) with that of benzo[3,4]tricyclo[3.2.1.$0^{2,7}$]octene[23] suggests the structure of the dinitro derivative of this octene (**12**). The composition of products from



12

the nitro brosylates was determined by integrating repeatedly the area of the –CH–OAc proton and that of the vinyl protons on the 60-MHz nmr spectra of the reaction mixture, using the aromatic protons as internal reference. Yields compatible with the product composition thus obtained were recorded by the amounts of products isolated by thin layer chromatography.

Substituents do not significantly affect the product distribution in the acetolysis of endo brosylates. As in the reported case of the parent **B**-OBs,[3] predominant formations of 7-NO_2-**D**-(ax and eq)-OAc and $(NO_2)_2$-**D**-(ax and eq)-OAc were respectively observed in the acetolyses of 7-NO_2-**B**-OBs and $(NO_2)_2$-**B**-OBs (97 and 79% yields). Only in the reaction of $(NO_2)_2$-**B**-OBs were the acetate of retention in 9% yield and the hydrocarbons [4% of $(NO_2)_2$-**E** and 5% of **12**] observed. The previous experiments[24] indicate that all the products, mentioned here and their ratio are those of kinetically controlled solvolyses.

Discussion

The 6-methoxy rate-accelerating effect in the benzonorbornen-2(*exo*)-yl system was the largest yet observed for a neighboring *p*-anisyl group (a factor of 178).[5b,6a,7a] Participation effects in the present system are again strikingly large. The 6-methoxy substituent here accelerates the rate by the same order of magnitude (a factor of 224 in Table I). On the other hand, the homo-meta 7-methoxy substituent depresses the rate slightly (a factor of 0.58), just as in electrophilic aromatic substitution reactions. In these solvolyses, the aryl group controls the stereospecificity and composition of products, so that the **A** and **C** derivatives, in the roughly constant ratio of 8:2, were the exclusive products. The 7-nitro substituent decelerates the rate by a factor of 3.4×10^{-3} and some amounts of the inverted product and the **D** acetate were now found. Ordinarily, rate effects due to a neighboring aryl group in acyclic or cyclic β-arylethyl systems are extremely modest, in spite of its significant product control which leads predominantly to retained configuration and rearrangement.[25-28] The aryl group has thus been considered by Winstein as a "marginal" neighboring group. However, both in the present system and in the previous benzonorbornenyl system the ability of aryl groups to participate both in rate determination and product distribution was demonstrated to be very great. Why should this be so? The solvolysis process of β-arylalkyl systems has been widely discussed in terms of a pair of discrete, independent, competing mechanistic pathways: the aryl-assisted route (k_Δ) and the aryl-unassisted but solvent-assisted route (k_s). With the right substrate structure and solvent, k_s becomes equal to an idealized process (k_c) in which neither aryl nor solvent assist.[29] Since Winstein's proposal, the solvolysis of simple primary systems has been considered to proceed with strong assistance in both k_Δ and k_s routes and with the absence of crossover (no leakage)

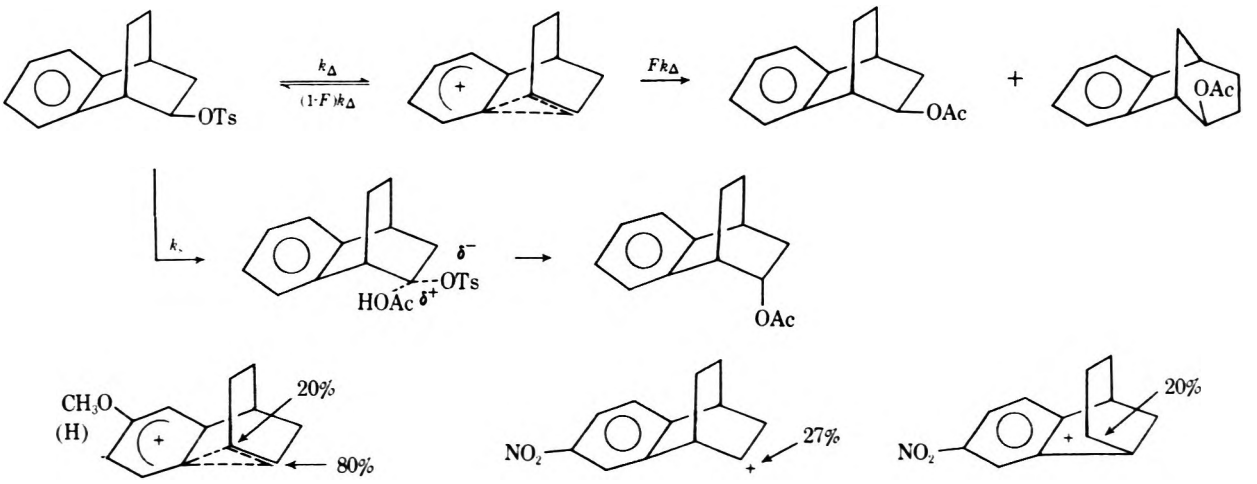
(23) R. C. Hahn and L. J. Rothman, *J. Amer. Chem. Soc.*, **91**, 2409 (1969).
(24) Reference 3, footnote 7.

(25) (a) H. C. Brown, K. J. Morgan, and F. J. Chloupek, *J. Amer. Chem. Soc.*, **87**, 2137 (1965); (b) H. C. Brown and C. J. Kim, *ibid.*, **90**, 2082 (1968); (c) C. J. Kim and H. C. Brown, *ibid.*, **91**, 4286, 4287, 4289 (1969).
(26) C. J. Lancelot and P. v. R. Schleyer, *ibid.*, **91**, 4291 (1969), and subsequent three communications; J. M. Harris, F. L. Schadt, and P. v. R. Schleyer, *ibid.*, **91**, 7508 (1969).
(27) J. E. Nordlander and W. G. Deadman, *ibid.*, **90**, 1590 (1968); J. E. Nordlander and W. J. Kelly, *ibid.*, **91**, 996 (1969).
(28) J. I. Coke, F. E. McFarlane, M. C. Mourning, and M. G. Jones, *ibid.*, **91**, 1154 (1969); M. G. Jones and J. I. Coke, *ibid.*, **91**, 4284 (1969).
(29) S. Winstein, *Bull. Soc. Chim. Fr.*, 55C (1951); S. Winstein and L. L. Ingraham, *J. Amer. Chem. Soc.*, **77**, 1738 (1955); S. Winstein, E. Allred, R. Heck, and R. Glick, *Tetrahedron*, **3**, 1 (1958).

between k_Δ and k_s, so that product composition (or product stereochemistry) is well correlated with the proportions of k_Δ and k_s. The interpretation in terms of these discrete k_Δ and k_s processes has not been convincing for secondary systems, like the present one, until recently.[30] However, discrete k_Δ and k_s for a secondary system was postulated and experimentally rationalized recently by Schleyer[26] and Winstein.[31] We have employed the interpretation in terms of k_Δ and k_s for the results from benzonorbornen-2-yl brosylates.[7] It has been well recognized that nucleophilic displacement reactions of the SN2 type are extremely difficult at a ring carbon of strained, bridged cyclic compounds. For the same reason, a transition state involving a strong solvent assistance is disfavored, and, as the k_Δ and k_s routes are competing with each other, such an unfavorable situation for k_s enhances k_Δ greatly. The large substituent effects on rate and the stereospecific formation of products are entirely the results of enhanced k_Δ.

7-NO_2-**B**-OAc in 15% yield can be considered as a direct result of k_s. However, generally weak solvent assistance in the molecule of this kind would not prevent leakage.[7b] Some products besides 7-NO_2-**B**-OAc could arise from a leakage of k_s.

A and **C** derivatives were not produced from the reaction of $(NO_2)_2$-**A**-OBs suggesting the absence of aryl participation. The formation of $(NO_2)_2$-**B**-OAc in 49% yield would be a direct result of k_s. Plotting logarithms of the observed relative rates of the 6-CH_3O, H, 7-CH_3O, 7-NO_2, and 6-NO_2 compounds against σ^+ yields a straight line with a ρ of -3.25 at 77.6° (correlation coefficient 0.999, Figure 2). However, the point of the $(NO_2)_2$ compound is far above the line defined by the first-named compounds. In the plotting, replacement of the rate for the 7-NO_2 compound into the Fk_Δ rate constant, 47% of k_t (a fraction of k_Δ leading to product in an event of internal return[26,28,31]), produces correlation of anchimerically assisted rates and σ^+ constants, with a ρ of -3.52 and a correlation



Of significance is the **A**-OAc/**C**-OAc product ratio from 7-NO_2-**A**-OBs, ~1.3, which is different from the constant ratio, ~4, obtained from the 6-CH_3O, H, and 7-CH_3O compounds. On the other hand, in the acetolysis of the benzonorbornen-2(*exo*)-yl brosylates, the exo 2-acetates were produced through retention as well as through rearrangement and the ratio of retention to rearrangement was ~1 over the range of substituents from 6-CH_3O to 6,7-dinitro.[7a] The constant ratios suggest no leakage from k_Δ. The ratio of the 7-NO_2 compound, decreased from 4 to 1.3, may suggest leakage from k_Δ of the deactivated nitrobenzene ring. The observed formation of 7-NO_2-**D**-OAc could arise from this leakage. It would be of considerable interest to investigate whether or not the k_Δ process of the 7-NO_2 compound forms an intermediate of the same structure to those resulting from the k_Δ process of the 6-CH_3O, H, and 7-CH_3O compounds. A detailed study of optically active derivatives may be instructive for this interesting problem.[32] The inverted coefficient of 0.995 (Figure 3). Because of the absence of product data, the 6-NO_2 point is omitted in this correlation. Extrapolation of the first line gives a σ^+ value of 1.01 for $(NO_2)_2$-**A**-OBs, which is considerably less than the value of 1.46 obtained by simple addition of each substituent constant, and that of the Fk_Δ line gives an estimated Fk_Δ of 3.91×10^{-8} sec^{-1} at 77.6° for $(NO_2)_2$-**A**-OBs, which amounts to only 1.7% of the observed rate. The smaller σ^+ than that obtained by simple addition is not abnormal, because two ortho nitro groups are not usually independent and sterically or electronically interact each other. No detection of $(NO_2)_2$-**A**-OAc and $(NO_2)_2$-**C**-OAc in products is compatible with the estimated Fk_Δ value.

Compared to those in the exo series, the substituent effects on rate in the endo series are small; $k_H/k_{7\text{-}NO_2}$ = 290 *vs.* 13. The composition of products from the endo brosylates is independent of substituents, except the minor formation of $(NO_2)_2$-**B**-OAc and $(NO_2)_2$-**E** from $(NO_2)_2$-**B**-OBs. The rates of all the endo brosylates are well correlated with σ, yielding a ρ of -1.50 (correlation coefficient 1000) (Figure 4), so that participation by the aryl group is unimportant here. No deviation

(30) Indeed, a referee informed us of Winstein's statement, "with simple primary systems there is no crossing over; with secondary and tertiary systems it (the solvolysis) is more likely to have crossover between the different routes." S. Winstein, "Chemica Theorica," Conferenze VIII, Corso Estivo di Chemica, Academia Nationale dei Lincei, Rome, 1965, p 251.

(31) A. F. Diaz and S. Winstein, *J. Amer. Chem. Soc.*, **91**, 4300 (1969).

(32) The present results from the 6-CH_3O, H, and 7-CH_3O exo brosylates prefer an intermediate of the phenonium ion type[11,33] rather than a nonclassical cation which may involve participation of the $C_{1,6}$-methylene bond, but not that of the benzene π electrons, or rapidly equilibrating set of classical ions, which we considered at an early stage of this research where data from the H brosylate only had been obtained.[3]

(33) D. J. Cram, *J. Amer. Chem. Soc.*, **71**, 3863 (1949); **86**, 3767 (1964). D. J. Cram and T. A. Thomson, *ibid.*, **89**, 6766 (1967); **91**, 1778 (1969).

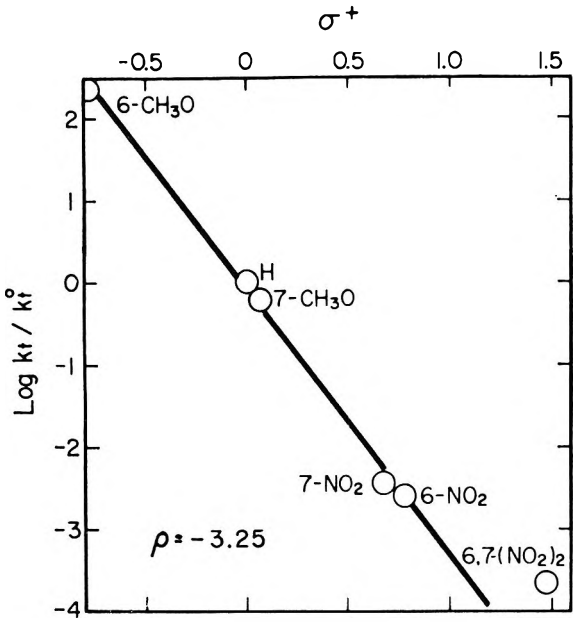


Figure 2.—The ρ–σ^+ treatment of the observed rates in solvolyses of 1,4-ethano-1,2,3,4-tetrahydronaphthalen-2(*exo*)-yl derivatives.

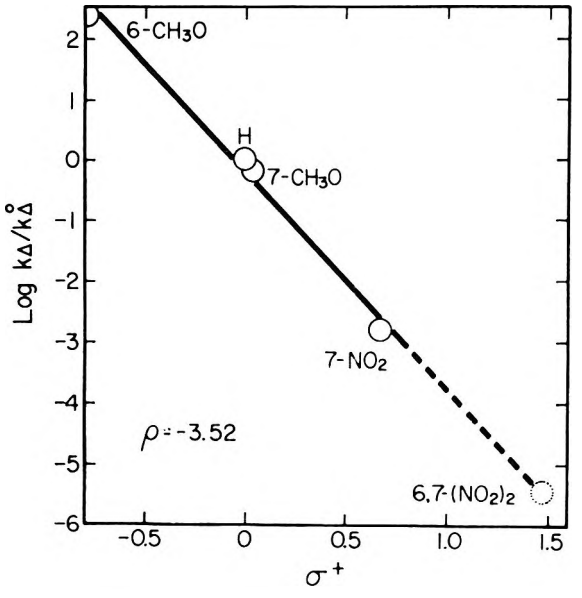


Figure 3.—The ρ–σ^+ treatment of the aryl-assisted rates in solvolyses of 1,4-ethano-1,2,3,4-tetrahydronaphthalen-2(*exo*)-yl derivatives.

of the $(NO_2)_2$ point, in contrast to the exo series, can be understood in terms of the major effect of substituents here being uniformly inductive, not conjugative as in the exo series, so that any interaction between two ortho groups would be much less serious.

The point of interest we should mention finally is the exo:endo rate ratios. The ratio decreases from 2.9 for the H compounds to 0.13 for the 7-NO_2 compounds and then, reaches a plateau value, 0.10 for the 6-NO_2 and 0.11 for the $(NO_2)_2$ compound. Such a constant value was not observed for the benzonorbornenyl system and the ratios decreased steadily over the range of substituents, to a value of ~4 for the dinitro compound.[7b] As the benzene ring in both the exo [2.2.1] and [2.2.2] systems is more and more deactivated, k_s tends to become major in solvolysis. However, the

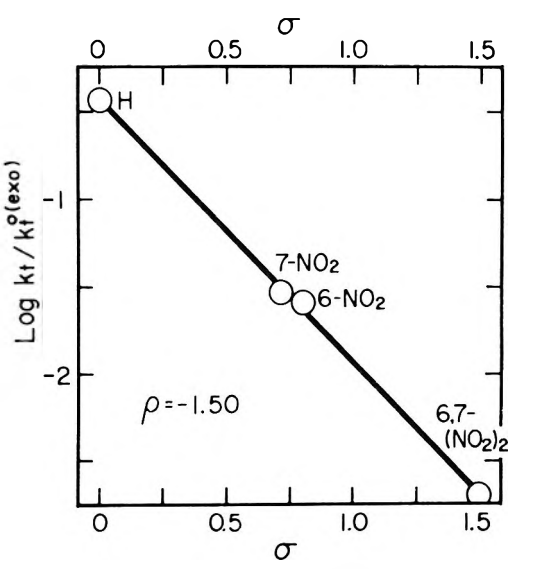


Figure 4.—The ρ–σ treatment of acetolysis rates of 1,4-ethano-1,2,3,4-tetrahydronaphthalen-2(*endo*)-yl brosylates relative to the aromatic-unsubstituted exo brosylate.

appearance of k_s with deactivating substituents varies from the [2.2.1] to the [2.2.2] system. In the [2.2.1] system a notable degree of k_s needs substitution by the two nitro groups, while in the [2.2.2] system the mononitro substituent is enough to cause a substantial degree of k_s, and substitution by the two nitro groups lowers k_Δ to 1.7% of the total rate and leads to solvolysis by k_s entirely. Any reaction of the SN2 type is not a factor for the exo:endo rate ratio, so that the [2.2.2] system produces a plateau value. The reason why the [2.2.2] system undergoes k_s easier than the [2.2.1] system must be the same to that for the well-known fact that the endo side of [2.2.1] compounds strongly hinders any approaching nucleophile. If correction for k_s is made on the assumption that k_s produces only the **B** acetates from the exo brosylates, the ratios would be 0.11 for the 7-NO_2 compounds and 0.056 for the $(NO_2)_2$ compounds. If the correction is made assuming that k_s produces all the products other than the **A** and **C** acetates, the ratios would be 0.061 for the 7-NO_2 compounds and 0 (infinitely small) for the $(NO_2)_2$ compounds. Constant decrease is seen.

Experimental Section

Melting points were taken by capillary and are corrected. Boiling points are uncorrected. Infrared spectra were determined with a Nippon Bunko DS-402-G spectrometer, ultraviolet spectra with a Beckman DK-2A spectrometer, and nmr spectra with a Varian A-60A and/or HA-100. Vpc analyses were performed on a Hitachi Model K-53.

Properties and analyses of the new compounds prepared in the present study are summarized in Table III. Nmr data of the protons at C_2 and bridgeheads, which are useful for discrimination of the present ring systems, are summarized in Table IV.

Kinetic Measurements.—The acetolysis conditions and procedure were the same as previously reported.[3,21]

For hydrolysis, the chlorides were dissolved at a concentration of 0.02 *M* in 70% (v/v) aqueous acetone, which was prepared by mixing seven parts of acetone and 1 part of water at 24°. Aliquots (2-ml portions) were sealed into ampoules, which were then placed in a constant temperature bath. Ampoules were removed at recorded intervals and rapidly cooled, and the contents were run into 20 ml of cold (0°) dry acetone to stop the reaction. Hydrogen chloride generated was titrated with 0.0046 *N* sodium hydroxide using a Metrohm Herisau Potentiograph E 336A.

TABLE III
PROPERTIES AND ANALYSES

Ring system[a]	Substituent: In aromatic	Substituent: In aliphatic	Mp or bp[b] (mm), °C	Formula
A	6-CH_3O	2-OH	128–129	$C_{13}H_{16}O_2$[g]
	6-CH_3O	2-Cl	[116–117 (3)][c]	$C_{13}H_{15}ClO$[g]
	7-CH_3O	2-Cl	[120–121 (2)][d]	$C_{13}H_{15}ClO$
	H	2-Cl	[97–98 (3)][e]	$C_{12}H_{13}Cl$
	6-NO_2	2-OH	114.5–116.0	$C_{12}H_{13}NO_3$[g]
	6-NO_2	2-OBs	153–154[f]	$C_{18}H_{16}BrNO_5S$[g]
	7-NO_2	2-OH	130–131.5	$C_{12}H_{13}NO_3$[g]
	7-NO_2	2-OBs	145–146[f]	$C_{18}H_{16}BrNO_5S$[g]
	7-NO_2	2-OAc	116–117	$C_{14}H_{15}NO_4$[g]
	6,7-$(NO_2)_2$	2-OH	139.5–140.5	$C_{12}H_{12}N_2O_5$[g]
	6,7-$(NO_2)_2$	2-OBs	174–175	$C_{18}H_{15}BrN_2O_7S$[g]
	6,7-$(NO_2)_2$	2-OAc	144.5–145.5	$C_{14}H_{14}N_2O_6$[g]
B	6-NO_2	2-OH	141.5–142.5	$C_{12}H_{13}NO_3$[g]
	6-NO_2	2-OBs	133–134[f]	$C_{18}H_{16}BrNO_5S$[g]
	7-NO_2	2-OH	111–112	$C_{12}H_{13}NO_3$[g]
	7-NO_2	2-OBs	140–141[f]	$C_{18}H_{16}BrNO_5S$[g]
	7-NO_2	2-OAc	99.5–101	$C_{14}H_{15}NO_4$[g]
	6,7-$(NO_2)_2$	2-OH	105–106	$C_{12}H_{12}N_2O_5$[g]
	6,7-$(NO_2)_2$	2-OBs	160–161	$C_{18}H_{15}BrN_2O_7S$[g]
	6,7-$(NO_2)_2$	2-OAc	123.5–124.5	$C_{14}H_{14}N_2O_6$[g]
C	8-NO_2	2-OAc	112–113.5	$C_{14}H_{15}NO_4$[g]
D	7-NO_2	5(ax)-OAc	102–103	$C_{14}H_{15}NO_4$[g]
	7,8-$(NO_2)_2$	5(ax)-OAc	154.5–155	$C_{14}H_{14}N_2O_6$[g]
F	6-NO_2	2-One	138.5–139.5	$C_{12}H_{11}NO_3$[g]
	7-NO_2	2-One	147–148	$C_{12}H_{11}NO_3$[g]
	6,7-$(NO_2)_2$	2-One	146.5–147	$C_{12}H_{10}N_2O_5$[g]

[a] The symbols A–D for ring systems are referred to in the introduction. [b] The boiling points are presented in brackets. [c] $n^{25}D$ 1.5687. [d] $n^{25}D$ 1.5668. [e] $n^{25}D$ 1.5696. [f] Decomposition. [g] Satisfactory combustion analytical data (±0.4%) were provided for those compounds. Ed.

The runs were followed to about 80% completion and first-order plots were linear. As one exception, plots beyond 30% completion for *p*-CH_3O-**A**-Cl showed a little upward curvature (the reaction became slower); so here the rate constants were calculated by plotting until 30% reaction.

Addition of Diborane to 1,4-Ethano-1,4-dihydronaphthalene (E).—To a stirred solution of 46.8 g of **E** in 250 ml of tetrahydrofuran, there was introduced at about 5° gaseous diborane which was generated by adding 120 g of boron trifluoride etherate to a solution of 22.8 g of sodium borohydride in 250 ml of diglyme. After standing overnight at room temperature, the excess hydride was decomposed, and the organoborane formed was oxidized with 150 ml of 3 *N* sodium hydroxide and 50 ml of 30% hydrogen peroxide. After 2 hr at room temperature, the reaction mixture was concentrated by distilling the tetrahydrofuran under reduced pressure and extracted with ether. The extract was washed with dilute hydrochloric acid and water, dried, and evaporated. Excess **E** was recovered by distillation under reduced pressure, and the remainder was acetylated with acetic anhydride. Vacuum distillation gave 46 g of a mixture of **A**-OAc and **B**-OAc at the ratio 3:7.

6- and 7-Nitro-1,4-ethano-1,2,3,4-tetrahydronaphthalen-2-one (6-NO_2-F and 7-NO_2-F).—Procedures for mononitration and dinitration of the 3:7 mixture of **A**-OAc and **B**-OAc were essentially the same as performed for benzonorbornen-2-yl acetates.[7a] A mixture of the mononitrated acetates was hydrolyzed by refluxing it in a mixture of 10% hydrochloric acid and ethanol, and then converted into a mixture of ketones by treatment with chromic anhydride–pyridine. Treatment by preparative layer chromatography on Kieselgel GF_{254} pack Stahl (Merck) isolated samples of 6-NO_2-**F** and 7-NO_2-**F**, which were repeatedly recrystallized to constant melting points.

100-MHz nmr spectra in acetone-d_6: 6-NO_2-**F** reveals C_5H at τ 1.78 (singlet), C_7H at 1.82 (quartet), and C_8H at τ 2.43 (ortho coupling, J = 7.5 Hz); 7-NO_2-**F** reveals C_5H at τ 2.38 (ortho coupling, J = 7.0 Hz), C_6H at 1.79 (quartet), and C_8H at 1.84 (singlet). For 6-NO_2-**F**, ir (CCl_4) 1738.5 cm^{-1}; uv max (95% C_2H_5OH) 221.5 mμ (ε 9260) and 276 (8820), a shoulder at 302 (5890). For 7-NO_2-**F**, ir (CCl_4) 1744.5 cm^{-1}; uv max (95% C_2H_5OH) 213.5 mμ (ε 17600) and 275 (9450).

6-Nitro-1,4-ethano-1,2,3,4-tetrahydronaphthalen-2(*exo* and *endo*)-ols (6-NO_2-A-OH and 6-NO_2-B-OH).—Reduction of 6-NO_2-**F** with lithium borohydride in tetrahydrofuran led to a mixture of 6-NO_2-**A**-OH and 6-NO_2-**B**-OH, which were separated by elution chromatography over alumina. Preparation of 7-NO_2-**A**-OH and 7-NO_2-**B**-OH was similar.

6,7-Dinitro-1,4-ethano-1,2,3,4-tetrahydronaphthalen-2(*exo* and *endo*)-ols [$(NO_2)_2$-A-OH and $(NO_2)_2$-B-OH].—A mixture of four isomeric mononitroacetates (homo-para and -meta, and exo and endo) was further nitrated. After work-up, elution chromatography over alumina gave $(NO_2)_2$-**A**-OH and $(NO_2)_2$-**B**-OH.

The Enone 2.—Detailed accounts of dimerization of cyclohexadiene have been reported.[16a] The dimer used here showed bp 88–90° (8 mm) and $n^{25}D$ 1.525. To a stirred solution of chromic anhydride–pyridine complex, prepared from 62.5 g of the anhydride and 600 ml of pyridine under nitrogen atmosphere, was added a solution of 20 g of the dimer in 40 ml of pyridine, and the mixture was allowed to stand for 65 hr at room temperature with stirring. The organic components in the reaction mixture were extracted with four 500-ml portions of ethyl acetate. The acetate extracts were passed through neutral alumina and evaporated *in vacuo*. Treatment of the residue (17 g) by elution chromatography over alumina, using a mixture solvent of petroleum ether and ether, gave **2** in 46% yield: bp 108–110° (3 mm); $n^{24.5}D$ 1.5584; ir (CCl_4) 1673 cm^{-1} (C=O); uv max (95% C_2H_5OH) 251 mμ (ε 14,200); nmr ($CDCl_3$) τ 3.80 (m, 2, -CH=CH-), 4.20 (d, 1, =CH-C=O). The semicarbazone had mp 218–219°.

Anal. Calcd for $C_{13}H_{17}N_3O$: C, 67.50; H, 7.41; N, 18.17. Found: C, 67.52; H, 7.40; N, 18.28.

6-Methoxy-1,4-ethano-1,4-dihydronaphthalene (CH$_3$O-E).—To a stirred solution of 10 g (57.5 mmol) of **2** in 400 ml of anhydrous dioxane containing 1% hydrogen chloride gas was added 16.9 g (74.7 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. After stirring for 2 hr at room temperature, precipitated hydroquinone was filtered off and washed with benzene. The combined dioxane and benzene solution was poured into a mixture of 800 ml of ethyl acetate and 500 ml of 3% aqueous sodium bicarbonate. The ethyl acetate layer was separated, washed with saturated sodium chloride solution, then with water, dried, and evaporated. The residue was dissolved in chloroform and passed through a column packed with Kieselgel, 0.2–0.5 mm (Merck). Evaporation of the chloroform left 2.95 g (17.2 mmol) of crude 6-hydroxy-1,4-ethano-1,4-dihydronaphthalene (OH-**E**). Methylation of OH-**E** was carried out with 4.33 g (34.4 mmol) of dimethyl sulfate in 160 ml of acetone, in which was suspended 4.75 g of anhydrous potassium carbonate. The work-up gave 2.08 g of CH_3O-**E**: bp 92–94° (3 mm); $n^{25}D$ 1.5660; uv max (95% EtOH) 230 mμ (ε 3750), 278 (1940), 284 (1710).

Anal. Calcd for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 84.08; H, 7.64.

6- and 7-Methoxy-1,4-ethano-1,2,3,4-tetrahydronaphthalen-2(*exo*)-yl Chlorides (6-CH_3O-A-Cl and 7-CH_3O-A-Cl).—A mixture of exo and endo epimers of 6- and 7-methoxy-1,4-ethano-1,4-dihydronaphthalen-2-ols (the exo:endo ratio was 3:7) was prepared from CH_3O-**E**, by a similar hydroboration to that described above. To enrich the exo component, the mixture (5.2 g) was added to a solution of 6.75 g of aluminum isopropoxide in 130 ml of xylene containing 3–4 drops of acetone, and heated for 15 hr at 150°. The mixture was poured into 170 ml of ice–water containing 2 g of sodium hydroxide and extracted with ether. Evaporation of ether left a 4:6 mixture of the exo and endo epimeric alcohols, which were separated by elution chromatography on neutral alumina containing 6% water. The exo mixture (1.09 g) (6-CH_3O-**A**-OH plus 7-CH_3O-**A**-OH) was treated with 3.82 g of thionyl chloride in 40 ml of ether to produce a mixture of chlorides (1.21 g), whose vpc showed three peaks in the ratio of 70:28:2. The peak of 70 was considered to be due to 6-CH_3O-**A**-Cl plus 7-CH_3O-**A**-Cl and that of 28 to be due to 8-CH_3O-**C**-Cl. The peak of 2 was CH_3O-**E**. Hydrolysis of this mixture at 80° for 6 hr in 55 ml of 70% aqueous acetone containing 907 mg of sodium bicarbonate produced a mixture of alcohols and chlorides, the alcohol fraction of which was separated by elution chromatography over Kieselgel, 0.2–0.5 mm (Merck). This fraction was shown by vpc to be composed of 6-CH_3O-**A**-OH and a rearranged alcohol, for which the structure of 7-CH_3O-**C**-OH was assigned, in the ratio 79:21. Recrystallization from ether gave as pure crystals the main 6-CH_3O-**A**-OH, in which the absence of 7-CH_3O-**A**-OH

TABLE IV

NMR CHEMICAL SHIFTS, τ, IN $CDCl_3$ AT 60 MHz[a]

Compd				
	Substituent			
Ring	In aromatic	In aliphatic	>CH-X	Bridgehead
A	H	2-OH	~6.1 (m)	~7.0 (2 H, m′)
	H	2-OAc	~5.2 (m)	6.79 (qua), 7.01 (qui)
	H	Cl	~6.0 (m)	6.82 (qua), 7.00 (qui)
	6-NO_2	2-OH	6.10 (m)	6.81 (2 H, m′)
	7-NO_2	2-OH	6.18 (m)	6.83 (2 H, m′)
	7-NO_2	2-OAc	5.25 (m)	6.64 (qua), 6.83 (qui)
	6,7-$(NO_2)_2$	2-OH	6.05 (m)	6.75 (2 H, m′)
	6,7-$(NO_2)_2$	2-OAc	~5.2 (m)	6.54, 6.73
	6-CH_3O	2-OH	~6.1 (m)	~7.1 (2 H, m′)
	6-CHO_3	2-Cl	~6.0 (m)	6.90 (qua), 7.08 (qui)
	7-CH_3O	2-Cl	~6.0 (m)	6.90 (qua), 7.08 (qui)
B	H	2-OH	~6.0 (m)	7.00 (2 H, m′)
	H	2-OAc	~4.9 (m)	6.80, 6.97
	6-NO_2	2-OH	5.82 (d-t), $J_{2,3}$ = 8.8 Hz	6.80 (2 H, m′)
	7-NO_2	2-OH	5.82 (d-t), $J_{2,3}$ = 8.8 Hz	6.83 (2 H, m′)
		2-OAc	4.87 (d-t), $J_{2,3}$ = 9.0 Hz	6.64, 6.83
B	6,7-$(NO_2)_2$	2-OH	5.75 (d-t), $J_{2,3}$ = 8.6 Hz	6.73 (2 H, m′)
	6,7-$(NO_2)_2$	2-OAc	4.82 (d-t), $J_{2,3}$ = 8.8 Hz	6.55, 6.75
C	H	2-OH	6.13 (m)	~6.9 (2 H, m′)
	H	2-OAc[b]	5.17 (m)	~6.8 (2 H, m′)
	8-NO_2	2-OAc	5.03 (m)	6.65 (2 H, m′)
	7-CH_3O	2-OAc[b]	5.20 (m)	~6.9 (2 H, m′)
D	7-NO_2	2(ax)-OAc	4.33 (d), $J_{4,5}$ = 2.7 Hz	6.75 (m), 7.30 (m)
	6,7-$(NO_2)_2$	2(ax)-OAc	4.33 (d), $J_{4,5}$ = 2.8 Hz	6.69 (m), 7.26 (m)
	6,7-$(NO_2)_2$	2(eq)-OAc	3.85 (d), $J_{4,5}$ = 5.0 Hz	

[a] d = doublet, t = triplet, qua = quartet, qui = quintet, m = multiplet, m′ = overlapping multiplet, and d-t = doublet of triplets. [b] In CCl_4.

was confirmed by transforming it into the ketone 6-CH_3O-**F**,[34] suitable for vpc analysis.

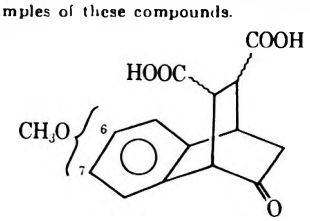
Treatment of 230 mg of 6-CH_3O-**A**-OH with 816 mg of thionyl chloride in 14 ml of ether gave 6-CH_3O-**A**-Cl, homogeneous on vpc.

The chloride fraction of the hydrolysis mixture (a mixture of 7-CH_3O-**A**-Cl and 8-CH_3O-**C**-Cl as well as the minor CH_3O-**E**) was further subjected to hydrolysis by treating it at 130° for 5 hr in 70% aqueous dimethylformamide containing sodium bicarbonate to change only the more reactive 8-CH_3O-**C**-Cl into alcohols. The work-up isolated a mixture of the unchanged chloride, 7-CH_3O-**A**-Cl, and the minor CH_3O-**E** from the alcohols formed. This mixture was treated by the standard hydroboration reaction to convert CH_3O-**E** into alcohols, without influence on 7-CH_3O-**A**-Cl. Thus, 7-CH_3O-**A**-Cl was easily separated in a pure state from the alcohols by elution chromatography over Kieselgel, 0.2–0.5 mm (Merck), using benzene.

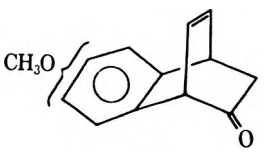
Gas Chromatographic Analyses.—Analyses were carried out on a Hitachi gas chromatograph Model K-53 equipped with a hydrogen flame ionization detector using any of the columns: (A) 2 m × 3 mm stainless steel column packed with 5% XE 60 on Chromosorb W; (B) a 1 m × 3 mm stainless steel column packed with 4% KF 54 on the same support; (C) a 1 m × 3 mm stainless steel column packed with 5% diethylene glycol succinate polyester on the same support. Nitrogen gas was used as a carrier gas. Retention times of **E** and CH_3O-**E** were 9 min 20 sec at 110° of column A with a pressure of 1 kg/cm² of nitrogen and 7 min at 130° of column B with a pressure of 1.5 kg/cm², respectively. Those of **A**-OH and **B**-OH were 9 min and 13 min 50 sec, respectively, at 130° of column B with a pressure of 1.0 kg/cm². Those of 6- and 7-CH_3O-**A**-OH were the same 11 min, and those of 6- and 7-CH_3O-**B**-OH were the same 13 min 6 sec, at 190° of column A with a pressure of 1.5 kg/cm². Those of 6-CH_3O-**A**-OH and 7-CH_3O-**C**-OH were 12 min 24 sec and 10 min 18 sec, respectively, at 150° of column B with a pressure of 1.5 kg/cm². That of 6-CH_3O-**F** was 16 min 12 sec at 190° of column A with a pressure of 1.5 kg/cm². Those of 6-CH_3O-**A**-Cl and 7-CH_3O-**A**-Cl were 6 min and 5 min 48 sec, respectively, at 150° of column C with a pressure of 1.5 kg/cm². Those of **E**, **C**-Cl, and **A**-Cl were 2 min 36 sec, 7 min 18 sec, and 8 min 24 sec, respectively, at 130° of column B with a pressure of 1.0 kg/cm².

Acetolysis Products from $(NO_2)_2$-B-OBs.—A solution of 145 mg (3×10^{-4} mol) of the brosylate in 15 ml of acetic acid containing 0.022 *M* sodium acetate was sealed in a tube and heated for 70 hr at 100°. The acetic acid was evaporated *in vacuo*, and the residue added into water and extracted with chloroform. The chloroform solution was washed with cold aqueous sodium carbonate, dried with anhydrous sodium sulfate, and evaporated. Preparative layer chromatography on Kieselgel GF_{254} (Merck)

(34) Treatment of the 6- and 7-methoxyketocarboxylic acids (**13** and **14**)[35] with lead tetraacetate in pyridine affords, respectively, the unsaturated ketones, **15** and **16**, though the yields are unsatisfactory. Hydrogenations of **15** and **16** gives compounds indentical with 6-CH_3O-**F** and 7-CH_3O-**F**. We thank Drs. K. Takeda and K. Kitahonoki for providing authentic samples of these compounds.



13, CH_3O at C-6
14, CH_3O at C-7



15, CH_3O at C-6
16, CH_3O at C-7

(35) K. Takeda, S. Hagishita, M. Sugiura, K. Kitahonoki, I. Ban, S. Miyazaki, and K. Kuriyama, *Tetrahedron*, **26**, 1435 (1970).

with a 9:1 solvent mixture of benzene and ether showed five bands. The first band, R_f 15.2, was shown by nmr to be composed of $(NO_2)_2$-**E** and the tricyclic **12**. The second band, R_f 10.2, was obtained as $(NO_2)_2$-**D**(ax)-OAc; the third band, R_f 9.6, as $(NO_2)_2$-**D**(eq)-OAc; the fourth band, R_f 8.5, as $(NO_2)_2$-**A**-OAc; the fifth band, R_f 6.2, as $(NO_2)_2$-**B**-OAc. The yields in Table II were determined by nmr spectroscopy and from the relative amounts of the thus isolated products. Because of insufficient amounts, isolation of samples of $(NO_2)_2$-**E** and **12**, satisfactory for analysis, was unsuccessful. The 100-MHz nmr of the crude **12** shows H_{6x} and H_{8x} at τ 8.03 (quartet, $J_{6x,6n}$ and $J_{8x,8n}$ = 11.6 Hz, $H_{6x,5}$ and $J_{8x,5}$ = 5.0 Hz), H_{6n} and H_{8n} at 9.03 (doublet), H_5 at 6.75 (triplet), H_2 at 7.66 (triplet, $J_{H_2H_1}$ and $J_{H_2H_7}$ = 7.4 Hz), and H_1, H_7 at 8.07 (doublet). Studies of products from other nitro brosylates were carried out in a similar way.

Infrared Hydroxyl Stretching Bands.—Spectra were taken in carbon tetrachloride and the concentration of alcohols were less than 0.003 *M*. **A**-OH, 6-NO_2-**A**-OH, and 7-NO_2-**A**-OH show only a free band at 3622, 3620, and 3620 cm^{-1}, respectively. **B**-OH shows a week free band at 3619 cm^{-1} and an associated band (OH$\cdots\pi$) at 3584 cm^{-1}. 6-NO_2-**B**-OH and 7-NO_2-**B**-OH show free bands at 3615 and 3613 cm^{-1}, respectively, as well as associated bands at 3594 and 3593 cm^{-1}, respectively. In both the nitro alcohols, the intensities of the associated bands are a little weak relative to those of the free bands.

Registry No.—**A** (Z, X) (6-CH_3O, 2-OH), 27142-14-9; (6-CH_3O, 2-Cl), 27142-15-0; (7-CH_3O, 2-Cl), 27142-16-1; (H, 2-Cl), 27189-22-6; (H, 2-OH), 13153-77-0; (H, 2-OBs), 16938-83-3; (H, 2-OAc), 16938-84-4; (6-NO_2, 2-OH), 27142-17-2; (6-NO_2, 2-OBs), 27142-18-3; (7-NO_2, 2-OH), 27142-19-4; (7-NO_2, 2-OBs), 27142-20-7; (7-NO_2, 2-OAc), 27142-21-8; (6,7-$(NO_2)_2$, 2-OH), 27142-22-9; (6,7-$(NO_2)_2$, 2-OBs), 27189-23-7; (6,7-$(NO_2)_2$, 2-OAc), 27150-76-1; **B** (Z, X) (H, 2-OH), 13153-78-1; (H, 2-OBs), 16938-82-2; (H, 2-OAc), 27149-76-4; (6-NO_2, 2-OH), 27149-77-5; (6-NO_2, 2-OBs), 27149-78-6; (7-NO_2, 2-OH), 27149-79-7; (7-NO_2, 2-OBs), 27149-80-0; (7-NO_2, 2-OAc), 27149-81-1; (6,7-$(NO_2)_2$, 2-OH), 27149-82-2; (6,7-$(NO_2)_2$, 2-OBs), 27149-83-3; (6,7-$(NO_2)_2$, 2-OAc), 27149-84-4; **C** (Z, X) (H, 2-OH), 16938-90-2; (H, 2-OAc), 27149-86-6; (8-NO_2, 2-OAc), 27149-87-7; (7-CH_3O, 2-OAc), 27149-88-8; **D** (Z, X) (7-NO_2, 2(ax)-OAc), 27149-89-9; (7-NO_2, 5(ax)-OAc), 27149-90-2; (6,7-$(NO_2)_2$, 2(ax)-OAc), 27149-91-3; (6,7-$(NO_2)_2$, 2(eq)-OAc), 27149-92-4; (7,8-$(NO_2)_2$, 5(ax)-OAc), 27149-93-5; **E** (Z) (CH_3O), 27150-77-2; **F** (Z, X) (6-NO_2, 2-one), 27150-78-3; (7-NO_2, 2-one), 27150-79-4; (6,7-$(NO_2)_2$, 2-one), 27150-80-7; **2**, 27150-81-8.

Acknowledgments.—We thank Drs. K. Tori and M. Otsuru for helpful discussion concerning nmr spectra and Drs. K. Kitahonoki and Y. Takano for an exchange of information.

The 1-Aza-2,4,6-cyclooctatriene–7-Azabicyclo[4.2.0]octadiene Valence Tautomeric Equilibrium. A Study of Substituent Effects and an Attempted Synthesis of Azetes (Azacyclobutadienes)[1]

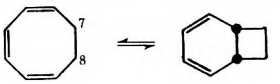
LEO A. PAQUETTE,* TSUYOSHI KAKIHANA,[2] AND JOHN F. KELLY

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

Received July 30, 1970

Five derivatives of the 1-aza-2,4,6-cyclooctatriene system have been prepared. The concentration of each polyene in equilibrium with its valence tautomeric 7-azabicyclo[4.2.0]octatriene form has been evaluated quantitatively by nmr spectroscopy. It was noted that the bicyclic form is favored in all instances, although to varying degrees, and explanations of such behavior are advanced. The attempted utilization of these substances in the preparation of azete (azacyclobutadiene) derivatives is described.

The last two decades have witnessed the methodical compilation of much experimental data concerning reversible transformations that occur without the migration of atoms or groups, now commonly referred to as valence tautomeric equilibria.[3] However, despite the fact that quantitative evidence for a wide variety of structural types is currently available, our basic understanding of the causative factors that control the individual positions of equilibrium is lacking in many instances. Particularly relevant examples in this connection are the cycloheptatriene–norcaradiene,[4] cyclooctatriene–bicyclo[4.2.0]octadiene,[5] oxepin–benzene oxide,[3d,f] 1*H*-azepine–azanorcaradiene,[3f,6] and azocine–azabicyclo[4.2.0]octatriene[7] tautomeric pairs. To illustrate, Huisgen and coworkers[5d] have recently determined the equilibrium position of the 1,3,5-cyclooctatriene (**1**)–bicyclo[4.2.0]octadiene (**2**) valence tauto-



1 **2**

(1) Unsaturated Heterocyclic Systems. LXXVII. For the previous paper in this series, see L. A. Paquette and T. Kakihana, *J. Amer. Chem. Soc.*, **93**, 174 (1971).

(2) Goodyear Tire and Rubber Co. Fellow, 1969–1970.

(3) For recent reviews, consult (a) E. Vogel, *Angew. Chem., Int. Ed. Engl.*, **2**, 1 (1963); (b) W. von E. Doering and W. R. Roth, *ibid.*, **2**, 115 (1963); (c) S. J. Rhoads, "Molecular Rearrangements," part I, P. de Mayo, Ed., Wiley, New York, N. Y., 1963, p 655; (d) E. Vogel and H. Günther, *Angew. Chem., Int. Ed. Engl.*, **6**, 385 (1967); (e) G. Maier, *ibid.*, **6**, 402 (1967); (f) L. A. Paquette, "Nonbenzenoid Aromatics," Vol. I, J. Snyder, Ed., Academic Press, New York, N. Y., 1969, pp 249–310.

(4) (a) E. J. Corey, H. J. Burke, and W. A. Remers, *J. Amer. Chem. Soc.*, **78**, 180 (1956); (b) R. B. Turner, W. R. Meador, W. von E. Doering, L. H. Knox, J. R. Mayer, and D. W. Wiley, *ibid.*, **79**, 4127 (1957); (c) J. B. Lambert, L. J. Durham, P. Lepoutre, and J. D. Roberts, *ibid.*, **87**, 3896 (1965); (d) H. Günther and H. H. Hinrichs, *Tetrahedron Lett.*, 787 (1966); (e) F. A. L. Anet, *J. Amer. Chem. Soc.*, **86**, 458 (1964); (f) F. R. Jensen and L. A. Smith, *ibid.*, **86**, 955 (1964); (g) M. Battiste, *Chem. Ind. (London)*, 550 (1961); (h) D. M. Gale, W. J. Middleton, and C. G. Krespan, *J. Amer. Chem. Soc.*, **87**, 657 (1965); **88**, 3617 (1966); (i) E. Ciganek, *ibid.*, **87**, 652, 1149 (1965); **89**, 1454, 1458 (1967); (k) T. Mukai, H. Yubota, and T. Toda, *Tetrahedron Lett.*, 3581 (1967); (k) T. Toda, M. Nitta, and T. Mukai, *ibid.*, 4401 (1969).

(5) (a) A. C. Cope, A. C. Haven, F. L. Ramp, and E. R. Trumbull, *J. Amer. Chem. Soc.*, **74**, 4867 (1952); (b) R. Huisgen, F. Mietzsch, G. Boche, and H. Seidl, *Chem. Soc., Spec. Publ.*, **19**, 3 (1965); (e) E. Vogel, O. Roos, and K.-H. Disch, *Justus Liebigs Ann. Chem.*, **653**, 55 (1962); (d) R. Huisgen, G. Boche, A. Dahmen, and W. Hechtl, *Tetrahedron Lett.*, 5215 (1968).

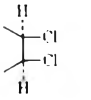
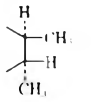
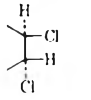
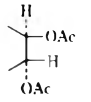
(6) (a) L. A. Paquette, J. H. Barrett, and D. E. Kuhla, *J. Amer. Chem. Soc.*, **91**, 3616 (1969); (b) L. A. Paquette, D. E. Kuhla, J. H. Barrett, and R. J. Haluska, *J. Org. Chem.*, **34**, 2866 (1969); (c) L. A. Paquette, D. E. Kuhla, and J. H. Barrett, *ibid.*, **34**, 2879 (1969).

(7) (a) L. A. Paquette and T. Kakihana, *J. Amer. Chem. Soc.*, **90**, 3897 (1968); (b) L. A. Paquette and J. C. Philips, *ibid.*, **90**, 3898 (1968); (c) L. A. Paquette, T. Kakihana, J. F. Hansen, and J. C. Philips, *ibid.*, **93**, 152 (1971).

merism as a function of the substituents at the 7 and 8 positions. Their results are summarized in Table I.

TABLE I

INFLUENCE OF 7 AND 8 SUBSTITUENTS ON THE VALENCE TAUTOMERIC EQUILIBRIUM OF CYCLOOCTA-1,3,5-TRIENES[a,b]

Substituents	% bicyclic	Substituents	% bicyclic
	0.01 (100°)		80
	0.4		
	6.6		81
	10.8		94
	35		99 (−30°)
	53		
			>95
			>95

[a] Values taken from ref 5d. [b] At 60°, unless otherwise specified.

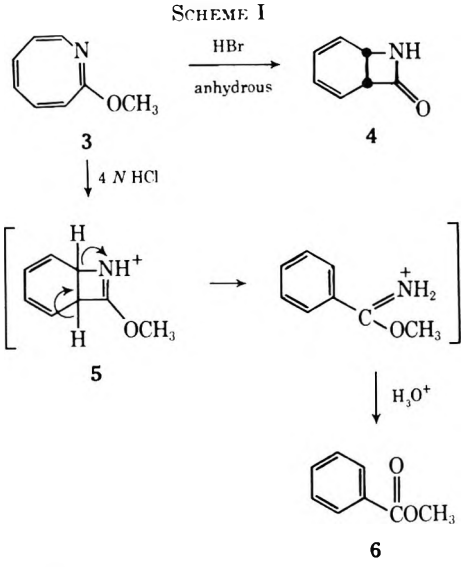
The German group was forced to conclude that the large variation in the proportions of the monocyclic and bicyclic forms of the 12 derivatives examined did not lend itself to ready theoretical interpretation at the present time.

A general synthesis of azocines (azacyclooctatetraenes) was devised recently in these laboratories.[7] Concurrently, an examination of the question of dynamic valence bond isomerization in nitrogen analogs of **1** and **2** was initiated. Because of the obvious structural relationship between the two series, knowledge of the behavior of 1-aza-2,4,6-cyclooctatriene derivatives was expected to provide valuable information on the influence of electronic, steric, and strain effects in medium ring compounds. The possibility of reconciling the behavior of cyclooctatrienes in such an indirect fashion also presented itself.

Synthetic Considerations.—Exposure of 2-methoxyazocine (**3**) to a dry solution of ethereal hydrogen bromide, followed by dissolution of the resulting salt in acetone at room temperature for 3 hr, gave 7-azabicyclo[4.2.0]octa-2,4-dien-8-one (**4**) in 17% yield. This lactam displayed an intense infrared carbonyl stretching vibration ($CHCl_3$) at 1765 cm^{-1} and exhibited ultraviolet absorption [$\lambda_{max}^{C_2H_5OH}$ 263 nm (ϵ 3220)] typical of 1,3-cyclohexadiene derivatives.[8] In contrast, aqueous hydrolysis of **3** with 4 *N* hydrochloric acid at room temperature for 20 min afforded methyl benzoate (**6**) in 47% yield. At the mechanistic level, the formation of

(8) The discussion of nmr spectra is deferred to the subsequent section of this paper.

SCHEME I

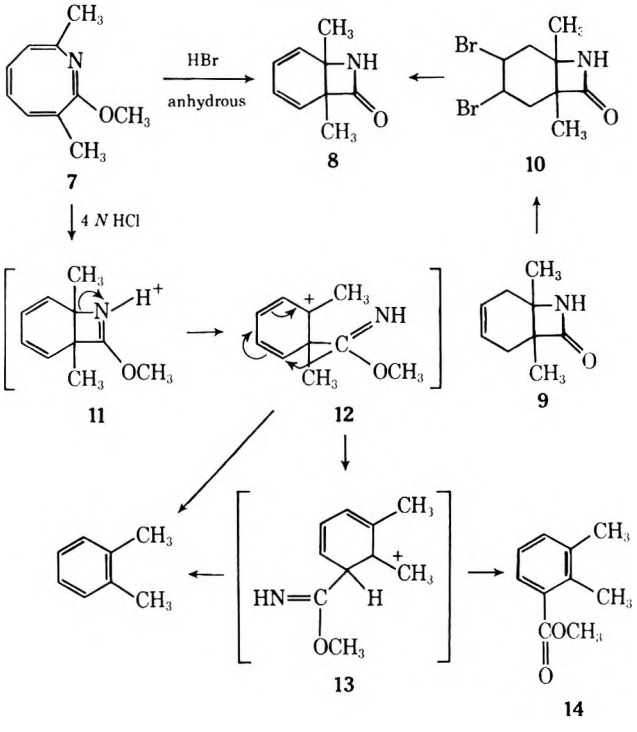


3 **4** **5** **6**

6 may be attributed to the aromatization of **5**, the bicyclic valence tautomer of protonated **3** (Scheme I).

1,6-Dimethyl-7-azabicyclo[4.2.0]octa-2,4-dien-8-one (**8**) was similarly prepared by treating 3,8-dimethyl-2-methoxyazocine (**7**) with anhydrous hydrogen bromide. Lactam **8** was also available from the bromination of **9**, followed by dehydrobromination with 1,5-diazabicyclo[4.3.0]non-5-ene in benzene. On the other hand, **7** was found to undergo hydrolysis in 4 *N* hydrochloric acid with the formation of *o*-xylene and methyl 2,3-dimethylbenzoate (**14**). The presumed pathway leading to **14** is shown in Scheme II. Since aromatization is not

SCHEME II



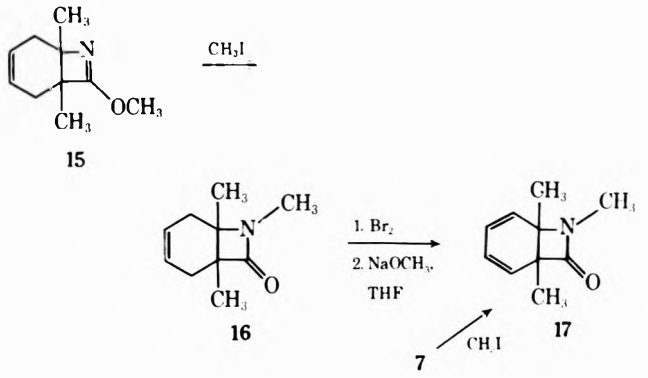
7 **8** **9** **10** **11** **12** **13** **14**

directly available to **11**, ionization to **12** apparently intervenes. At this point, the structure of the final product requires that imidate carbon migrate to an electron-deficient center with greater ease than a methyl group. However, this eventuality is not unexpected

in view of the established –COOR > $-CH_3$ reactivity order noted in certain related carbonium ion processes.[9,10] Finally, intermediate **13** may eject a proton to afford **14** or transform itself into *o*-xylene by loss of the functionalized side chain. The data do not, of course, rule out the possibility that *o*-xylene could result directly from cation **12**. β-Lactam **8** was characterized by an intense carbonyl band ($CHCl_3$) at 1750 cm^{-1} and an ultraviolet maximum (C_2H_5OH) at 261 nm (ε 3780).[8]

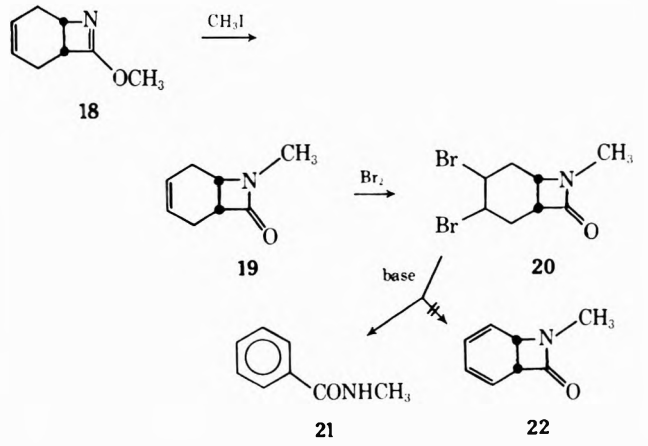
For comparison purposes, the *N*-methyl derivatives of **4** and **8** were sought. To this end, azetine **15** was allowed to react with methyl iodide at ambient temperature for 7 hr.[11] There was obtained by direct distillation a 93% yield of **16** (Scheme III). Bromination of **16** and dehydrohalogenation of the resultant dibromide with sodium methoxide in refluxing tetrahydrofuran gave **17** in 34% overall yield. In a less favorable reaction, heating of **7** in excess methyl iodide for 45 hr also afforded **17**, but only in low yield (12%).

SCHEME III



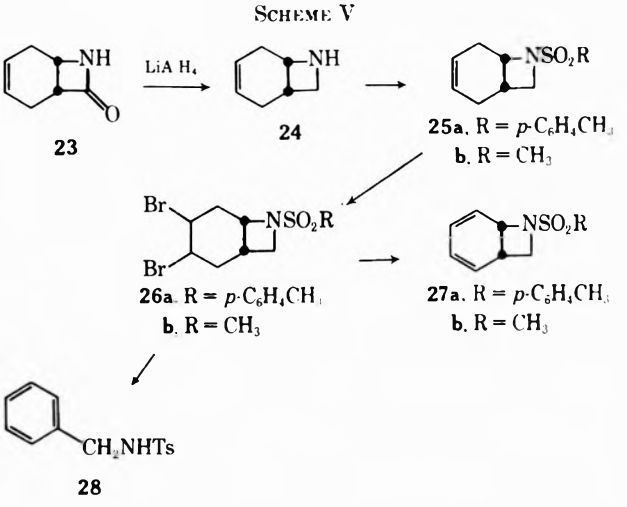
Similarly, azetine **18** was found to give rise to **19** when refluxed with methyl iodide for 9 hr. Although the bromination of **19** proceeded as expected, all attempts to dehydrohalogenate this intermediate (**20**) led only to *N*-methylbenzamide (**21**, Scheme IV). Attempts to transform **3** directly into **22** by reaction with methyl iodide were also to no avail.

SCHEME IV

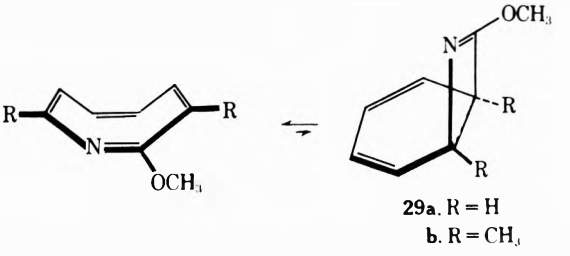


Reduction of **23** with lithium aluminum hydride furnished azetidine **24**, treatment of which with *p*-toluenesulfonyl and methanesulfonyl chlorides gave **25a** and **25b**, respectively, in quantitative yield. Bromination of these sulfonamides with an equivalent amount of bromine was readily achieved. However, as expected from earlier observations, the dehydrobromination of **26a** and **26b** required strictly controlled conditions to arrive at **27a** and **27b** (Scheme V). To illustrate, it soon became apparent that the action of excess potassium *tert*-butoxide on **26a** invariably led to **28**. In contrast, when 2 equiv of base was employed at 0°, **27a** could be isolated in 69% yield.

SCHEME V



Valence Tautomeric Considerations.[12]—Previously, **3** and **7** were shown to exhibit temperature invariant (−75 to 185°) nmr spectra which fail to provide any suggestion of the presence of bicyclic imino ethers of type **29**.[7] However, the presence in **3** and **7** of spectroscopically undetectable quantities of **29a** and **29b**, respectively, was apparent from the diene behavior of 2-methoxyazocines in Diels–Alder reactions and the ease with which **3** is converted to benzonitrile with strong base. A reliable estimate of the proportion of **29** in these equilibria is ≤2%. The high equilibrium concentrations of the monocyclic forms suggests that the strain generated in passing to the bicyclic 1-azetine derivatives (**29**) is sufficiently large to overcome the loss of stabilization derived from the noncontiguous overlap of π orbitals in **3** and **7** (due to the preferred tub conformation). These characteristics therefore parallel closely those of cyclooctatetraene in which the concentration of the bicyclic tautomer at 100° is only 0.01%.[5b,d]



29a, R = H
b, R = CH3

(9) H. Plieninger, L. Arnold, and W. Hoffmann, *Chem. Ber.*, **101**, 981 (1968).

(10) The virtually complete absence of methyl migration was evidenced by the fact that the isolated ester showed no contamination by methyl 2,6-dimethylbenzoate (vpc analysis).

(11) (a) L. A. Paquette and N. A. Nelson, *J. Org. Chem.*, **27**, 1085 (1962); (b) L. A. Paquette and G. Slomp, *J. Amer. Chem. Soc.*, **85**, 765 (1963).

(12) For a preliminary report of these results, see L. A. Paquette, T. Kakihana, J. F. Kelly, and J. R. Malpass, *Tetrahedron Lett.*, 1455 (1969).

In marked contrast, 1,2-dihydroazocin-2-one (**30a**) exists predominantly as bicyclic tautomer **4**. The percentage composition values for **30a** (and also **31a** and **31b**) were derived from the following equation

$$\% \text{ monocyclic} = \frac{\text{area of vinyl absorption} - 2(\text{area of bridgehead absorption})}{\text{total area}}$$

and the pertinent chemical shifts are collected in Table II. Variable temperature nmr studies gave evidence

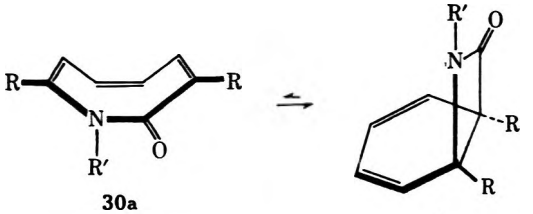
TABLE II

PERTINENT CHEMICAL SHIFT DATA FOR THE DIHYDROAZOCINES (δ UNITS)

Tautomeric pair	Vinyl protons	Bridgehead protons
4–30a	5.62–6.08	3.86–4.26
27a–31a	5.48–6.04	4.58–4.85, 2.75–3.15
27b–31b	5.62–6.20	4.98–5.27, 3.05–3.55

Tautomeric pair	>C—CH₃	>C—CH₃
8–30b	1.94 (broad)	1.39, 1.40 (sharp)
17–30c		1.24, 1.28 (sharp)

that the concentration levels of **30a** rise progressively with temperature. For example, in tetrachloroethylene solution the percentage of **30a** in the mixture varied in the following fashion: 60°, 2.4%; 85°, 3.5%; 100°, 8.4%; 115°, 15.3%.



30a
b
c

4
8
17

R = R′ = H
R = CH₃; R′ = H
R = R′ = CH₃

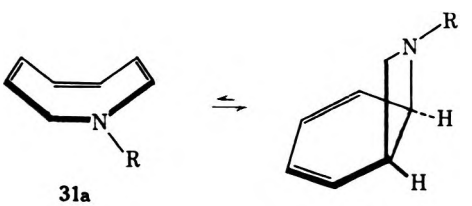
Lactam **30b** behaved analogously. For **30b** and **30c**, integration of the areas of the C-methyl absorptions was employed to establish the positions of equilibrium (see Table II). By comparison to **30a**, however, the percentage of monocyclic form was seen to be relatively greater and to vary somewhat less with temperature: 38°, 19.5%; 95°, 20.7% (CCl_2=CCl_2 solution). Also, the position of equilibrium did not appear to be affected significantly by changes in solvent (all measurements at 38°): benzene-d_6, 20.3%; acetone-d_6, 20.4%; acetic acid-d_4, 22.2%. It should be mentioned that throughout this entire study, the solutions were allowed to equilibrate for 4–5 hr prior to spectral examination. Additionally, the spectra were rerecorded after 1 week to guard against a situation where a particularly slow rate of valence isomerization was operative.

The effect of a methyl group on the lactam nitrogen of **30b** influences the positions of equilibrium to an amazing extent. Thus, the nmr spectrum of **30c** indicated the substance to be totally bicyclic (at least at the spectroscopic detection limit) over a substantial temperature range (38–120°). Above 120°, **17** decomposes rapidly to *o*-xylene and methyl isocyanate.[13] These data are to be contrasted with the valence tautomeric situation prevalent in cyclooctatrienone which is 93.4% monocyclic at 60°.[5d]

The presence of the amide function in **30** clearly has several consequences. First, the strain in the β-lactam portion of the valence tautomers is not so great as in a 1-azetine ring. Secondly, for electrostatic reasons the electropositive carbon of the carbonyl group can be expected to exercise a preference for bonding to sp^3- rather than sp^2-hybridized carbon (the former is less electronegative). These factors, in conjunction with the stabilization resulting from more effective π overlap in the planar diene tautomers (**4**, **8**, and **17**), can be anticipated to favor the bicyclic structures. The somewhat greater concentration of the monocyclic tautomer in **8** ⇆ **30b** can be attributed to the eclipsed methyl–methyl interactions in **8** which are relieved in passing to **30b**. In **17** ⇆ **30c**, this eclipsing interaction exists also, but relief of the newly generated steric interference between *N*-methyl and carbonyl oxygen is overriding. The bicyclic form is favored to a greater extent in this instance because the external bond angles in the four-membered ring are appreciably wider than those in the azocine tautomer, thereby substantially reducing this destabilizing interaction. Pronounced changes in the reactivity of medium-ring lactams have been reported to occur upon N-methylation, presumably because of analogous nonbonded interactions.[14]

It now becomes important to reconcile the differing behavior of cyclooctatrienone and the 1,2-dihydroazocinones. Dreiding models of **30** indicate that the amide linkage in the medium-sized ring is noticeably distorted from planarity. This out-of-plane twisting causes reduced resonance interaction between the nonbonded nitrogen electron pair and the carbonyl π bond. In the bicyclic tautomers, however, the planar conformation enforced on the β-lactam ring results in restoration of total delocalization and accordant stabilization. On the other hand, cyclooctatrienone enjoys no such prerogative and the strain associated with the cyclobutanone ring in the bicyclic form is the dominant destabilizing factor.

Sulfonamides **31a** and **31b** likewise give evidence of existing only as azabicyclooctadienes **27a** and **27b**. Because **27a** and **27b** are air sensitive and thermally labile



31a
b

27a
b

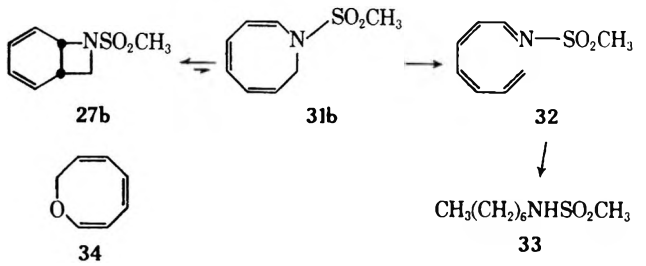
substances, temperatures in excess of 100° could not be employed. Under conditions such as refluxing toluene, for example, **27b** is transformed into unstable tetraene

(13) For a discussion of the stereochemical consequences of β-lactam thermolyses, see L. A. Paquette, M. J. Wyvratt, and G. R. Allen, Jr., *J. Amer. Chem. Soc.*, **92**, 1763 (1970). The relative ease of pyrolytic ring fission in this instance is attributable to the presence of aromatic character in the transition state (if a concerted process) or of enhanced free-radical stabilization (if stepwise).

(14) L. A. Paquette and L. D. Wise, *ibid.*, **87**, 1561 (1965).

32, presumably by thermal bond reorganization of **31b** with ring opening (Scheme VI). The imine was cata-

SCHEME VI

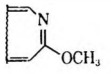
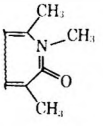
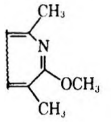
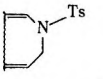
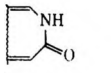
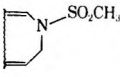
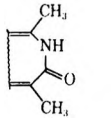


lytically hydrogenated to sulfonamide **33** which was identical with material prepared in unequivocal fashion from *n*-heptylamine. Demonstration of the feasibility of the electrocyclic reaction which is followed in the conversion of **27b** to **32**[15] may explain why oxocin (**34**) has proven to be a substance which has defied isolation and characterization to date.[16]

As with **17** ⇆ **30c**, the steric interference between the $>NSO_2-$ substituent and the methylene group appears to be significant in causing **27a** and **27b** to be energetically favored. Also, other factors such as the absence of significant strain in the azetidine ring and effective diene π-orbital overlap in **27** can be expected to stabilize the bicyclic form relative to **31**. The data compiled herein is summarized in Table III.

TABLE III

INFLUENCE OF SUBSTITUENTS ON VALENCE TAUTOMERIC EQUILIBRIA IN THE AZOCINE SERIES ($Cl_2C{=}CCl_2$ SOLUTIONS)[a]

Substituents	% bicyclic	Substituents	% bicyclic
	<2		>98
	<2		>98
	97.6[b]		>98
	80.5[c]		

[a] Accuracy level is ±2%. [b] At 60°. [c] At 38°.

The Electronic Nature of Azete and Attempted Synthesis of Certain Derivatives.—Preliminary Hückel MO calculations for azete (azacyclobutadiene, **35**) have

35

indicated that this heterocycle can be expected to possess a greater degree of delocalization energy than cyclobutadiene.[17] Also, as with azocine,[18] the degeneracy of the NBMO's has been removed by the inclusion of the nitrogen atom in the molecular π framework. As always, the largest problem in calculations of this sort for heteroatomic systems is the selection of appropriate parameters.[19] Although numerous values for nitrogen have been assigned, k_{CN} is usually taken as unity and h_N as 0.5 or unity. The illustrated theoretical

$$\alpha_N = \alpha_0 + h_N\beta_0 \qquad \beta_{CN} = k_{CN}$$

results (Tables IV and V) suggest that **35** may, in fact,

TABLE IV

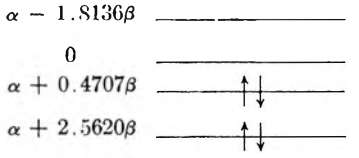
HÜCKEL MO TREATMENT OF **35**

h_N	k_{CN}	D.E. (β)[a]
1.0	1.0	0.391
0.5	1.0	0.224
0.1	1.0	0.049

[a] Delocalization energy for cyclobutadiene = 0.

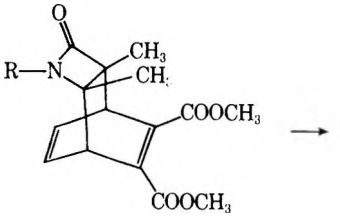
TABLE V

ORBITAL ENERGY DIAGRAM FOR **35**

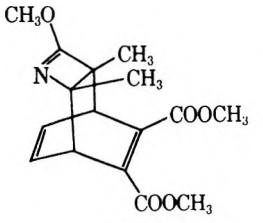


be endowed with modest stability. Also, in passing from the neutral molecule to the azete dianion, there should be a marked proclivity for the formation of the 6π electron "aromatic" structure.

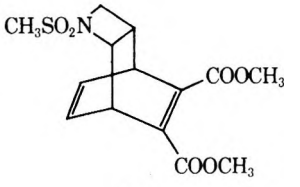
Accordingly, we investigated the retrograde Diels–Alder approach[20] to derivatives of azete. The condensation of **8** and **17** with dimethyl acetylenedicarboxylate proceeded readily to give **36a** and **36b**. O-Methylation of **36a** at the β-lactam functionality with



36a, R = H
b, R = CH_3



37



38

(15) Such an isomerization sequence may also be followed by the *N*-carbethoxy analog of **31b**: W. H. Okamura, *Tetrahedron Lett.*, 4714 (1969).

(16) R. W. Begland, unpublished results. For the preparation of a suitable precursor to **34**, see L. A. Paquette and R. W. Begland, *J. Org. Chem.*, **32**, 2723 (1967).

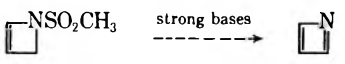
(17) For a recent MO treatment of cyclobutadiene, consult M. J. S. Dewar and G. J. Gleicher, *J. Amer. Chem. Soc.*, **87**, 3255 (1965).

(18) L. A. Paquette, J. F. Hansen, and T. Kakihana, *ibid.*, **93**, 168 (1971).

(19) A. Streitwieser, "Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1961, Chapter 5.

(20) H. Kwart and K. King, *Chem. Rev.*, **68**, 415 (1968).

trimethyloxonium fluoroborate served to provide **37**.[21] Under similar cycloaddition conditions, **27b** was transformed into **38**. The intent in this last example was to prepare **39** which in the presence of strong bases could conceivably be subject to elimination of methanesulfinic acid[22] and formation of **35**. However, all attempts to pyrolyze **36a**, **36b**, and **38** (200–325°, usually under



39 **35**

reduced pressure) led uniquely to dimethyl phthalate and tarry residues. In contrast, **37** was notably more stable and could be heated to 300° for long periods of time in an inert atmosphere with minimal decomposition. Higher temperatures did cause composition, but only small amounts of dimethyl phthalate could be detected.

Increasingly frequent reports of successful photochemically induced reverse Diels–Alder reactions[23] prompted an examination of this alternative. However, it soon became clear that unsaturated four-membered nitrogen-containing rings could not be isolated from a variety of such photolyses. Low yields of dimethyl phthalate were again encountered, but attempts to trap the proposed azete derivatives with such dienes as *trans*-piperylene and isoprene[23d] were unsuccessful.[24]

Experimental Section[25]

7-Azabicyclo[4.2.0]octa-2,4-dien-8-one (4).—To a stirred solution of 3.78 g of a mixture of 2-methoxyazocine (40%) and benzonitrile (60%)[7c] in 100 ml of petroleum ether (bp 30–60°) cooled to −78° was added dropwise a saturated ethereal solution of hydrogen bromide until the yellow azocine color faded. The colorless mushy precipitate was separated by decantation while still cold, washed with petroleum ether, and dissolved in 70 ml of acetone. The solution was stirred at room temperature for 3 hr during which time a color change from pale yellow to dark brown was noted. Evaporation of the solvent under reduced pressure gave a dark viscous oil. Column chromatography of this oil on Florisil (12 g) using ether as eluent gave 248 mg (17%) of a faintly yellow solid. Recrystallization from hexane afforded **4** as white crystals: mp 70–73°; $\nu_{max}^{CHCl_3}$ 3350, 1765, 1650, and 1580 cm^{-1}; $\lambda_{max}^{ethanol}$ 263 nm (ϵ 3220); $\delta_{TMS}^{CDCl_3}$ 6.82–7.41 (br s, 1, >NH), 5.51–6.10 (m, 4, vinyl), and 3.84–4.35 (m, 2, allylic).

Anal. Calcd for C_7H_7NO: C, 69.40; H, 5.83; N, 11.56. Found: C, 69.32; H, 5.88; N, 11.56.

Aqueous Acid Hydrolysis of 2-Methoxyazocine (3).—A solution of 328 mg (2.4 mmol) of **3** in 6 ml of 4 *N* hydrochloric acid was stirred at room temperature for *ca.* 20 min. The dark red solution was extracted with ether (three 30-ml portions) after initial dilution with water (50 ml). The combined organic layers were neutralized by washing with aqueous sodium bicarbonate, dried, and evaporated at 0° to yield an orange oil (171 mg). Molecular distillation (90°, 0.15 mm) afforded 154 mg (47%) of a colorless mobile liquid which was identical with authentic methyl benzoate (**6**) in all respects.

1,6-Dimethyl-7-azabicyclo[4.2.0]octa-2,4-dien-8-one (8). A. Hydrolysis of 7.—A 9.90-g (60 mmol) sample of **7**[7c] in 250 ml of pentane cooled to −78° was treated with ethereal hydrogen bromine as above, followed by 6 hr in acetone at 25°. After chromatography, there was obtained 3.26 g (37%) of **8** as white needles: mp 104–105° (from ethyl acetate–hexane); $\nu_{max}^{CHCl_3}$ 3370, 1750, 1630, and 1580 cm^{-1}; $\lambda_{max}^{ethano.}$ 261 nm (ϵ 3780); for discussion of nmr spectrum, see text.

Anal. Calcd for $C_9H_{11}NO$: C, 72.45; H, 7.55; N, 9.39. Found: C, 72.32; H, 7.55; N, 9.52.

B. Bromination–Dehydrobromination of 9.—To a stirred solution of 5.0 g (33 mmol) of **9**[7c] in 100 ml of methylene chloride cooled to −78° was added dropwise a solution of 5.8 g (36.3 mmol) of bromine in 10 ml of the same solvent during 15 min. The solution was allowed to warm during 30 min and evaporated under reduced pressure. Recrystallization of the product from ethyl acetate gave 4.91 g (47%) of **10** as colorless crystals: mp 149–149.5°; $\nu_{max}^{CHCl_3}$ 3400 and 1760 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 6.56–6.88 (br s, 1, >NH), 4.42–4.77 (m, 2, >CHBr), 2.00–2.82 (m, 4, methylene), 1.39 and 1.27 (s, 3 each, methyl groups).

Anal. Calcd for $C_9H_{13}Br_2NO$: C, 34.75; H, 4.21; N, 4.50. Found: C, 34.75; H, 4.21; N, 4.43.

A solution of 4.03 g (13 mmol) of **10** and 4.85 g (39 mmol) of 1,5-diazabicyclo[4.3.0]non-5-ene in 30 ml of anhydrous benzene was heated at 72° with stirring for 4.5 hr. After cooling, the supernatant liquid was poured into 100 ml of water, and the mixture was extracted with ether (two 100-ml portions). The ethereal solution was washed with 2 *N* sulfuric acid (two 30-ml portions) and 20% aqueous potassium carbonate (one 50-ml portion), dried, and filtered. Recrystallization of the resulting semisolid from ethyl acetate gave 380 mg (20%) of **8**, mp 148–149°.

Aqueous Acid Hydrolysis of 7.—A solution of 1.0 g of **7** in 6 ml of 4 *N* hydrochloric acid was refluxed with stirring for 30 min. The cooled reaction mixture was poured into an ice-cold aqueous solution containing 1 equiv of sodium hydroxide. Extraction with ether (two 50-ml portions) and normal processing yielded 651 mg of a pale yellow oil, vpc analysis of which indicated the composition to be 28% *o*-xylene and 72% methyl 2,3-dimethylbenzoate (**14**). Comparison of samples isolated by preparative vpc to authentic materials confirmed the structural assignments.

1,6,7-Trimethyl-7-azabicyclo[4.2.0]oct-3-en-8-one (16).—A mixture of 3.29 g (20 mmol) of **15**[7c] and 14.20 g (0.10 mol) of methyl iodide was stirred at room temperature for 7 hr. Evaporation of the excess methyl iodide, followed by distillation under reduced pressure afforded 3.06 g (93%) of **16** as a colorless oil, bp 62–63° (0.2 mm). The analytical sample was prepared by crystallization and recrystallization from cold hexane, followed by molecular distillation: $\nu_{max}^{CCl_4}$ 1750 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 5.45–6.03 (m, 2, vinyl), 2.56 (s, 3, >NCH$_3$), 1.45–2.68 (m, 4, allyl), 1.28 and 1.19 (s, 3 each, methyls).

Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.88; H, 9.16; N, 8.80.

1,6,7-Trimethyl-7-azabicyclo[4.2.0]octa-2,4-dien-8-one (17). A. Methylation of 7.—A mixture of 3.50 g (21.4 mmol) of **7** and 7.6 g (54 mmol) of methyl iodide was refluxed for 45 hr. The excess methyl iodide was evaporated and the residue was chromatographed on neutral alumina (40 g, Baker, activity I). Elution with ether led to the recovery of 362 mg (10.4%) of **7**, whereas elution with 10% methanol–ether gave a viscous brown semisolid. Recrystallization of this material from hexane gave 367 mg (11.5%) of **17**: mp 81–82.5°; $\nu_{max}^{CCl_4}$ 1750 and 1585 cm^{-1}; $\lambda_{max}^{ethanol}$ 262 nm (ϵ 3440); for discussion of nmr spectrum, see text.

Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.21; H, 7.89; N, 8.46.

B. Bromination–Dehydrobromination of 16.—A 2.31-g (14 mmol) sample of **16** was brominated (3.36 g, 21 mmol) in the usual way in methylene chloride (30 ml) at −78°. A solution of the crude dibromide in 50 ml of anhydrous tetrahydrofuran was added during 10 min to a stirred, refluxing suspension of sodium methoxide (from 7.13 g of sodium) in 200 ml of the same solvent. Heating was continued for 4 hr, the solids were removed by filtration, and the dark filtrate was reduced to one-fifth its volume and diluted with 150 ml of water. Extraction of the product with ether, followed by the customary work-up afforded 4.37 g (34%) of **17**, mp 81–82.5°, after recrystallization from hexane.

7-Methyl-7-azabicyclo[4.2.0]oct-3-en-8-one (19).—A mixture of 1.85 g (13.4 mmol) of **18**[7c] and 9.60 g (67.5 mmol) of methyl iodide was refluxed for 9 hr. Evaporation of the excess methyl iodide and distillation of the residue gave 1.56 g (85%) of **19** as a colorless mobile liquid, bp 63° (0.20 mm). The analytical sample was obtained by preparative scale vpc followed by molecular distillation: $\nu_{max}^{CCl_4}$ 1760 cm^{-1}; $\delta_{TMS}^{CCl_4}$ 5.27–5.82 (m, 2, vinyl), 3.35–

(21) Not unexpectedly, attempts to condense 2-methoxyazocines with dimethyl acetylenedicarboxylate gave rise to ill-defined polymeric substances, presumably as a result of initial nucleophilic attack at the triple bond by the nitrogen atom.

(22) For examples of analogous elimination reactions of sulfonamides, consult (a) W. Paterson and G. R. Proctor, *J. Chem. Soc.*, 485 (1965); (b) E. Negishi and A. R. Day, *J. Org. Chem.*, **30**, 43 (1965).

(23) (a) B. B. Roquitte, *J. Amer. Chem. Soc.*, **90**, 415 (1968); (b) R. K. Murray, Jr., and H. Hart, *Tetrahedron Lett.*, 4995 (1968); (c) H. Nozaki, H. Kato, and R. Noyori, *Tetrahedron*, **25**, 1661 (1969); (d) R. D. Miller and E. Hedaya, *J. Amer. Chem. Soc.*, **91**, 5401 (1969).

(24) S. F. Nelsen and J. P. Gillespie, *Tetrahedron Lett.*, 5059 (1969).

(25) All melting points were taken in open capillaries and are corrected, while boiling points are uncorrected.

3.52 (m, 1, >CHN<), 2.93–3.29 (m, 1, >CHCO–), 2.56 (s, 3, >NCH_3), and 1.70–2.42 (m, 4, allyl).

Anal. Calcd for $C_8H_{11}NO$: C, 70.04; H, 8.08. Found: C, 70.25; H, 8.37.

3,4-Dibromo-7-methyl-7-azabicyclo[4.2.0]octan-8-one (20).—A 2.52-g (18.4 mmol) sample of **19** in 30 ml of methylene chloride was brominated with a solution of 3.22 g (20.2 mmol) of bromine in 10 ml of the same solvent at −78°. There was obtained 3.82 g (70%) of **20** as white crystals: mp 110–117° (from ethyl acetate); $\nu_{max}^{CHCl_3}$ 1750 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 4.31–4.69 (m, 2, >CHBr), 3.59–3.98 (m, 1, >CHN<), 3.16–3.55 (m, 1, >CHCO–), 2.82 (s, 3, >NCH_3), and 2.24–2.90 (m, 4, methylene).

Anal. Calcd for $C_8H_{11}Br_2NO$: C, 32.35; H, 3.73; N, 4.72. Found: C, 32.98; H, 3.92; N, 4.45.

Attempted Dehydrobromination of 20.—A solution of 2.97 g (10 mmol) of crude **20** in 10 ml of anhydrous tetrahydrofuran was added dropwise during 30 min to a stirred suspension of sodium methoxide (prepared from 570 mg of sodium metal) in 50 ml of the same solvent. After stirring at room temperature for 5 hr, the dark solution was filtered, concentrated *in vacuo* to one-fifth its volume, and diluted with 50 ml of water. The aqueous mixture was extracted with ether (two 60-ml portion), and the combined organic layers were dried, filtered, and evaporated to give a solid residue admixed with an oil. This mixture was filtered and the solid washed with a minimum amount of cold ether to afford 690 mg (51%) of *N*-methylbenzamide, mp 80–81° (from ether). The mother liquor gave upon molecular distillation 487 mg (36%) of methyl benzoate, which presumably arose from the action of acid on the 2-methoxyazoeine contaminant.

7-Azabicyclo[4.2.0]oct-3-ene (24).—A solution of 61.5 g (0.5 mol) of 7-azabicyclo[4.2.0]oct-3-en-8-one (**23**)[7c] in 200 ml of anhydrous tetrahydrofuran was added during 30 min to a stirred slurry of 16 g (0.4 mol) of lithium aluminum hydride in 300 ml of the same solvent. The mixture was stirred for 3 hr at reflux and then cooled to 0° in an ice bath. Water (16 ml) was slowly added, followed by 16 ml of 30% sodium hydroxide solution, and 30 ml of water. Anhydrous magnesium sulfate (25 g) was added to the resulting mixture and this was filtered. The solvent was evaporated and the residue was distilled to give 19.5 g (38%) of **24**: bp 53° (3.5 mm); ν_{max}^{neat} 3410 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 5.95–6.20 (m, 2, vinyl), 4.00–4.35 (m, 1, bridgehead, >CHN<), 3.50–3.85 (m, 1, one $-CH_2N<$), 2.65–3.25 (m, 2, other $-CH_2N<$ and >NH), and 1.90–2.25 (m, 5, bridgehead and allyl).

Anal. Calcd for $C_7H_{11}N$: C, 77.01; H, 10.16. Found: C, 76.98; H, 10.17.

***N*-Tosyl-7-azabicyclo[4.2.0]oct-3-ene (25a).**—To a well-stirred, cold mixture of 5.5 g (0.05 mol) of **24** and 25 ml of 30% aqueous sodium hydroxide was added 12 g (0.065 mol) of *p*-toluenesulfonyl chloride in small portions over a 10-min period. The mixture was stirred at 0° for another 15 min and extracted, and the residue was recrystallized from hexane to give 13.2 g (100%) of **25a**: mp 100–101°; ν_{max}^{KBr} 1333 and 1170 cm^{-1}.

Anal. Calcd for $C_{14}H_{17}NO_2S$: C, 63.90; H, 6.61; N, 5.24. Found: C, 63.86; H, 6.51; N, 5.32.

3,4-Dibromo-7-tosyl-7-azabicyclo[4.2.0]octane (26a).—Treatment of 13.2 g (0.05 mol) of **25a** with 8.0 g (0.05 mol) of bromine in the predescribed fashion furnished 17.5 g (82.9%) of **26a**: mp 143–154° (from tetrahydrofuran–hexane); ν_{max}^{KBr} 1333 and 1165 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 7.20–7.80 (m, 4, aryl), 4.25–4.80 (m, 2, >CHBr), 3.15–4.15 (m, 3, >CHN<), 2.10–3.00 (m, 7, other ring protons), and 2.46 (s, 3, methyl).

Anal. Calcd for $C_{14}H_{17}Br_2NO_2S$: C, 39.60; H, 4.04; N, 3.26. Found: C, 39.73; H, 4.03; N, 3.31.

Dehydrobromination of 26a. A. With Excess Base.—To a cold (0°) stirred solution of 1.05 g (2.50 mmol) of **26a** in 10 ml of dry tetrahydrofuran was slowly added a suspension of 1.12 g (0.01 mol) of potassium *tert*-butoxide in 10 ml of the same solvent. The resulting mixture was stirred for 1 hr at 0°, evaporated *in vacuo*, and extracted with ether (two 25-ml portions). Evaporation of the ether and recrystallization of the residue from ether–hexane afforded 450 mg (69%) of *N*-tosylbenzylamine, mp 115°. This substance was identical with an authentic sample prepared from benzylamine and tosyl chloride.

B. With an Equivalent of Base.—Treatment of 4.23 g (0.01 mol) of **26a** with 2.20 g (0.0195 mol) of potassium *tert*-butoxide in analogous fashion at 0° gave 1.6 g (62%) of **27a**, mp 89–91°. The product was isolated by evaporation of the tetrahydrofuran *in vacuo*, extraction of the residue with ether, filtration through Celite, and evaporation, followed by extraction with boiling petroleum ether (30–60°), and cooling of the extracts to −20°. Principal infrared bands were seen at 1610, 1342, 1165, and 1148 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 7.35–8.05 (m, 4, aryl), 5.60–6.35 (m, 4, vinyl), 4.65–4.95 (m, 1, bridgehead, >CHN<), 3.85–4.35 (m, 2, $-CH_2-N<$), 2.75–3.30 (m, 1, methine), and 2.50 (s, 3, methyl).

This substance decomposed somewhat rapidly and satisfactory elemental analyses could not be obtained. Therefore its *N*-phenylmaleimide adduct was prepared (ether solvent, 12 hr, 25°) in 91% yield, mp 281–282° (from acetone).

Anal. Calcd for $C_{24}H_{22}N_2O_4S$: C, 66.34; H, 5.10; N, 6.45. Found: C, 66.38; H, 5.15; N, 6.41.

***N*-Methanesulfonyl-7-azabicyclo[4.2.0]oct-3-ene (25b).**—From 5.5 g (0.05 mol) of **24** and 7.0 g (0.062 mol) of methanesulfonyl chloride, there was obtained a quantitative yield of **25b**: mp 89–90° (from hexane); ν_{max}^{KBr} 1318, 1160, and 1135 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 5.95–6.20 (m, 2, vinyl), 4.45–4.80 (m, 1, bridgehead, >CHN<), 3.74 (m, 2, $-CH_2N<$), 2.85–3.10 (m, 1, methine), 2.86 (s, 3, methyl), and 1.90–2.50 (m, 4, allyl).

Anal. Calcd for $C_8H_{13}NO_2S$: C, 51.31; H, 7.00; N, 7.48. Found: C, 51.34; H, 7.16; N, 7.49.

3,4-Dibromo-7-mesyl-7-azabicyclo[4.2.0]octane (26b).—Bromination of **25b** (3.75 g, 0.02 mol) in the customary fashion afforded 4.6 g (66.3%) of **26b**: mp 109–126° (from ether–hexane); ν_{max}^{KBr} 1350, 1155, and 1147 cm^{-1}.

Anal. Calcd for $C_8H_{13}Br_2NO_2S$: C, 27.68; H, 3.78; N, 4.04. Found: C, 27.91; H, 3.91; N, 3.90.

7-Mesyl-7-azabicyclo[4.2.0]octa-2,4-diene (27b).—To a solution of 1.80 g (5.2 mmol) of **26b** in 40 ml of dry tetrahydrofuran was added dropwise at 0° a suspension of 1.10 g (9.9 mmol) of potassium *tert*-butoxide in 30 ml of the same solvent. The mixture was stirred for 30 min upon completion of the addition and the solvent was then evaporated. Work-up in the predescribed fashion afforded 0.70 g (70%) of **27b**: mp 59–60° (from pentane); ν_{max}^{KBr} 1332, 1315, and 1135 cm^{-1}; $\lambda_{max}^{CH_3OH}$ 265 nm (ε 2800); $\delta_{TMS}^{CDCl_3}$ 5.60–6.30 (m, 4, vinyl), 5.00–5.30 (m, 1, bridgehead, >CHN<), 4.20 (m, 2, $-CH_2N<$), 3.10–3.55 (m, 1, methine), and 2.90 (s, 3, methyl).

Because of the ease of decomposition of this substance, satisfactory combustion data could not be obtained. Therefore, its *N*-phenylmaleimide adduct was prepared (ether solvent, 24 hr, 25°) in 99% yield, mp 251–252° (from acetone).

Anal. Calcd for $C_{18}H_{18}N_2O_4S$: C, 60.32; H, 5.06; N, 7.82. Found: C, 60.23; H, 5.15; N, 7.58. Found: C, 60.23; H, 5.06; N, 7.82.

Thermal Rearrangement of 27b.—A solution of 100 mg of **27b** in 20 ml of toluene was refluxed under nitrogen for 2 hr. The crude product was distilled *in vacuo* to give a small quantity of **32**: ν_{max}^{neat} 1342, 1320, and 1160 cm^{-1}; $\lambda_{max}^{CH_3OH}$ 264 nm (ε 3160), 273 (3860), and 289 (3860); $\delta_{TMS}^{C_2Cl_4}$ 6.40–6.60 (br d, J = 7 Hz, $-CH{=}N-$), 4.90–6.10 (m, 7, vinyl), and 2.83 (s, 3, methyl).

A second pyrolysis sample (70 mg) was immediately hydrogenated over Adams catalyst at 50 psig in ethanol solution. The catalyst was separated by filtration, the solvent evaporated, and the residue recrystallized several times from methanol to give 20 mg (26.7%) of *N*-mesylheptylamine, mp 55–56°, which was identical with an authentic sample prepared from the reaction of *n*-heptylamine and methanesulfonyl chloride: $\delta_{TMS}^{CDCl_3}$ 2.75–3.30 (m, 2, $-CH_2N<$), 2.96 (s, 3, $-SO_2CH_3$), 1.00–1.80 (m, 10, methylene), and 0.89 (t, J = 7 Hz, 3, methyl).

Anal. Calcd for $C_8H_{19}NO_2S$: C, 49.71; H, 9.91; N, 7.25. Found: C, 49.66; H, 9.93; N, 7.15.

Diels–Alder Reactions with Dimethyl Acetylenedicarboxylate.—A solution of 326 mg (2.18 mmol) of **8** and 342 mg (2.4 mmol) of dimethyl acetylenedicarboxylate in 6 ml of benzene was heated at reflux for 6 hr. Removal of the solvent under reduced pressure gave a viscous yellow oil, crystallization of which from ethyl acetate afforded 433 mg (67%) of **36a**: mp 140–141°; $\nu_{max}^{CHCl_3}$ 3490, 1775, 1740, 1655, and 1615 cm^{-1}; $\delta_{TMS}^{CHCl_3}$ 6.22–6.64 (m, 3, vinyl and NH), 3.63–4.03 (m, 2, bridgehead), 3.79, 1.37, and 1.28 (s, 6, 3, and 3, methyls).

Anal. Calcd for $C_{15}H_{17}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.28; H, 5.05; N, 5.24.

From 2.48 g (1.5 mmol) of **17** and 2.14 g (1.5 mmol) of dimethyl acetylenedicarboxylate in 30 ml of benzene (10 hr reflux), there was obtained 3.78 g (82%) of **36b** as colorless crystals: mp 132–133° (from ethyl acetate); $\nu_{max}^{CHCl_3}$ 1745, 1725, 1645, and 1610 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 6.24–6.71 (m, 2, vinyl), 3.59–4.08 (m, 2, bridgehead), 3.82, 2.59, 1.32, and 1.26 (s, 6, 3, 3, and 3, methyls).

Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 63.11; H, 6.25; N, 4.72.

From 100 mg (0.54 mmol) of **27b** and 70 mg (0.50 mmol) of dimethyl acetylenedicarboxylate in 10 ml of ether (48 hr, 25°), there was obtained 130 mg (76.4%) of **38**: mp 116–117° (from ether); ν_{max}^{KBr} 1755, 1718, 1310, 1160, and 1138 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 6.40–6.70 (m, 2, vinyl), 4.00–4.45 (m, 2, bridgehead), 3.60–3.85 (m, 1, >CHN<), 3.75 (s, 6, carboxylate methyls), 3.00–3.25 (m, 2, $-CH_2N<$), 2.81 (s, 3, CH_3SO_2-), and 2.50–2.90 (m, 1, methine).

Anal. Calcd for $C_{14}H_{17}NO_6S$: C, 51.37; H, 5.23. Found: C, 51.57; H, 5.40.

O-Methylation of 36a.—A mixture of 6.49 g (24 mmol) of **36a** and 3.5 g (2.8 mmol) of trimethyloxonium fluoroborate in 60 ml of dry methylene chloride was stirred at 0° for 10 hr. Aqueous sodium carbonate solution was carefully added until the solution became neutral. The organic layer was separated, washed with water, dried, and evaporated to give a viscous oil. This oil was dissolved in 50 ml of anhydrous ether and ethanolic perchloric acid (1:1) was added dropwise with cooling until the supernatant liquid showed no cloudiness. Filtration of the crystals, followed by thorough rinsing with ether and drying, afforded 7.86 g (86%) of **37** perchlorate, mp 162–164.5° (from methanol). Liberation of the free base from the purified perchlorate furnished **37** as a colorless crystalline solid: mp 85–87° (from ether–pentane); $\nu_{max}^{CCl_4}$ 1745, 1725, 1635, 1623, and 1603 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 6.54–6.73 (m, 2, vinyl), 3.99 (s, 9, $-OCH_3$), 3.90–4.25 (m, 2, bridgehead), 1.61 and 1.49 (s, 3 and 3, methyls).

Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.95; H, 6.27; N, 4.59. Found: C, 63.22; H, 6.27; N, 4.52.

Registry No.—**4**, 27070-39-9; **8**, 24321-92-4; **10**, 27062-83-5; **16**, 27062-84-6; **17**, 27062-85-7; **19**, 27062-86-8; **20**, 27062-87-9; **24**, 27062-88-0; **25a**, 27062-89-1; **25b**, 27062-90-4; **26a**, 27062-91-5; **26b**, 27062-92-6; **27a**, 27062-93-7; **27a** *N*-phenylmaleimide adduct, 27062-94-8; **27b**, 27062-95-9; **27b** *N*-phenylmaleimide adduct, 27062-96-0; **36a**, 27111-68-8; **36b**, 27062-43-7; **37**, 27062-44-8; **37** perchlorate, 27062-45-9; **38**, 27062-46-0.

Acknowledgment.—The authors are grateful to the National Institutes of Health and the Lilly Research Laboratories for grants which contributed to the financial support of this research.

Neighboring-Group Participation by Sulfonamide Nitrogen. The 7-Azabicyclo[4.2.0]oct-3-ene to 6-Azabicyclo[3.2.1]oct-2-ene Rearrangement[1]

LEO A. PAQUETTE* AND JOHN F. KELLY

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

Received July 30, 1970

The addition of bromine to *N*-sulfonyl derivatives of 1,6-dimethyl-7-azabicyclo[4.2.0]oct-3-ene (**3**) resulted in skeletal rearrangement and formation of *N*-sulfonyl-1,2-dimethyl-4-bromo-6-azabicyclo[3.2.1]oct-2-enes (30–37%). The structures (including exo stereochemistry for the bromo substituent) were assigned on the basis of their 100-MHz nmr spectra, their ready dehydrohalogenation to conjugated dienes, and the chemical behavior of these dienes. The rearrangements probably proceed by way of intramolecular Sn2 displacement of trans-disposed bromine by neighboring sulfonamide nitrogen. Furthermore, a significant portion of **3** undergoes rupture of the azetidine ring with ultimate formation of dibromide **5** and the derived sulfonamide. A possible mechanism is presented.

Despite the extensive amount of research which has been accorded to skeletal rearrangements of carbobicyclic structures, similar transformations of related nitrogen heterocycles are notably few in number at the present time. The first reported example appears to be the racemization of L-(+)-2-α-tropanol,[2] which proceeds with participation of an amino nitrogen. At a later date, the isoquinuclidine system was shown to be particularly prone to conversion into derivatives of azabicyclo[3.2.1]octane, even when neighboring-group participation by amide nitrogen is required.[3] More recently, skeletal rearrangement of bicylic nitrenium ions has been demonstrated to be a general reaction type.[4] In the course of work directed at the synthesis of polyolefinic medium-ring nitrogen compounds,[1] we observed an unprecedented and unusual example of sulfonamide nitrogen migration with skeletal reorganization. In this paper we describe the details of several such transformations together with a number of affiliated chemical changes.

Results

cis-1,6-Dimethyl-7-azabicyclo[4.2.0]oct-3-ene (**2**) was prepared by treating previously described β-lactam **1**[5] with lithium aluminum hydride. Reaction of **2** with *p*-toluenesulfonyl, benzenesulfonyl, and methanesulfonyl chlorides readily afforded **3a**, **3b**, and **3c**, respectively. After addition of bromine to **3a** at 0°, the product was refluxed in hexane for 30 min. Direct crystallization of the reaction mixture led to the isolation of **4b** in 37% yield; chromatographic purification of the residual material on silica gel afforded 4,5-dibromo-4,5-dimethyl-1-cyclohexene (**5**, 17%), *p*-toluenesulfonamide (**6**, 29%), and a dibromosulfonamide identified as **7** (12%). *N*-Sulfonylazetidines **3b** and **3c** have similarly been found to undergo ready conversion to **4b** and **4c**. The structures of **4a–4c** follow from analyses, infrared and ultraviolet, and particularly nmr spectra. Spin-decoupling studies of **4b** at 100 MHz, for example, showed that vinyl proton H_c is coupled vicinally to H_d (J = 4.4 Hz), allylically to the low field methyl absorp-

(1) Unsaturated Heterocyclic Systems. LXXVIII. For the previous paper in this series, see L. A. Paquette, T. Kakihana, and J. F. Kelly, *J. Org. Chem.*, **36**, 435 (1971).

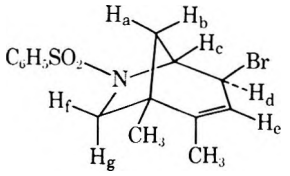
(2) S. Archer, T. R. Lewis, M. R. Bell, and J. W. Schulenberg, *J. Amer. Chem. Soc.*, **83**, 2386 (1961).

(3) (a) G. Büchi, D. L. Coffen, K. Kocsis, P. E. Sonnet, and F. E. Ziegler, *ibid.*, **88**, 3099 (1966); (b) J. W. Huffman, T. Tamiya, and C. B. S. Rao, *J. Org. Chem.*, **32**, 700 (1967), and pertinent references cited in these papers; (c) J. D. Hobson and W. D. Riddell, *Chem. Commun.*, 1178 (1968).

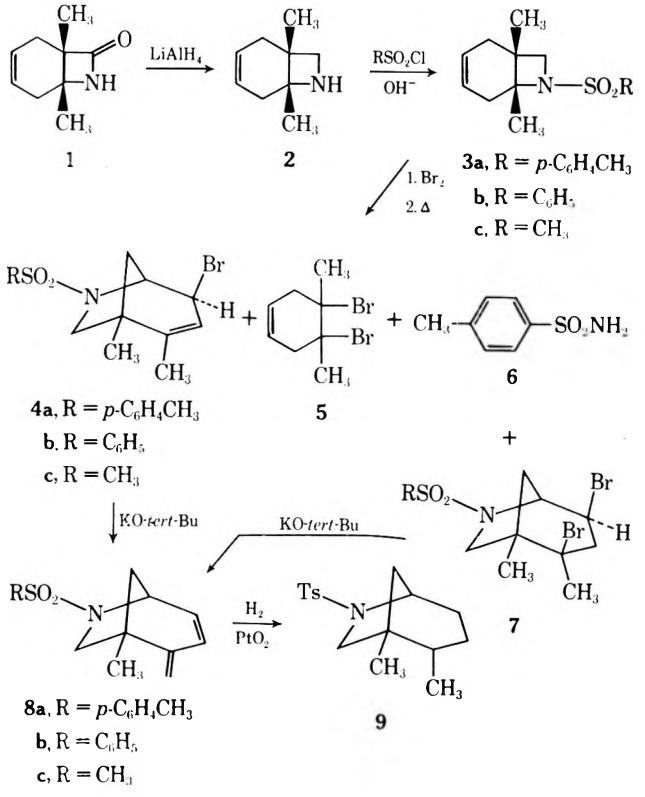
(4) P. G. Gassman, *Accounts Chem. Res.*, **3**, 26 (1970).

(5) L. A. Paquette, T. Kakihana, J. F. Hansen, and J. C. Philips, *J. Amer. Chem. Soc.*, **93**, 152 (1971); L. A. Paquette and T. Kakihana, *ibid.*, **90**, 3897 (1968).

tion (J = 1.3 Hz), and long range to H_c (J = 1.5 Hz) because of their W-plan arrangement. The expected

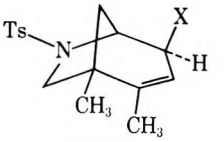


magnetic nonequivalence of the two sets of methylene protons was clearly in evidence, there being the predictable $J_{a,b}$ = 11.3 Hz and $J_{f,g}$ = 8.4 Hz. Furthermore, the differing long-range interactions of the individual methylene bridge protons ($J_{b,g}$ = 1.5 Hz, $J_{a,d} \approx$ 0.5 Hz) clearly attests to the determinative influence exerted by the rigid molecular skeleton in enforcing two



somewhat unequivalent W-plan atomic arrangements. In a result that stems from differing dihedral angle relationships,[6] H_c is strongly coupled to H_a ($J_{a,c}$ = 5.5 Hz), but very weakly spin related to H_b ($J_{b,c} < 0.5$ Hz). The stereochemistry at C_4, the halogen-bearing center, was established as exo on the basis of the previously mentioned long-range spin interaction of H_d with H_a and the magnitude of its coupling constants with H_e (4.4 Hz) and H_c (1.5 Hz).[7]

The most direct proof of structure for **4a–4c** is based on their dehydrohalogenation in the presence of potassium *tert*-butoxide which proceeds smoothly to give the conjugated dienes **8a–c**, respectively. Ultraviolet absorption bands of these sulfonamides at 235–239 nm (ϵ 10,000–12,000) indicate the introduction of extended conjugation,[8] whereas the presence of two singlets in the δ 4.9 region are diagnostic for the presence of a terminal methylene group.[7a] Catalytic reduction of **8a** over Adams' catalyst proceeded rapidly with the uptake of 2 mol of hydrogen to give **9**. The conjugated nature of the diene moiety in **8a** was additionally evident in its capability to react with various reagents by way of 1,4 addition. For example, dissolution of **8a** in aqueous hydrobromic acid at room temperature regenerated **4a**, whereas exposure to aqueous hydrochloric acid and methanol afforded **10a** and **10b**, respectively. The

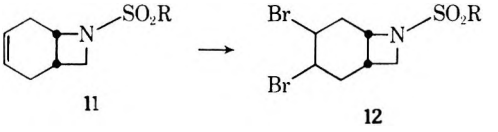


10a, X = Cl
b, X = OCH_3

exo stereochemistry of the functional groups newly introduced in these reactions follows from the nmr spectra of the products, the previously established configuration of **4**, and the recognized preference of bicyclo[3.2.1]oct-2-enes to give rise to products of exo attack at the allylic site.[9]

Discussion

The rearrangement of **3** to **4** represents a unique situation involving a 1,4 shift of sulfonamide nitrogen. The fact that this rearrangement does not occur in the related structures (**11** → **12**) lacking the two methyl substituents (which brominate normally and are thermally stable[1]) indicates that considerable cationic character develops at the carbon center to which the nitrogen substituent is originally attached; *i.e.*, the developing tertiary carbonium ion in **3** renders the process energetically feasible.



11 **12**

With this in mind, it is now possible to view the rearrangement as involving ionization of the C–N bond to place a negative charge on nitrogen, thereby endowing it with significant nucleophilic character. At this stage, two possibilities exist: the sulfonamide functionality could intramolecularly displace a trans-disposed bromine at C_4 (*cf.* **13**) to give **15**; or, the Sn2 displacement could occur at C_3 in **16** to give **4**. However, no products corresponding to **15** are observed. Although this may signify that **3** is brominated exclusively to afford trans dibromide **16**, this conclusion is not totally unequivocal since a significant portion of **3** is diverted to an alterna-

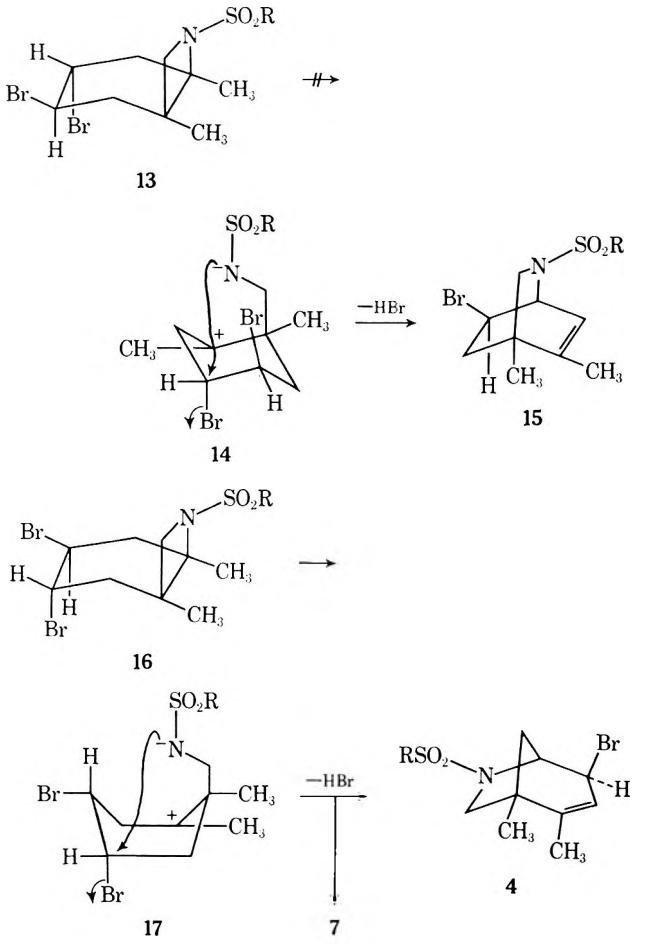
(6) M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2870 (1963); *J. Chem. Phys.*, **30**, 11 (1959).

(7) We wish to draw attention to the striking parallel between the vicinal, allylic, and long-range couplings experienced by **4a–4c** and related interactions in the bicyclo[3.2.1]oct-2-ene system: C. W. Jefford, J. Gunsher, and K. C. Ramey, *J. Amer. Chem. Soc.*, **87**, 4384 (1965), and earlier references cited therein.

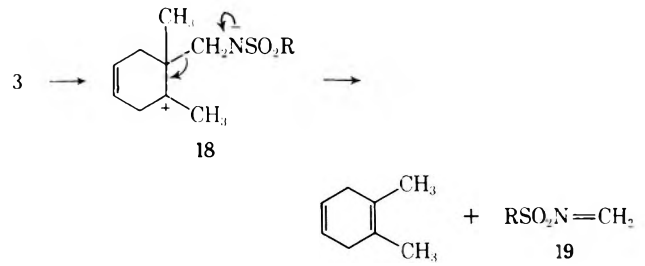
(8) Compare the ultraviolet spectrum of 3-bromo-4-methylenebicyclo[3.2.1]oct-2-ene: $\lambda_{max}^{cyclohexane}$ 242 nm (ϵ 20,000) [ref 7a and C. W. Jefford and W. Wojnarowski, *Tetrahedron Lett.*, 199 (1968)].

(9) C. W. Jefford and E. H. Yen, *ibid.*, 4477 (1966).

tive fragmentation pathway leading to the formation of dibromide **5** and *p*-toluenesulfonamide (**6**).



The genesis of **5** and **6** would appear to be founded also in the lability of the more highly substituted C–N bond in **3** under the conditions of bromination. This concomitant reaction could involve initial heterolytic fragmentation of **3** to give **18**, followed by ejection of **19** and production of 1,2-dimethyl-1,4-cyclohexadiene.



Hydrolysis of **19** during the work-up would rationalize the isolation of **6** and related sulfonamides, whereas selective bromination of the diene (also established independently) would give **5**. The remarkable observation that rupture of the C–N bond in **3** is facilitated in the presence of molecular bromine merits further consideration.

Experimental Section[10]

1,6-Dimethyl-7-azabicyclo[4.2.0]oct-3-ene (2).—To a stirred suspension of 12.0 g (0.32 mol) of lithium aluminum hydride in 300 ml of anhydrous tetrahydrofuran was added dropwise a solution of 50 g (0.32 mol) of **1**[5] in 150 ml of the same solvent. The resulting mixture was stirred at reflux for 30 hr, cooled in ice, and treated sequentially with 12 ml of water, 12 ml of 30% sodium hydroxide solution, 25 ml of water, and finally 10 g of anhydrous magnesium sulfate. The solids were separated by filtration, the filtrate was evaporated, and the residue was distilled to give 28 g (62%) of **2**: bp 57° (2 mm); ν_{max}^{neat} 3205 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 6.10–6.25 (m, 2, vinyl), 3.20 (s, 2, $-CH_2-N<$), 1.85–2.10 (m, 4, allyl), 1.45–1.75 (m, 1, >NH), 1.29 and 1.20 (s, 3 each, methyls).

Anal. Calcd for $C_9H_{15}N$: C, 78.77; H, 11.02. Found: C, 78.78; H, 11.26.

From the residue of the distillation, 5.5 g (11%) of β-lactam **1** was recovered.

***N*-*p*-Toluenesulfonyl-1,6-dimethyl-7-azabicyclo[4.2.0]oct-3-ene (3a).**—To a vigorously stirred mixture of 13.7 g (0.10 mol) of **2** and 100 ml of 30% aqueous sodium hydroxide solution cooled in an ice bath was added 23 g (0.12 mol) of tosyl chloride in small portions during 10 min. The mixture was stirred for 30 min at room temperature and extracted with ether (four 50-ml portions). The combined ether extracts were dried, filtered, and evaporated to give 29 g (100%) of **3a**: mp 69–70°; ν_{max}^{KBr} 1340, 1330, and 1160 cm^{-1}.

Anal. Calcd for $C_{16}H_{21}NO_2S$: C, 65.94; H, 7.26; N, 4.82. Found: C, 65.92; H, 7.29; N, 4.82.

***N*-Benzenesulfonyl-1,6-dimethyl-7-azabicyclo[4.2.0]oct-3-ene (3b)** was obtained analogously in quantitative yield, mp 86–87°.

Anal. Calcd for $C_{15}H_{19}NO_2S$: C, 64.96; H, 6.91; N, 5.05. Found: C, 64.83; H, 6.99; N, 5.07.

***N*-Methanesulfonyl-1,6-dimethyl-7-azabicyclo[4.2.0]oct-3-ene (3c).**—From 3.0 g (0.022 mol) of **2** and 4.0 g (0.026 mol) of methanesulfonyl chloride, there was obtained 4.1 g (82%) of **3c**, mp 60–61°.

Anal. Calcd for $C_{10}H_{17}NO_2S$: C, 55.78; H, 7.96; N, 6.51. Found: C, 55.78; H, 7.95; N, 6.41.

Reaction of 3a with Bromine.—To an ice-cold stirred solution of 2.91 g (0.01 mol) of **3a** in 15 ml of methylene chloride was added dropwise 1.6 g (0.01 mol) of bromine. The solvent was evaporated and the residue was refluxed with 50 ml of hexane for 30 min. The residue was then extracted with additional boiling hexane (five 20-ml portions), and the combined hydrocarbon extracts were permitted to stand at −20° for 3 days. The precipitated solid was removed by filtration and recrystallized from hexane to give 1.25 g (36.8%) of **4a**: mp 152–154°; ν_{max}^{KBr} 1335 and 1155 cm^{-1}; $\lambda_{max}^{isooctane}$ 230 nm (ε 11,800);[11] $\delta_{TMS}^{CDCl_3}$ 7.25–7.85 (AB pattern, 4, aryl), 5.40–5.60 (m, 1, vinyl), 4.65–4.90 (m, 1, >CH-Br), 4.15–4.40 (m, 1, >CH–N<), 3.05 (AB pattern, J_{AB} = 9 Hz, $\Delta\nu_{AB}$ = 27 Hz, B portion exhibits fine splitting, J = 1.5 Hz, $-CH_2N<$), 2.45 (s, 3, aryl methyl), 2.08 (dd, J = 1.3 and 12 Hz, 1, bridge methylene proton), 1.73 (t, J = 1.2 Hz, 3, allylic methyl), 1.31 (dd, J = 6 and 12 Hz, 1, other bridge proton), and 1.11 (s, 3, saturated methyl).

Anal. Calcd for $C_{16}H_{20}BrNO_2S$: C, 51.89; H, 5.44; N, 3.78. Found: C, 51.92; H, 5.50; N, 3.69.

The filtrate from above was concentrated and chromatographed on silica gel. Elution with hexane gave 0.30 g (17%) of 4,5-dibromo-4,5-dimethylcyclohex-1-ene (**5**), mp 140–141°, which was identical in all respects with the monobromination product of 1,2-dimethyl-1,4-cyclohexadiene:[12] $\delta_{TMS}^{CDCl_3}$ 5.72 (m, 2, vinyl), 2.80–2.97 (m, 4, allyl), and 2.00 (s, 6, methyls).

Elution with hexane–ether (4:1) afforded 550 mg (12.2%) of **7**: mp 149–150°; ν_{max}^{KBr} 1335 and 1150 cm^{-1} (SO_2); $\delta_{TMS}^{CDCl_3}$ 7.20–7.85 (AB pattern, 4, aryl), 4.00–4.50 (m, 2, >CHBr and >CHN<), 3.48 (d, J = 11 Hz, 1), 2.90 (d, J = 11 Hz, 2), 2.59 (d, J = 4 Hz, 2), 2.41, 1.71, and 1.14 (singlets, 3 each, methyls), and 1.0–1.30 (m, 1).

Anal. Calcd for $C_{16}H_{21}Br_2NO_2S$: C, 42.59; H, 4.80; N, 3.17. Found: C, 42.74; H, 4.76; N, 3.02.

Elution with ether–hexane (3:2) led to the isolation of 0.50 g (29.2%) of *p*-toluenesulfonamide (**6**), mp 137°, identical with an authentic sample prepared from tosyl chloride and ammonia.

Reaction of 3b with Bromine.—Treatment of 20.0 g (0.072 mol) of **3b** with 11.6 g (0.072 mol) of bromine in the predescribed manner afforded 7.95 g (31%) of **4b**: mp 149–151°; ν_{max}^{KBr}

(10) Melting points were taken in open capillaries and are corrected, while boiling points are uncorrected.

(11) For the ultraviolet spectrum of *p*-toluenesulfonamide hydrate in ethanol, consult L. Lang, Ed., "Absorption Spectra in the Ultraviolet and Visible Region," Vol. 2, Academic Press, New York, N. Y., 1961, Spectrum No. 117.

(12) L. A. Paquette and J. H. Barrett, *Org. Syn.*, **49**, 62 (1969).

1375, 1190, and 1180 cm^{-1}; $\lambda_{max}^{isooctane}$ 223 nm (ϵ 11,400), $\delta_{TMS}^{CDCl_3}$ 7.40–8.00 (m, 5, aryl), 5.40–5.55 (m, 1, vinyl), 4.65–4.85 (m, 1, >CHBr), 4.15–4.40 (m, 1, H_c), 3.04 (AB pattern, J_{AB} = 8.4 Hz, $\Delta\nu_{AB}$ = 27 Hz, B portion exhibits fine splitting, J = 1.5 Hz, 2, $-CH_2N<$), 2.08 (dd, J = 11.3 and 1.5 Hz, H_b), 1.73 (t, J = 1.3 Hz, 3, allylic methyl), 1.28 (dd with fine splitting, J = 11.3 and 5.5 Hz, H_a), and 1.11 (s, 3, methyl).

Anal. Calcd for $C_{15}H_{18}BrNO_2S$: C, 50.57; H, 5.09; N, 3.93; Br, 22.43. Found: C, 50.44; H, 5.15; N, 3.92; Br, 22.82.

Chromatography of the residue afforded products analogous to those obtained with **3a**.

Reaction of 3c with Bromine.—Treatment of 1.15 g (5.0 mmol) of **3c** with 0.8 g (5.0 mmol) of bromine as described above gave 0.50 g (32.5%) of **4c**: mp 130–132°; ν_{max}^{KBr} 1320, 1170, 1150, and 1143 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 5.45–5.65 (m, 1, vinyl), 4.65–4.85 (m, 1, >CHBr), 4.20–4.45 (m, 1, >CHN<), 2.90–3.30 (m, 2, $-CH_2N<$), 2.90 (s, 3, $-SO_2CH_3$), 2.15–2.50 (m, 1, bridge methylene proton), 1.20–1.70 (m, 1, other bridge proton), 2.80 (t, J = 1.3 Hz, 3, allylic methyl), and 1.29 (s, 3, methyl).

Anal. Calcd for $C_{10}H_{16}BrNO_2S$: C, 40.82; H, 5.48; N, 4.76. Found: C, 40.77; H, 5.44; N, 4.60.

Chromatography of the residue afforded products analogous to those obtained with **3a**.

Dehydrohalogenation of 4a.—To an ice-cold stirred solution of 1.1 g (2.7 mmol) of **4a** in 15 ml of dry tetrahydrofuran was added a suspension of 560 mg (5.0 mmol) of potassium *tert*-butoxide in 15 ml of the same solvent. The mixture was stirred at 0° for 15 min and the solvent was evaporated *in vacuo*. The residue was extracted with boiling ether (two 25-ml portions) and the combined extracts were filtered and evaporated. Recrystallization of the residue from hexane gave 650 mg (92.2%) of **8a**: mp 109–111°; ν_{max}^{KBr} 1335 and 1165 cm^{-1}; $\lambda_{max}^{ethanol}$ 235 nm (ϵ 12,000); $\delta_{TMS}^{CDCl_3}$ 7.20–7.90 (AB pattern, 4, aryl), 6.00–6.20 (m, 2, ring vinyls), 4.82 and 4.92 (s, 1 each, exo methylenes), 4.30–4.65 (m, 1, bridgehead), 3.22 (s, 2, $-CH_2N<$), 2.45 (s, 3, aryl methyl), 1.45–1.85 (m, 2, bridge methylenes), and 1.30 (s, 2, methyl).

Anal. Calcd for $C_{16}H_{19}NO_2S$: C, 66.40; H, 6.59; N, 4.84. Found: C, 65.96; H, 6.62; N, 4.75.

Dehydrohalogenation of 4b.—From 1.75 g (4.0 mmol) of **4b**, there was obtained 1.05 g (94.4%) of **8b**: mp 83–84°; ν_{max}^{KBr} 1335 and 1165 cm^{-1}; $\lambda_{max}^{isooctane}$ 233 nm (ϵ 12,800); $\delta_{TMS}^{CDCl_3}$ 7.40–8.00 (m, 5, aryl), 5.95–6.15 (m, 2, ring vinyls), 4.82 and 4.92 (s, 1 each, exo methylenes), 4.30–4.55 (m, 1, bridgehead), 3.22 (s, 2, $-CH_2N<$), 1.45–1.85 (m, 2, bridge methylenes), and 1.28 (s, 3, methyl).

Anal. Calcd for $C_{15}H_{17}NO_2S$: C, 65.43; H, 6.22; N, 5.08. Found: C, 65.30; H, 6.29; N, 5.06.

Dehydrohalogenation of 4c.—From 930 mg (3.3 mmol) of **4c**, there was obtained 110 mg (16%) of crude **8c**, mp 53–57°. This compound could not be purified because of decomposition and apparent polymerization: ν_{max}^{KBr} 1330 and 1152 cm^{-1}; $\lambda_{max}^{isooctane}$ 239 nm (ϵ 9780); $\delta_{TMS}^{CDCl_3}$ 6.18 (m, 2, ring vinyls), 4.90 and 4.97 (s, 1 each, exo methylenes), 4.15–4.55 (m, 1, bridgehead), 3.21 (AB pattern, J_{AB} = 11 Hz, $\Delta\nu_{AB}$ = 9 Hz, 2, $-CH_2N<$), 2.77 (s, 3, $-SO_2CH_3$), 1.65–2.10 (m, 2, bridge methylenes), and 1.38 (s, 3, methyl).

***N*-*p*-Toluenesulfonyl-1,2-dimethyl-6-azabicyclo[3.2.1]octane (9).**—A solution of 0.50 g of **8a** in 50 ml of ethanol was hydrogenated over 10% palladium on charcoal at 50 psig in a Parr apparatus. The usual processing gave 0.48 g (96%) of **9**: mp 115–116°; ν_{max}^{KBr} 1340, 1172, and 1163 cm^{-1}.

Anal. Calcd for $C_{16}H_{23}NO_2S$: C, 65.51; H, 7.90; N, 4.78. Found: C, 65.50; H, 7.90; N, 4.78.

Hydrobromination of 8a.—A mixture of 580 mg (2.0 mmol) of **8a** and 20 ml of 4 *N* hydrobromic acid was stirred at room temperature for 1 hr and then extracted with ether (three 25-ml portions). The combined extracts were dried, filtered, and evaporated to give 546 mg (74%) of **4a**, mp 152–154°, after recrystallization from hexane.

Hydrochlorination of 8a.—A mixture of 580 mg (2.0 mmol) of **8a** and 20 ml of 4 *N* hydrochloric acid was stirred at room temperature for 1 hr and then worked up as above to give 450 mg (71%) of **10a**: mp 118–119°; ν_{max}^{KBr} 1350, 1332, 1175, 1160, and 1150 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 7.25–7.85 (AB pattern, 4, aryl), 5.30–5.50 (m, 1, vinyl), 4.40–4.70 (m, 1, >CHCl), 4.05–4.30 (m, 1, >CHN<), 3.00 (AB pattern, J_{AB} = 8.5 Hz, $\Delta\nu_{AB}$ = 27 Hz, $-CH_2N<$), 2.42 (s, 3, aryl methyl), 2.04 (d with fine structure, J = 11 Hz, 1, bridge methylene proton), 1.74 (t, $J \approx$ 1 Hz, 3, allylic methyl), 1.20 (m, 1, other bridge proton), and 1.11 (s, 3, methyl).

Anal. Calcd for $C_{16}H_{20}ClNO_2S$: C, 58.97; H, 6.19; N, 4.30. Found: C, 58.77; H, 6.28; N, 4.24.

4-Methoxy-1,2-dimethyl-6-tosyl-6-azabicyclo[3.2.1]oct-2-ene (10b).—A solution of 290 mg (1.0 mmol) of **8a** in 15 ml of methanol was refluxed for 1 hr.[13] The solvent was evaporated and the residue was recrystallized from hexane to afford 240 mg (74.6%) of **10b**: mp 153–154°; ν_{max}^{KBr} 1337, 1178, and 1163 cm^{-1}; $\delta_{max}^{CDCl_3}$ 7.25–7.90 (AB pattern, 4, aryl), 5.30–5.65 (m, 1, vinyl), 4.00–4.35 (m, 1, >CHN<), 3.65–3.85 (m, 1, >CHO–), 3.44 (s, 3, $-OCH_3$), 2.97 (AB pattern, J_{AB} = 7.5 Hz, $\Delta\nu_{AB}$ = 29 Hz, with B coupled to anti bridge proton, J = 1 Hz, 2, $-CH_2N<$), 2.45 (s, 3, aryl methyl), 1.75 (t, J = 1.5 Hz, allylic methyl), *ca.* 1.83 (m partially masked by methyl absorption, 1, bridge methylene), 1.10 (s, 3, methyl), and *ca.* 1.05 (m, 1, other bridge methylene).

Anal. Calcd for $C_{17}H_{23}NO_3S$: C, 63.52; H, 7.21; N, 4.36. Found: C, 63.17; H, 7.22; N, 4.19.

Dehydrohalogenation of 7.—To a solution of 65 mg (0.14 mmol) of **7** in 5 ml of anhydrous tetrahydrofuran was added 47 mg (0.42 mmol) of powdered potassium *tert*-butoxide. After stirring at room temperature for 10 min, the solvent was evaporated and the residue was extracted with ether. The ether extract was filtered and evaporated, and the residue was recrystallized once from hexane to give 42 mg (78.5%) of **8a**, mp 108–110°.

Registry No.—**2**, 27070-26-4; **3a**, 27070-27-5; **3b**, 27070-28-6; **3c**, 27070-29-7; **4a**, 27111-67-7; **4b**, 27070-30-0; **4c**, 27070-31-1; **7**, 27070-32-2; **8a**, 27070-33-3; **8b**, 27070-34-4; **8c**, 27070-35-5; **9**, 27070-36-6; **10a**, 27070-37-7; **10b**, 27070-38-8.

Acknowledgment.—Appreciation is expressed to the National Institutes of Health for their generous support of this research.

(13) This reaction is presumably catalyzed by traces of acid present in this solution.

Tetrazolo–Azido Isomerization in Heteroaromatics. I. Syntheses and Reactivities of Some Tetrazolopolyazines[1]

TADASHI SASAKI,* KEN KANEMATSU, AND MASAYOSHI MURATA

Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University, Nagoya, 464, Japan

Received May 18, 1970

The tetrazolo–azido transformation for eight model compounds (**3**, **4a–c**, **5–8**) are discussed. The tetrazolo–azido equilibrium in **3a,b** is much influenced by the solvent, but the pyridazine derivatives (**4a–c**) exist entirely as the tetrazoles in various solvents. Compounds **5** and **6** are demonstrated to exist exclusively as the azido form in the solid state because of the destabilization of the fused rings by electron-attracting tetrazolo and triazolo moieties. The tetrazolo–azido equilibrium in *as*-triazine derivatives **7** and **8** is observed in chloroform, but the tetrazolo form is predominant. Photochemical and thermal reactions of **3** give the imidazoles.

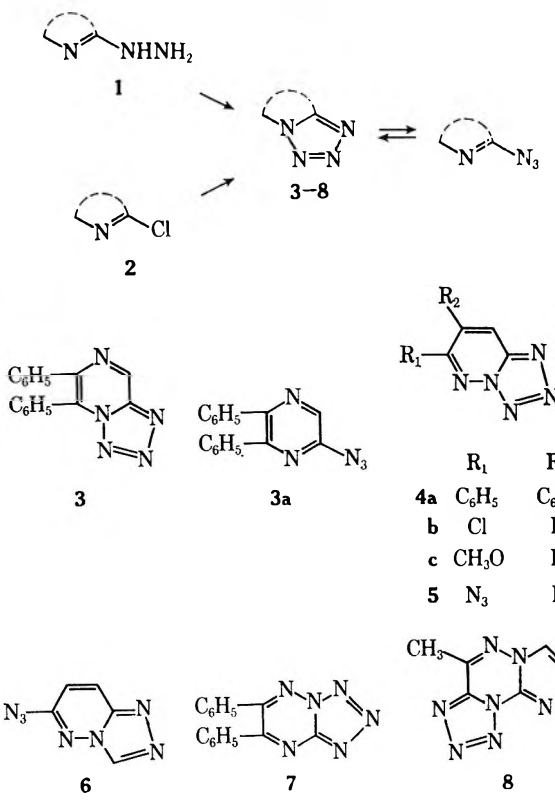
The chemistry of heteroaromatic nitrenes has received little attention[2] compared to that of arylnitrenes generated from aromatic azides[3] and aromatic nitro compounds,[4] although several heterocycles bearing an azido group adjacent to the annular nitrogen have been investigated with regard to cyclization to a fused tetrazolo ring in order to establish their structures.[5]

In continuation of our recent studies on the syntheses of bicyclo heteroaromatics such as benzo-1,2,4-triazines, polyazaindolidines, and pyrazolopyridines,[6] this paper presents spectral evidence for tetrazolo–azido isomerizations in some bicyclic tetrazolopolyazines and chemical properties of these systems.

Results and Discussion

Syntheses and Spectral Studies of Tetrazolopolyazines.—The compounds (**3–8**) were synthesized from the corresponding hydrazino compound (**1**) with sodium nitrite and/or the corresponding halogeno compounds (**2**) with sodium azide as shown in Scheme I.

SCHEME I



Marked differences in the ir are observed between the solid state and dimethyl sulfoxide solution, and other solutions; azido absorptions in the solid state and DMSO solution are shown by strong bands at 2160 and 2144 cm^{-1} for **5** and **6**, respectively, but are absent for **3**, **4a–c**, **7**, and **8**. In chloroform, tetrahydrofuran, and trifluoroacetic acid solutions, **3**, **5**, and **6** show the strong azido bands at 2145, 2160, and 2144 cm^{-1}, but **7** and **8** indicate only the weak bands at 2160 and 2170 cm^{-1}, respectively. These data are summarized in Table I.

The nmr spectrum of **3** discloses the presence of the tetrazolo–azidoazomethine equilibrium (10:3 ratio) in chloroform solution which is indicated by two singlet signals at τ 0.29 and 1.77. However, in DMSO-d_6, exclusively the tetrazolo tautomer was present as shown by a singlet at τ 0.04; in trifluoroacetic acid only the azido tautomer was present (τ 1.72). These spectral results are in good accordance with observations in 2-azidopyrimidines.[7]

Since the ir spectra of **4b** and **4c** show no azido absorptions in chloroform, the signals at τ 2.26 and 1.44 for **4b**, and those at τ 2.74 and 1.68 for **4c**, were attributable to the ring protons at C_5 and C_6 of the tetrazolopyridazines. On the other hand, **5** and **6** retain the corresponding azido structures **5a** and **6a** but not tricyclic structures such as **5a** and **6a**, probably because of the destabilization of the fused rings by electron-attracting tetrazolo and triazolo groups, on the basis of the spectral data described above (Scheme II). It is to be noted that the isomerization of 6-azido-7-methyltetrazolo[1,5-*b*]pyridazine to 6-azido-8-methyltetrazolo-[1,5-*b*]pyridazine is demonstrated by means of the nmr spectrum,[8] and the existence of the monocyclic 3-azidopyridazine 1-oxide is explained by the influence with the electron-attracting *N*-oxide group.[9]

The tetrazolo:azido ratios at the equilibrium for **3**, **4b–c**, **5**, and **6** in the various solvents determined by

(1) Part XLIX. Studies on Heteroaromaticity. For part XLVIII see T. Sasaki, K. Kanematsu, and K. Hayakawa, *J. Chem. Soc. C*, in press.

(2) For recent reviews, see (a) W. D. Crow and C. Wentrup, *Chem. Commun.*, 1387 (1969); (b) R. Huisgen and K. von Fraunberg, *Tetrahedron Lett.*, 2595, 2599 (1969), and references cited therin.

(3) W. von E. Doering and R. A. Odum, *Tetrahedron*, **22**, 81 (1966).

(4) R. J. Sundberg, B. P. Das, and R. H. Smith Jr., *J. Amer. Chem. Soc.*, **91**, 658 (1969); R. J. Sundberg and S. R. Suter, *J. Org. Chem.*, **35**, 827 (1970).

(5) For recent brief reviews, see (a) G. L'abbé, *Chem. Rev.*, **69**, 345 (1969); (b) B. Stanovnik and M. Tišler, *Tetrahedron*, **25**, 3313 (1969), and references cited therin.

(6) (a) T. Sasaki, K. Kanematsu, Y. Yukimoto, and S. Ochiai, submitted to *J. Org. Chem.*; (b) T. Sasaki and M. Murata, *Chem. Ber.*, **102**, 3818 (1969).

(7) C. Temple and J. A. Montgomery, *J. Org. Chem.*, **30**, 286 (1965).

(8) Calculation for the temperature dependence of the equilibrium constants in the isomerization of the 7-methyl to the 8-methyl compound gives the values $\Delta H = -5.9$ kcal/mol (at 89 and 94°), and $E_a = 20.5$ kcal/mol; see ref 5b.

(9) T. Itai and S. Kamiya, *Chem. Pharm. Bull. (Tokyo)*, **11**, 348 (1963).

TABLE I

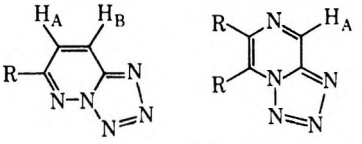
IR SPECTRA OF TETRAZOLOPOLYAZINES

	Absorption bands,[a] cm⁻¹							
	3	4a	4b	4c	5	6	7	8
KBr ν_{N_3}					2160	2144		
KBr $\nu_{C=N}$	1530	1610	1615	1612	1609	1605	1580	1627
$CHCl_3$ ν_{N_3}	2145 (s)				2160 (s)	2144 (s)		
							2160 (w)	2170 (w)
THF ν_{N_3}	2150 (s)				2160 (s)	2144 (s)	2160 (w)	2170 (w)
DMSO ν_{N_3}					2160 (s)	2144 (s)		
CF_3COOH ν_{N_3}	2148 (s)				2160 (s)	2144 (s)	2160 (w)	2170 (w)

[a] s = strong, w = weak.

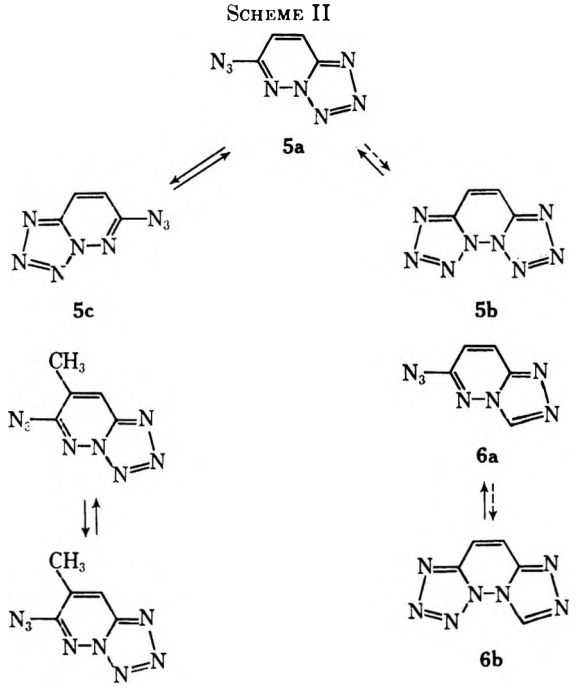
TABLE II

RATIOS OF THE TETRAZOLO–AZIDO EQUILIBRIUM COMPOUNDS IN VARIOUS SOLVENTS BY NMR



Compd no.	Solvent	Concn, w/v %	Azido:tetrazolo ratios	Chemical shifts, τ			
				H_A	$H_{A'}$	H_B	J_{AB}, Hz
3	$CDCl_3$	7	3:10	0.29	1.77		
	DMSO-d_6	8	0:10	0.04			
	CF_3COOH	7	10:0		1.72		
4b	$CDCl_3$	7	0:10	2.26		1.44	9.0
	DMSO-d_6	8	0:10	1.93		1.03	9.0
	CF_3COOH	8	0:10	1.93		1.16	9.0
	CD_3OD	7	0:10	2.11		1.36	9.0
4c	$CDCl_3$	8	0:10	2.74		1.68	9.2
	DMSO-d_6	9	0:10	2.45		1.30	9.2
	CF_3COOH	7	0:10	2.30		1.36	9.2
	CD_3OD	8	0:10	2.61		1.73	9.2
5	$CDCl_3$	10	0:10	2.68		1.49	9.5
6	$CDCl_3$	10	0:10	3.20		1.85	9.5

SCHEME II



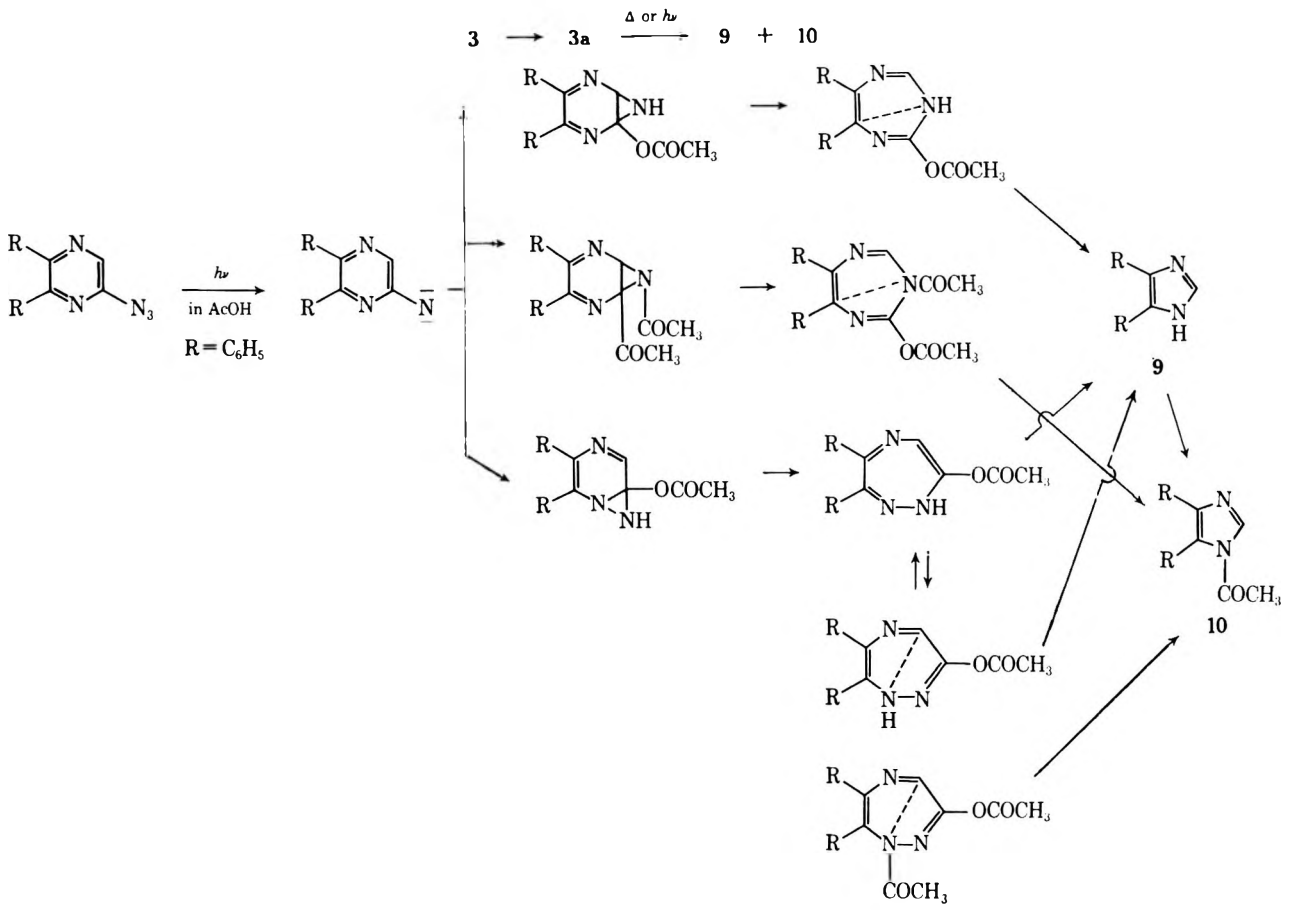
nmr are listed in Table II. In summary, electron-withdrawing substituents appear to be effective not only in destabilizing the electron-attracting tetrazolo ring, but also in stabilizing the electron-donating azido group. In addition to these factors, the stabilization of the tetrazolo and/or the azido form is influenced by the solvent effects.

Chemical Reactivities of Tetrazolopolyazines.—The existence of the reactive tautomeric azido forms in tetrazolopyridine, -pyrimidine, -triazine, and -benzothiazole by the reactions of enamines have been disclosed,[10] and recently Huisgen, *et al.*,[2] reported on the thermal decomposition and the cycloaddition reactions of 5,7-dimethyltetrazolo[1,5-*a*]pyrimidine and tetrazolo[1,5-*a*]pyridine

Reflux of 7,8-diphenyltetrazolo[1,5-*a*]pyrazine (**3**) in acetic acid for 11 hr afforded two products, **9** (56%) and **10** (13%). Similar treatment of **3** in acetic anhydride containing 14% acetic acid gave also **9** and **10** in 24 and 36% yields, respectively. In contrast to the thermolysis, the photochemical reaction of **3** in acetic acid using a 300-W high-pressure mercury lamp for 32 hr afforded **9** in only 10% yield together with 7% yield of benzoic acid and considerable amounts of recovered **3**. Compound **10**, which was also obtained by the treatment of **9** with acetic anhydride and sodium acetate, shows an ir absorption at 1735 cm^{-1} due to an acetyl group, and the nmr spectrum shows signals at τ 7.74 (3 H, s, $COCH_3$), 2.54, 2.62 (10 H, broad s, $2C_6H_5$), and 1.72 (1 H, s, olefinic proton). On the other hand, **9** shows signals at τ 2.62, 2.82 (10 H, each broad singlet, $2C_6H_5$), and 2.28 (1, H, s, olefinic proton). From this spectral

(10) R. Fusco, S. Rossi, and S. Maiorana, *Tetrahedron Lett.*, 1965 (1965), and references cited therein.

SCHEME III



and chemical evidence, compounds **9** and **10** were assigned as 4,5-diphenylimidazole and 1-acetyl-4,5-diphenylimidazole, respectively (Scheme III).

The mechanisms for the formation of 4,5-diphenylimidazole (**9**) could be explained by suggesting a nitrene intermediate, which may give rise probably to two kinds of bicyclic intermediates by addition of an acetoxyl group followed by the valence bond isomerization to the triazepine isomers to the imidazole, because of the thermal instability of the bicyclic ring.

By contrast, the mechanisms for the conversions of the pyrazine *N*-oxide to imidazoles have been proposed to proceed *via* the oxazirane intermediate,[11] while, in the case of 2,3-dihydropyrazines, the reaction proceeds *via* the irreversibly formed endiimine intermediate.[12]

Attempts to effect the thermal and photochemical isomerization of the tetrazolopyridazines, **4b** and **4c**, and the tetrazolo-*as*-triazines, **7** and **8**, in acetic acid were unsuccessful even under more drastic conditions, probably because of the absence or low concentration of the azido tautomer even at higher temperatures.

Treatment of **3** with dimethyl acetylenedicarboxylate in chloroform afforded a cycloadduct in 15% yield at 62°. The product was characterized as a triazole derivative **12** by the nmr and ir [1740, 1717 cm^{-1} ($COOCH_3$)]. The analogous reaction of **5** gave **13** in 40% yield but under more drastic conditions (boiling toluene), indicating the existence of the reactive tautomeric azido forms as a function of the temperature (Scheme IV). However, the cycloaddition reaction of **4b** and **4c**, which show no azide form, did not occur even in refluxing toluene or quinoline.

(11) N. Ikekawa and Y. Honma, *Tetrahedron Lett.*, 1197 (1967).
(12) P. Beak and J. L. Miesel, *J. Amer. Chem. Soc.*, **89**, 2375 (1967).

Experimental Section[13]

7,8-Diphenyltetrazolo[1,5-*a*]pyrazine (3).—To a solution of 2-hydrazino-5,6-diphenylpyrazine[14] (0.8 g), acetic acid (16 ml), and ethanol (2 ml) were added sodium nitrite (0.5 g) and water (5 ml) under at 0° for 30 min. The mixture was then stirred for 1 hr. The reaction mixture was poured into water and the precipitated material was filtered. Recrystallization from methanol gave pale yellow needles (0.8 g, 96%): mp 171–173°; $\lambda_{max}^{CHCl_3}$ 250 nm (sh) (log ε 4.18), 270 (4.14), 322 (sh) (3.88); λ_{max}^{EtOH} 248 nm (sh) (log ε 4.18), 275 (4.14), 318 (3.88); $\lambda_{max}^{EtOH\text{-}HCl}$ 290 nm (sh) (log ε 3.81), 324 (3.92).

Anal. Calcd for $C_{16}H_{11}N_5$: C, 70.31; H, 4.06; N, 25.63. Found: C, 70.56; H, 3.97; N, 25.42.

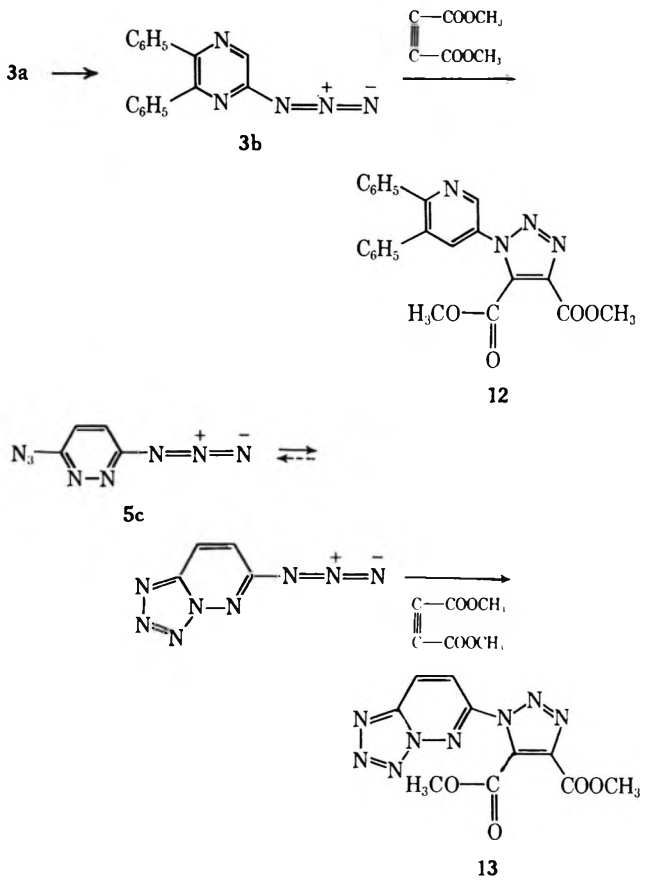
3,4-Diphenyl-6-chloropyridazine.—A solution of 3,4-diphenylpyridazone-6[15] (0.8 g) in phosphorus oxychloride (0.5 ml) was heated on a steam bath for 10 min and the reaction mixture was added to cracked ice water. The precipitated material was dissolved in chloroform, and then water was added to the chloroform solution. The solution was neutralized with aqueous sodium hydroxide (10%) under cooling. The chloroform layer was concentrated *in vacuo*, and the residue was recrystallized from ether to give colorless needles (0.65 g, 75%), mp 111–112°.

Anal. Calcd for $C_{16}H_{11}N_2Cl$: C, 72.05; H, 4.16; N, 10.50. Found: C, 72.45; H, 4.02; N, 10.89.

3,4-Diphenyl-6-hydrazinopyridazine.—A mixture of 3,4-diphenyl-6-chloropyridazine (0.65 g), pyridine (2 ml), ethanol (1

(13) The melting points were measured with a Yanagimoto micromelting point apparatus and were uncorrected. Microanalyses were performed on a Yanagimoto CHN-Corder, Model MT-1. The nmr spectra were taken with a JEOLCO, Model JNM-MH-60 nmr spectrometer and with a Varian A-60 spectrometer with tetramethylsilane as an internal standard. The chemical shifts are expressed in τ values. The ir spectra were taken with a JASCO Model IR-S spectrophotometer.
(14) P. J. Nelson and K. T. Potts, *J. Org. Chem.*, **27**, 3234 (1962).
(15) G. K. Almström, *Justus Liebigs Ann. Chem.*, **400**, 138 (1913).

SCHEME IV



ml), and 80% hydrazine hydrate (1 ml) was refluxed for 40 min. The solvent was removed *in vacuo* and the residue was poured into cracked ice. The precipitated material was filtered and was recrystallized from the organic solvent such as ethanol, chloroform, and benzene. However, the crystals were hygroscopic and were used in the following reactions without further purification (one spot by tlc).[16]

6,7-Diphenyltetrazolo[1,5-*b*]pyridazine (4a).—To 3,4-diphenyl 6-hydrazinopyridazine was added acetic acid (10 ml) and ethanol (2 ml). Then to the solution were added sodium nitrite (0.25 g) and water (0.5 ml) under cooling at 0°, and the reaction mixture was stirred for 2 hr. The precipitate was filtered and recrystallized from methanol to give a colorless powder (0.4 g, 77%): mp 166–167°; $\lambda_{max}^{CHCl_3}$ 244 nm (log ϵ 4.35), 309 (3.78); λ_{max}^{EtOH} 245 nm (log ϵ 4.31), 306 (3.69); $\lambda_{max}^{EtOH-HCl}$ 243 nm (log ϵ 4.24), 306 (3.66).

Anal. Calcd for $C_{16}H_{11}N_5$: C, 70.31; H, 4.06; N, 25.63. Found: C, 70.33; H, 3.80; N, 25.21.

6-Chlorotetrazolo[1,5-*b*]pyridazine (4b).—This compound was prepared by treatment of 3-chloro-6-hydrazinopyridazine with nitrous acid by the method of Takabayashi,[17] mp 108–109° (lit. 107°).

6-Methoxytetrazolo[1,5-*b*]pyridazine (4c).—This compound was prepared by the method of Takabayashi,[17] mp 155–157° (lit. 154.5°).

6-Azidotetrazolo[1,5-*b*]pyridazine (5).—This compound was prepared by treatment of 3,6-dichloropyridazine and sodium azide by the method of Takabayashi,[17] mp 130–131° (lit. 128–129°).

6-Azido-*s*-triazolo[4,3-*b*]pyridazine (6).—A mixture of 6-chloro-*s*-triazolo[4,3-*b*]pyridazine[17] (0.57 g), sodium azide (0.3 g), ethanol (6 ml), and water (6 ml) was refluxed for 18 hr. The solvents were evaporated to dryness, and the resulting mixture was extracted with hot chloroform for several times. The extracted chloroform solution was then evaporated to dryness. The residue was recrystallized from ethanol to give colorless needles (0.45 g, 77%): mp 168–170°; nmr ($CDCl_3$) τ 0.98 (s, H_3), 3.20 (d, H_7, J = 9.5 Hz), 1.85 (d, H_8, J = 9.5 Hz).

Anal. Calcd for $C_5H_3N_7$: C, 37.27; H, 1.88; N, 60.86. Found: C, 37.05; H, 2.01; N, 60.54.

5,6-Diphenyltetrazolo[1,5-*b*]-*as*-triazine (7).—This compound was prepared by the method of Takabayashi:[17] mp 201–202° (lit. 198°); $\lambda_{max}^{CHCl_3}$ 249 nm (log ϵ 4.07), 342 (3.82); λ_{max}^{EtOH} 248 nm (log ϵ 4.24), 333 (3.96); $\lambda_{max}^{EtOH-HCl}$ 240 nm (log ϵ 3.90), 330 (3.76).

4-Methyltetrazolo[1,5-*d*]-*s*-triazolo[4,3-*b*]-*as*-triazine (8).—This compound was prepared by the method of Sasaki, *et al.*,[18] mp 185–187°.

Thermal Reaction of Compound 3. A.—A solution of 7,8-diphenyltetrazolo[1,5-*a*]pyrazine (0.5 g) in acetic acid (10 ml) was refluxed in an oil bath for 11 hr. After the reaction mixture was left standing at room temperature for 10 hr, the precipitated crystals (**3**, 0.1 g) were filtered and the filtrate was concentrated *in vacuo*. Purification by chromatography (silic acid) using chloroform as an eluent followed by recrystallization from ethanol gave **9**[19] (mp 235–237°, 0.226 g, 56%) and **10** (mp 153–155°, 0.063 g, 13%).

9: ν_{max} (KBr) 2980 (NH), 1068 cm^{-1} (C=N); τ (CD_3OD) 2.28 (1 H, s), 2.62–2.82 (10 H, multiplet, $2C_6H_5$); λ_{max}^{EtOH} 216 nm (log ϵ 4.10), 252 (3.78), 282 (3.97); mass spectrum M^+ *m/e* 220.

Anal. Calcd for $C_{15}H_{12}N_2$: C, 81.79; H, 5.49; N, 12.72. Found: C, 81.81; H, 5.25; N, 12.61.

10: ν_{max} (KBr) 1735 cm^{-1} (C=O); nmr τ ($CDCl_3$) 1.72 (1 H, s), 2.54–2.62 (10 H, multiplet, $2C_6H_5$), 7.74 (3 H, CH_3, s); mass spectrum M^- *m/e* 262.

Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.55; H, 4.93; N, 10.86.

B.—A solution of **3** (0.6 g) in acetic anhydride (12 ml) and acetic acid (2 ml) was refluxed for 25 hr. Work-up as described above afforded **9** (0.118 g, 24%) and **10** (0.2111 g, 36%).

Photolysis of Compound 3.—A solution of **3** (1.13 g) in acetic acid (400 ml) was irradiated using a high-pressure mercury lamp (300 W) for 32 hr. The solution was concentrated *in vacuo*, and work-up as described above afforded **9** (10%), benzoic acid (7%), and recovered **3** (0.78 g).

1,3-Dipolar Cycloaddition of 3 with Dimethyl Acetylenedicarboxylate.—A mixture of **3** (0.28 g), dimethyl acetylenedicarboxylate (0.15 g), and chloroform (4 ml) was heated at 70° in an oil bath for 15 hr. After cooling, work-up involved filtration, evaporation of the solution, and chromatography (silic acid) of the residue using chloroform as a eluent.

Colorless needles of **12** (0.075 g, 15%), mp 194–196°, were obtained from the eluent: ν_{max} (KBr) 1740, 1717, 1253, 1210, 1170 cm^{-1} ($COOCH_3$).

Anal. Calcd for $C_{22}H_{17}N_5O_4$: C, 63.61; H, 4.13; N, 16.86. Found: C, 63.81; H, 4.00; N, 16.72.

1,3-Dipolar Cycloaddition of 5 with Dimethyl Acetylenedicarboxylate.—A solution of **5** (0.3 g), dimethyl acetylenecarboxylate (0.26 g), and toluene (10 ml) was heated at 120° for 47 hr. The solution was concentrated *in vacuo*, and work-up as described above of the residue afforded **13** (0.23 g, 39%): mp 153–155°; ν_{max} (KBr) 1740, 1710, 1275, 1240 cm^{-1} ($COOCH_3$).

Anal. Calcd for $C_{10}H_3N_8O_4$: C, 39.48; H, 2.65; N, 36.84. Found: C, 39.50; H, 2.80; N, 36.59.

Registry No.—**3**, 27062-47-1; **4a**, 27062-48-2; **4b**, 21413-15-0; **4c**, 27062-50-6; **5**, 14393-79-4; **6**, 14393-80-7; **7**, 2762-35-8; **8**, 21119-79-9; **9**, 668-94-0; **10**, 27062-55-1; **12**, 27062-56-2; **13**, 27062-57-3; 3,4-diphenyl-6-chloropyridazine, 27062-58-4.

(16) Thin layer chromatography was carried out on alumina and silica plates by using a benzene–methanol mixture as developing solvents and iodine as a developing reagent.

(17) N. Takabayashi, *Yakugaku Zasshi*, **75**, 1242 (1955).

(18) T. Sasaki, K. Minamoto, and M. Murata, *Chem. Ber.*, **101**, 3969 (1968).

(19) D. Davison, M. Weiss, and M. Jelling, *J. Org. Chem.*, **2**, 328 (1937).

Synthesis of Substituted 1,5- and 1,7-Naphthyridines and Related Lactams[1]

BENJAMIN FRYDMAN, MARIO LOS, AND HENRY RAPOPORT*

Facultad de Farmacia y Bioquimica, Universidad de Buenos Aires, Junin 954, Buenos Aires, and Department of Chemistry, University of California at Berkeley, Berkeley, California 94720

Received July 24, 1970

Reductive cyclization of ethyl 2-methoxy-5-nitro-4-pyridinepyruvate and of ethyl 6-methoxy-3-nitro-2-pyridinepyruvate afforded the corresponding 1,2,3,4-tetrahydro-3-oxy-6-methoxy-1,7-naphthyridin-2-one and 1,2,3,4-tetrahydro-3-oxy-6-methoxy-1,5-naphthyridin-2-one. Treatment of the latter compounds with *p*-toluenesulfonyl chloride in pyridine afforded 6-methoxy-1,7-naphthyridin-2(1*H*)-one and 6-methoxy-1,5-naphthyridin-2(1*H*)-one, which by treatment with phosphorus oxychloride were transformed into 2-chloro-6-methoxy-1,7-naphthyridine, 2-chloro-6-methoxy-1,5-naphthyridine, and 2,6-dichloro-1,5-naphthyridine. The 2-chloronaphthyridines were transformed into 2-hydrazinonaphthyridines and reduced with cupric ion to the parent naphthyridines. 2-Chloro-1,5-naphthyridine afforded 2-methoxy-1,5-naphthyridine by mild treatment with sodium methoxide. Hydrogenation of 6-methoxy-1,7-naphthyridin-2(1*H*)-one afforded 1,2,3,4-tetrahydro-6-methoxy-1,7-naphthyridin-2-one. Treatment of 6-methoxy-1,7-naphthyridin-2(1*H*)-one and its 1,5 analog with hydrogen bromide afforded the 1,2,6,7-tetrahydro-1,7-naphthyridine-2,6-dione and 1,2,6,7-tetrahydro-1,5-naphthyridine-2,6-dione, which were reduced to the *cis*-decahydro-1,7- and -1,5-naphthyridine-2,6-diones. The bicyclic lactams could not be hydrolyzed to the amino acids, which were prepared by acid hydrolysis of *meso*- and *rac*-2,2′-bi(pyrrolidine)-5,5′-dione. When the diethyl *meso*- and *rac*-4,5-diaminosuberate dihydrochlorides were equilibrated at pH 7.5, they cyclized to the six-membered bicyclic lactams, *trans*- and *cis*-decahydro-1,5-naphthyridine-2,6-dione, respectively.

In a previous paper[2] we reported that the reductive cyclization of ethyl 2-methoxy-5-nitro-4-pyridinepyruvate (**1**) proceeded in good yield to ethyl 5-methoxy-6-azaindole-2-carboxylate or, alternatively, yielded 1,2,3,4-tetrahydro-3-oxy-6-methoxy-1,7-naphthyridin-2-one (**2**). The determining factor was the catalyst used in the respective procedures, palladium on carbon or platinum oxide. Since then we have described the synthesis of a considerable number of substituted 6-azaindoles and 4-azaindoles,[3,4] obtained by reductive cyclization, using palladium on carbon, of substituted pyridinepyruvates of type **1** and **11**. We now report the synthesis of the corresponding 1,5- and 1,7-naphthyridine derivatives obtained from the same precursors by the alternative pathway, reductive cyclization using platinum oxide.

The existing synthetic methods for naphthyridines are quite limited in scope.[5] The classical Skraup-type reaction on 3-aminopyridine was improved and used for the synthesis of 1,5-naphthyridine and its alkyl derivatives.[6] 1,7-Naphthyridine and its 6-amino derivative were recently[7] obtained by an intramolecular acid cyclization of 2-cyano-3-pyridylacetonitrile. Since the ethyl *o*-nitropyridinepyruvates **1** and **11** can be easily prepared on a large scale,[3,4] they provide excellent starting materials for the synthesis of new 1,7- and 1,5-naphthyridine derivatives. The procedure described[2] for the synthesis of the ethyl pyridinepyruvate **1** was found to be useful for the synthesis of analogous ethyl *o*-nitro-4- and -2-pyridinepyruvates,[8,9] therefore, the proposed naphthyridine synthesis undoubtedly can be extended to a large number of compounds. Moreover, ethyl 2-methoxy-3-nitro-4-pyridinepyruvate (**1**) and ethyl 6-methoxy-3-nitro-2-pyridinepyruvate (**11**) can be C-alkylated and C-acylated to a number of derivatives, thus greatly increasing the number and variation of substituted 1,7- and 1,5-naphthyridines obtainable.

Discussion

The reductive cyclization of the ethyl pyridinepyruvates **1** and **11** can proceed in two directions: either a new five-membered ring can be formed giving an azaindole, or a new six-membered ring can be formed and a tetrahydronaphthyridine obtained. Formation of a five-membered ring can be expected to prevail as long as the carbonyl group is available. This is the case under mild hydrogenation conditions, in ethanol over 10% palladium on charcoal.[3,4] However, if the reaction is carried out over a relatively large amount of platinum oxide (20%), then the carbonyl group is reduced and the 3-oxynaphthyridinones **2** and **12** are obtained in good yields as the only products of the reaction. It is crucial for the course of the reaction to have the pyridinepyruvates highly purified, otherwise partial inactivation of the catalyst leads to a mixture of azaindole and naphthyridine.

The tetrahydronaphthyridines **2** and **12** are readily dehydrated by treatment with *p*-toluenesulfonyl chloride in pyridine and the corresponding 1,7- and 1,5-naphthyridinones **3** and **13** were obtained. A strong band at 1690 cm^{-1} in the ir indicated that compounds **3** and **13** exist in the lactam form, as expected, and not as 2-hydroxynaphthyridines. The amide band in the tetrahydronaphthyridines **2** and **12** was also at 1690

(1) This work was supported by the Consejo Nacional de Investigaciones and Secretaria de Salud Publica (Argentina) and the National Institutes of Health, U. S. Public Health Service.

(2) B. Frydman, M. E. Despuy, and H. Rapoport, *J. Amer. Chem. Soc.*, **87**, 3530 (1965).

(3) B. Frydman, S. J. Reil, J. Boned, and H. Rapoport, *J. Org. Chem.*, **33**, 3762 (1968).

(4) B. Frydman, S. J. Reil, M. E. Despuy, and H. Rapoport, *J. Amer. Chem. Soc.*, **91**, 2338 (1969).

(5) For references on naphthyridine ring synthesis prior to 1960, see M. J. Weiss in R. C. Elderfield, *Heterocycl. Compounds*, **7**, 198 (1961). Recent naphthyridine syntheses are (a) Skraup-type [W. W. Paudler and T. J. Kress, *J. Org. Chem.*, **31**, 3055 (1966); **32**, 832 (1967); W. Czuba, *Rocz. Chem.*, **41**, 289 (1967)]; (b) ethoxymethylenemalonic ester method [A. Albert and W. L. Armarego, *J. Chem. Soc.*, 4237 (1963); G. Y. Lesher, U. S. Patent 3,429,887 (1968); *Chem. Abstr.*, **70**, 344 (1969)]; (c) *via o*-disubstituted pyridines [H. E. Baumgarten, H. C. F. Su, and R. R. Barkley, *J. Heterocycl. Chem.*, **3**, 357 (1966); F. Zymalkowski and P. Messinger, *Arch. Pharm.*, **300**, 91 (1967)]; (d) *via* ammonia insertion in azachromanones [S. A. Vartanyan and Sh. L. Sagbatyan, *Khim. Geterotsikl. Soedin*, **3**, 427 (1966)].

(6) H. Rapoport and A. D. Batcho, *J. Org. Chem.*, **28**, 1753 (1963).

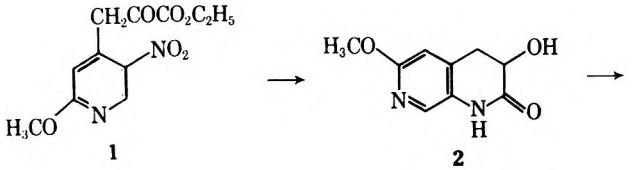
(7) R. Tam and A. Taurins, *Tetrahedron Lett.*, 1233 (1966).

(8) L. N. Yakhontov, V. A. Azimov, and E. I. Lapan, *ibid.*, 1909 (1969).

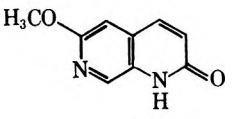
(9) M. H. Fisher and A. R. Matzuk, *J. Heterocycl. Chem.*, **6**, 775 (1969).

cm^{-1} and in the naphthyridinone **19** (prepared by an independent synthesis)[10] it was at 1700 cm^{-1}.

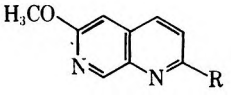
The transformation of the naphthyridinones, **3** and **13**, into naphthyridines was achieved by treatment with phosphorus oxychloride. In this step the properties of the 1,7-naphthyridine and 1,5-naphthyridine series diverged. While the 6-methoxy-1,7-naphthyridin-2(1*H*)-one (**3**) was easily transformed into the 2-chloro-1,7-naphthyridine (**4**), the analogous 6-methoxy-1,5-naphthyridinone (**13**) was demethylated and yielded the 2,6-dichloro-1,5-naphthyridine (**15**). However, when the reaction was carried out at room temperature for several days, demethylation was avoided, and 2-chloro-6-methoxy-1,5-naphthyridine (**14**) was obtained. Hydrogenolysis of the chloronaphthyridines was accompanied by ring reduction; the 2-hydrazino derivatives were then prepared and reduced with cupric sulfate to the corresponding naphthyridines. The 2,6-dichloro-1,5-naphthyridine (**15**) yielded only a monohydrazino derivative **16** which was reduced to 2-chloro-1,5-naphthyridine (**17**). Treatment of **17** with sodium methoxide in boiling methanol readily yielded 2-methoxy-1,5-naphthyridine (**18**).



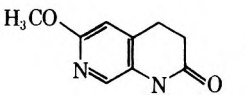
1 → **2**



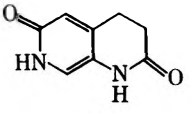
3



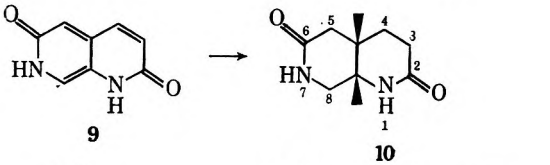
4, R = Cl
5, R = H_2NNH_2
6, R = H



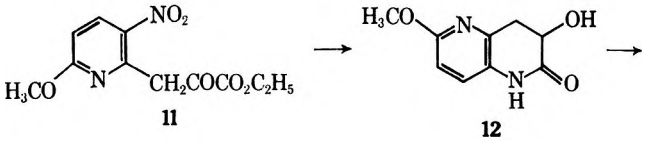
7



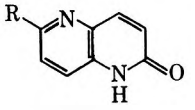
8



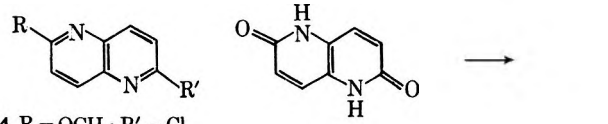
9 → **10**



11 → **12**

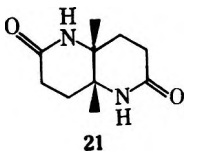


13, R = OCH_3
19, R = H



14, R = OCH_3; R′ = Cl
15, R = R′ = Cl
16, R = Cl; R′ = $NHNH_2$
17, R = Cl; R′ = H
18, R = OCH_3; R′ = H

20



21

It has already been noted that the hydrogenation of the 1,7- and 1,5-naphthyridine derivatives is difficult to control, often resulting in ring reduction. Thus, a controlled hydrogenation of **3** yielded the tetrahydro-1,7-naphthyridine **7**, but a similar hydrogenation of **13** resulted in overall ring reduction.[11] When the naphthyridine-2,6-diones **8**, **9**, and **20**, respectively, were prepared by treatment of **7**, **3**, and **13** with hydrobromic acid, they were smoothly reduced to the bicyclic lactams **10** and **21**. The naphthyridine-2,6-diones **9** and **20** existed predominantely in the α-pyridone form as shown by the strong amide band at 1690 cm^{-1} and by nmr data. The reduction of both compounds could potentially yield two pairs of diastereoisomeric lactams: the meso *cis*-decahydronaphthyridine-2,6-diones and the racemic *trans*-decahydronaphthyridine-2,6-diones. It was expected that the catalytic hydrogenation in acidic media would yield only the cis derivatives, and this was confirmed by the isolation of **10** and **21**. The bridge protons in **21** showed a sharp singlet at δ 4.4, and the bridge proton adjacent to the nitrogen in **10** was also a narrow singlet at δ 4.4, as expected from cis compounds. The bicyclic lactam **21** was reduced with lithium aluminum hydride to *cis*-decahydro-1,5-naphthyridine (**28**), identical with a sample of **28** prepared by a stereospecific reduction of 1,5-naphthyridine,[11] thus confirming the structure of **21**.

Surprisingly, the bicyclic lactams proved to be extremely resistent to hydrolysis. Mild treatments with various alkalis resulted in lactam recovery, and, when drastic conditions and a large excess of alkali were employed, no recognizable compounds could be isolated. When acidic hydrolysis conditions were invoked, lactam **21** was recovered unchanged and lactam **10** was partially hydrolyzed to **27**. The structure **27** was assigned on the basis of the nmr data. Attempted alkaline hydrolysis of **27** resulted in recovery of starting materials.[12] Since we were interested in comparing the stability of six-membered lactams *vs.* five-membered ones, we prepared the diaminosuberic esters **23** and **26**. Our starting material was the *meso*- and *rac*-2,2′-bi(pyrrolidine)-5,5′-diones (**22**) and (**25**), obtained photochemically by dimerization of 2-pyrrolidinone.[13] By an acid hydrolysis followed by esterification they were transformed into

(10) V. Petrov and B. Sturgeon, *J. Chem. Soc.*, 1157 (1949); modified according to ref 6.

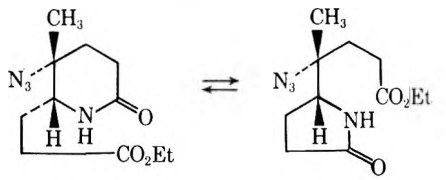
(11) Catalytic hydrogenation of 1,5-naphthyridine has been reported to yield decahydro-1,5-naphthyridine, but no decahydro-1,7-naphthyridine could be obtained by the same procedure: W. L. F. Armarego, *ibid.*, *C*, 377 (1967).

(12) It is noteworthy that the hydrolysis of five-membered bicyclic lactams was reported to proceed without difficulties: L. Birkofer and H. Feldmann, *Justus Liebigs Ann. Chem.*, **677**, 154 (1964).

(13) M. Pesaro, I. Felner-Caboga, and A. Eschenmoser, *Chimia*, **19**, 566 (1965).

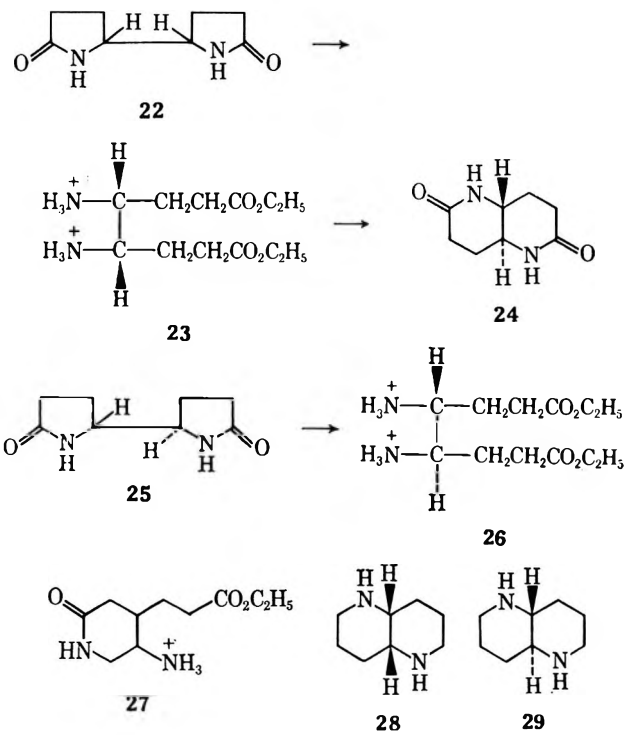
the hydrochlorides of diethyl *meso*-4,5-diaminosuberate (**23**) and diethyl *rac*-4,5-diaminosuberate (**26**). Equilibration of both hydrochlorides in neutral or slightly alkaline media could then lead to the starting five-membered lactams or to the bicyclic six-membered lactams **24** and **21**.

A prediction of the course of the reaction is difficult. In formation from an open-chain intermediate, kinetic control should give preference to a five-membered ring and thermodynamic control to a six-membered ring. However, in an equilibrium reaction between substituted six-membered lactam A and five-membered lactam B, the five-membered ring was predominant (in alkaline medium).[14]



A B

In our case we find that at pH 7.5, the *meso*-4,5-diaminosuberate **23** was quantitatively transformed into *trans*-decahydro-1,5-naphthyridine-2,6-dione (**24**) and the *rac*-diaminosuberate **26** into *cis*-decahydro-1,5-naphthyridine-2,6-dione (**21**). The transformation was unaffected by time or temperature. The identity of **24** was established by its nmr (J = 10 Hz for the bridge protons), and by its reduction with lithium aluminum hydride to **29**. *trans*-Decahydro-1,5-naphthyridine (**29**) was prepared for comparison by the stereospecific reduction of 1,5-naphthyridine in alkaline medium.[11] The ir spectra did not reveal in the equilibration products any trace of five-membered lactams **22** or **25**. These results indicate that, at least for unsubstituted bicyclic lactams, the equilibrium is displaced toward the six-membered rings.



22

23 24

25 26

27 28 29

(14) E. Bertele, H. Boos, J. D. Dunitz, F. Elsinger, A. Eschenmoser, I. Feiner, H. P. Gribi, H. Gschwend, E. F. Meyer, M. Pesaro, and R. Scheffold, *Angew. Chem., Int. Ed. Engl.*, **3**, 490 (1964).

Experimental Section[15]

1,2,3,4-Tetrahydro-3-oxy-6-methoxy-1,7-naphthyridin-2-one (2).—Six grams of ethyl 2-methoxy-5-nitro-4-pyridinepyruvate (**1**) was dissolved in 100 ml of ethanol and reduced during 2 hr at 40 psi with hydrogen over 1.2 g of platinum oxide. The catalyst was filtered out and washed with ethanol, the combined filtrate and washings were concentrated *in vacuo* to 10 ml, and the suspension was cooled for several hours. The resulting precipitate was crystallized from ethanol: 3.3 g (75%); mp 215°; uv max 248 nm (ε 14,700); nmr δ 3.7 (m, C-4 H_2), 4.4 (OCH_3), 5.0 (m, C-3 H), 7.6 (s, C-5 H), 8.2 (s, C-8 H).

Anal. Calcd for $C_9H_{10}O_3N_2$: C, 55.6; H, 5.2; N, 14.4. Found: C, 55.3; H, 5.1; N, 14.2.

1,2,3,4-Tetrahydro-3-oxy-6-methoxy-1,5-naphthyridin-2-one (12) was prepared following the same procedure used for the synthesis of the tetrahydro-1,7-naphthyridin-2-one **2**. Ethyl 6-methoxy-3-nitro-2-pyridinepyruvate (**11**) had to be previously purified by sublimation (115°, 5 μ) and crystallization from ethanol. From 6 g of ethyl pyridinepyruvate **11** (mp 122–123°) was obtained 3 g (69%) of **12**: mp 240°; uv max 255 nm (ε 12,300); nmr δ 3.8 (m, C-4 H_2), 4.4 (OCH_3), 5.1 (m, C-3 H), 7.5 (d, J = 10 Hz, C-7 H), 8.3 (d, J = 10 Hz, C-8 H).

Anal. Calcd for $C_9H_{10}O_3N_2$: C, 55.6; H, 5.2; N, 14.4. Found: C, 55.5; H, 5.1; N, 14.5.

6-Methoxy-1,7-naphthyridin-2(1*H*)-one (3).—Tetrahydro-3-oxy-6-methoxy-1,5-naphthyridin-2-one (**2**) (2 g) was dissolved in 10 ml of pyridine, 4 g of *p*-toluenesulfonyl chloride was added, and the mixture was heated at 150° for 4 hr. The mixture was poured over 250 g of crushed ice and filtered, and the precipitate was suspended in 10% sodium carbonate, centrifuged, washed with water, and filtered. Crystallization of the residue from ethanol gave 1.7 g (79%) of **3**: mp 250–254°; uv max 234 nm (ε 35,000); nmr δ 4.4 (OCH_3), 7.5 (d, J = 10 Hz, C-3 H), 7.9 (C-5 H), 8.5 (d, J = 10 Hz, C-4 H), 9.0 (C-8 H).

Anal. Calcd for $C_9H_8O_2N_2$: C, 61.3; H, 4.6; N, 16.1. Found C, 61.2; H, 4.6; N, 16.1.

6-Methoxy-1,5-naphthyridin-2(1*H*)-one (13) was prepared following the same procedure used for the synthesis of 5-methoxy-1,7-naphthyridin-2(1*H*)-one (**3**). From 2 g of tetrahydro-3-oxy-6-methoxy-1,5-naphthyridin-2-one (**12**) was obtained 1.8 g (83%) of **13** after sublimation at 210° (3 μ) and crystallization from ethanol: mp 244–246°; uv max 233 nm (ε 70,000); nmr δ 4.4 (OCH_3), 7.6 (d, J = 10 Hz, C-7 H), 7.9 (d, J = 10 Hz, C-3 H), 8.5 (d, J = 10 Hz, C-8 H), 8.8 (d, J = 10 Hz, C-4 H).

Anal. Calcd for $C_9H_8O_2N_2$: C, 61.3; H, 4.6; N, 15.9. Found: C, 61.3; H, 4.6; N, 16.0.

2-Chloro-6-methoxy-1,7-naphthyridine (4).—6-Methoxy-1,7-naphthyridin-2(1*H*)-one (**2**) (4.2 g) and 40 ml of phosphorus oxychloride were heated at reflux overnight. Excess phosphorus oxychloride was distilled *in vacuo*, the residue was treated with 100 g of ice water, the pH was adjusted to 6 with sodium hydroxide, and the aqueous phase was extracted continuously with chloroform for 48 hr. Evaporation of the chloroform and sublimation of the residue at 120° (3 μ) gave 3 g (63%) of **4**: mp 185–190° (from benzene–methylcyclohexane); uv max 242 nm (ε 17,000), 350 (1500).

Anal. Calcd for $C_9H_7N_2OCl$: C, 55.7; H, 3.6; N, 14.4. Found: C, 55.9; H, 3.5; N, 14.4.

2-Chloro-6-methoxy-1,5-naphthyridine (14).—6-Methoxy-1,5-naphthyridin-2(1*H*)-one (**13**) (2 g), purified by sublimation, and 50 ml of phosphorus oxychloride were stirred at 70° until total dissolution of the solid, and then left at room temperature for 72 hr. The same procedure used in the synthesis of **4** was then followed and 1.6 g (70%) of **14** was obtained after sublimation at 70° (2 μ): mp 130–134° (from cyclohexane); uv max 221 nm (ε 60,200), 314 (8000), 326 (9500); nmr δ 4.6 (s, OCH_3), 8.0 (d, J = 10 Hz, C-7 H), 8.5 (d, J = 10 Hz, C-3 H), 8.8 (d, J = 10 Hz, C-8 H), 9.2 (d, J = 10 Hz, C-4 H).

(15) All melting points were taken on the Kofler block; uv absorptions were measured in ethanol; ir spectra were obtained on potassium bromide wafers; and nmr spectra were taken in trifluoroacetic acid, unless otherwise noted. Microanalyses were performed by the Analytical Laboratory, University of California, Berkeley.

Anal. Calcd for $C_9H_7N_2OCl$: C, 55.7; H, 3.6; N, 14.4. Found: C, 55.4; H, 3.5; N, 14.3.

2-Hydrazino-6-methoxy-1,7-naphthyridine (**5**).—A solution of 6 g (0.03 mol) of 2-chloro-6-methoxy-1,7-naphthyridine (**4**) in 40 ml of ethanol and 33 ml (0.57 mol) of 85% hydrazine hydrate was heated at 100° for 1 hr. Evaporation of the solvent *in vacuo* left a crystalline residue which was crystallized from benzene giving 4.9 (84%) of **5**, mp 170–172°.

Anal. Calcd for $C_9H_{10}N_4O$: C, 56.8; H, 5.3; N, 29.4. Found: C, 57.0; H, 5.2; N, 29.6.

2,6-Dichloro-1,5-naphthyridine (**15**).—6-Methoxy-1,5-naphthyridin-2(1*H*)-one (**13**) (2 g) and 40 ml of phosphorus oxychloride were heated at reflux for 15 hr. The same procedure used for the preparation of **4** was then followed. The product obtained was sublimed at 134° (2 μ) and crystallized from benzene–cyclohexane, giving 5.1 g (57%) of **15**: mp 190–194; uv max 214 nm (ϵ 61,300), 256 (4250), 266 (2500), 310 (8300), 324 (9600); nmr δ 8.3 (d, J = 10 Hz, C-3 H, C-7 H), 9.1 (d, J = 10 Hz, C-4 H and C-8 H).

Anal. Calcd for $C_8H_4N_2Cl_2$: C, 48.6; H, 2.0; N, 14.1; Cl, 35.3. Found: C, 48.4; H, 2.2; N, 14.2; Cl, 35.2.

2-Hydrazino-6-chloro-1,5-naphthyridine (**16**) was prepared following the same procedure used for the preparation of **5**. From 3 g of 2,6-dichloro-1,5-naphthyridine (**15**) was obtained 2 g (70%) of **16**: mp 178–180° (sublimed at 130°, 2 μ); uv max 230 nm (ϵ 26,400), 284 (29,400), 364 (12,700).

Anal. Calcd for $C_9H_7N_4C$: C, 49.5; H, 3.6; N, 28.8; Cl, 18.0. Found: C, 49.7; H, 3.8; N, 29.0; Cl, 18.2.

6-Methoxy-1,7-naphthyridine (**6**).—2-Hydrazino-6-methoxy-1,7-naphthyridine (**5**) (2.1 g) was dissolved in a mixture of 20 ml of water and 5 ml of acetic acid, and 45 ml of a 10% aqueous solution of cupric sulphate was added dropwise. The resulting mixture was heated on the steam bath until gas evolution ceased (1 hr) and then adjusted to pH 8 with 4 *M* ammonium hydroxide. Continuous extraction with chloroform and evaporation of the solvent left a residue which was sublimed at 40° (2 μ) to give 0.8 g (45%) of **6**: mp 45–46° (from methylcyclohexane); uv max 224 nm (ϵ 29,100), 259 (3500), 339 (3200); nmr ($CDCl_3$) δ 4.0 (s, OCH_3), 7.1 (s, C-5 H), 9.3 (s, C-8 H), 7.5 (m, $J_{3,4}$ = 9 Hz, $J_{2,3}$ = 4 Hz, C-3 H), 8.1 (m, $J_{4,3}$ = 9 Hz, $J_{4,2}$ = 9 Hz, C-4 H), 9.0 (m, $J_{2,3}$ = 4 Hz, $J_{2,4}$ = 9 Hz, C-2 H).

Anal. Calcd for $C_9H_8ON_2$: C, 67.5; H, 4.9; N, 17.5. Found: C, 67.4; H, 4.9; N, 17.7.

2-Chloro-1,5-naphthyridine (**17**) was prepared following the same procedure used for the synthesis of 6-methoxy-1,7-naphthyridine (**6**). From 4 g of 2-hydrazino-6-chloro-1,5-naphthyridine (**16**) was obtained, after sublimation at 45° (2 μ) and crystallization from cyclohexane, 1.6 g (50%) of **17**: mp 110–112°; uv max 215 nm (ϵ 29,600), 242 (4000), 248 (4100), 258 (3700), 267 (2600), 302 (6400), 308 (6700), 316 (6600); nmr δ 8.3 (d, $J_{7,8}$ = 10 Hz, C-7 H), 9.6 (d, $J_{7,8}$ = 10 Hz, C-8 H), 8.6 (m, $J_{3,4}$ = 9 Hz, $J_{2,3}$ = 6 Hz, C-3 H), 8.9 (m, $J_{4,3}$ = 9 Hz, $J_{2,4}$ = 1.5 Hz, C-4 H), 9.4 (m, $J_{2,3}$ = 6 Hz, $J_{2,4}$ = 1.5 Hz, C-2 H).

Anal. Calcd for $C_8H_5N_2Cl$: C, 58.5; H, 3.0; N, 17.1; Cl, 21.3. Found: C, 58.8; H, 3.3; N, 17.1; Cl, 21.1.

The 2-chloro-1,5-naphthyridine was identical (melting point and ir) with a sample prepared by the action of phosphorus oxychloride on 2-hydroxy-1,5-naphthyridine (**19**).[16]

2-Methoxy-1,5-naphthyridine (**18**).—2-Chloro-1,5-naphthyridine (**17**) (1.3 g, 7.9 mmol) was added to a solution of 230 mg (10 g-atoms) of sodium in 20 ml of anhydrous methanol, and the mixture was heated under reflux for 4 hr. The solvent was evaporated *in vacuo*, the residue dissolved in 20 ml of chloroform, the solution washed with 5 ml of water, the chloroform evaporated, and the residue sublimed at 30° (2 μ) giving 450 mg (38%) of **18**: mp 38°; uv max 221 nm (ϵ 15,100), 311 (7500), 321 (7100).

Anal. Calcd for $C_9H_8ON_2$: C, 67.5; H, 4.9; N, 17.5. Found: C, 67.4; H, 4.8; N, 17.4.

1,2,3,4-Tetrahydro-6-methoxy-1,7-naphthyridin-2-one (**7**).—6-Methoxy-1,7-naphthyridin-2(1*H*)-one (**3**) (1.2 g) was dissolved in 100 ml of ethanol and reduced during 2 hr at 40 psi with hydrogen over 1 g of 10% palladium on charcoal. The catalyst was filtered off and thoroughly washed with ethanol and the combined filtrate and washings were concentrated *in vacuo* to 5 ml. Cooling gave a precipitate which was sublimed at 200° (1 μ) to give 0.9 g (75%) of **7**: mp 205–209; uv max 250 nm (ϵ 13,500), 300 (7500); nmr δ 3.05 (m, C-3 H_2), 3.45 (m, C-4 H_2), 7.5 (s, C-5 H), 8.15 (s, C-8 H), 4.3 (s, OCH_3).

(16) E. V. Brown and A. C. Plasz, *J. Org. Chem.*, **27**, 241 (1967).

Anal. Calcd for $C_9H_{10}N_2O_2$: C, 60.7; H, 5.7; N, 15.7. Found: C, 60.8; H, 5.7; N, 15.6.

1,2,3,4,6,7-Hexahydro-1,7-naphthyridine-2,6-dione (**8**).—The tetrahydro-1,7-naphthyridin-2-one (**7**) (0.6 g) was dissolved in 12 ml of 48% hydrobromic acid and heated at reflux for 2 hr. Excess acid was distilled *in vacuo*, the residue dissolved in 5 ml of water, and the solution adjusted to pH 7 with 10% sodium carbonate, concentrated to 1 ml, and cooled for several hours. The solid obtained was sublimed at 250° (2 μ) and crystallized from water, giving 0.21 g (38%) of **8**: mp 350° dec; uv max 254 nm (ϵ 6000), 320 (2000); nmr δ 3.1 (m, C-3 H_2), 3.4 (m, C-4 H_2), 7.55 (s, C-5 H), 8.15 (s, C-8 H).

Anal. Calcd for $C_8H_8N_2O_2$: C, 58.5; H, 4.9; N, 17.1. Found: C, 58.7; H, 5.2; N, 17.0.

1,2,6,7-Tetrahydro-1,7-naphthyridine-2,6-dione (**9**) was prepared following the same procedure used for the synthesis of the hexahydro derivative **8**. From 3 g of 6-methoxy-1,7-naphthyridin-2(1*H*)-one (**3**) was obtained 2.2 g (80%) of **9**, sublimed at 240° (1 μ) and crystallized from glacial acetic acid: mp 350°; uv max 236 nm (ϵ 27,600), 246 (26,700); nmr δ 7.5 (d, J = 10 Hz, C-3 H), 8.3 (d, J = 10 Hz, C-4 H), 7.8 (s, C-5 H), 9.0 (s, C-9 H).

Anal. Calcd for $C_8H_6N_2O_2$: C, 59.3; H, 3.7; N, 17.3. Found: C, 59.4; H, 3.8; N, 17.0.

1,2,5,6-Tetrahydro-1,5-naphthyridine-2,6-dione (**20**) was prepared following the same procedure used for the synthesis of the hexahydro derivative **8**. From 3 g of 6-methoxy-1,5-naphthyridin-2(1*H*)-one (**13**) was obtained 2.3 g (83%) of **20**, sublimed at 240° (1 μ) and crystallized from trifluoroacetic acid–water: mp dec above 350°; nmr δ 7.6 (d, J = 10 Hz, C-3 H and C-7 H), 8.4 (d, J = 10 Hz, C-4 H and C-8 H).

***cis*-Decahydro-1,7-naphthyridine-2,6-dione** (**10**).—1,2,6,7-Tetrahydro-1,7-naphthyridine-2,6-dione (**9**) (2 g) was dissolved in 50 ml of glacial acetic acid and reduced during 72 hr at 50 psi with hydrogen over a mixture of 0.5 g of platinum oxide and 0.5 g of 10% palladium on charcoal. The catalyst was filtered and washed with glacial acetic acid, and the filtrates were evaporated to dryness *in vacuo* at 50°. The crystalline residue was sublimed (250°, 1 μ) and crystallized from ethanol–water giving 2.1 g (80%) of **10**: mp 285°; ir 3230 (NH), 1690 (CO), 1660 cm^{-1} (CO); nmr δ 2.2 (b, 2, C-4 H_2), 3.0 (b, 5, C-3 H_2, C-5 H and C-4a H), 4.2 (b, C-8 H_2), 4.4 (s, 1, C-8a H).

Anal. Calcd for $C_8H_{12}O_2N_2$: C, 57.1; H, 7.1; N, 16.6. Found: C, 56.9; H, 7.2; N, 16.6.

***cis*-Decahydro-1,5-naphthyridine-2,6-dione** (**21**) was prepared following the same technique used for the synthesis of *cis*-decahydro-1,7-naphthyridine-2,6-dione (**10**). From 2 g of 1,2,5,6-tetrahydro-1,5-naphthyridine-2,6-dione (**20**) was obtained, after sublimation (280°, 1 μ) and crystallization from ethanol–water, 2.2 g (81%) of **21**: mp dec above 350; ir 3220 (NH), 1640–1660 cm^{-1} (CO); nmr δ 2.5 (b, 4, C-3 H_2 and C-7 H_2), 2.9 (b, 4, C-4 H_2 and C-8 H_2), 4.4 (s, 2, >CH).

Anal. Calcd for $C_8H_{12}O_2N_2$: C, 57.1; H, 7.1; N, 16.6. Found: C, 57.0; H, 7.3; N, 16.6.

Diethyl *meso*-4,5-Diaminosuberate Dihydrochloride (**23**).—*meso*-2,2′-Bi(pyrrolidine)-5,5′-dione (**22**) (300 mg, sublimed at 250°, 2 μ) was suspended in 5 ml of 6 *N* hydrochloric acid and the solution heated under reflux for 12 hr. Evaporation *in vacuo* left a residue which was dissolved in 5 ml of absolute ethanol saturated with hydrogen chloride and left at 5° for 48 hr. Evaporation *in vacuo* at 30° left a residue which was crystallized from ethanol–ether giving 236 mg (40%) of **23**: mp 160–162°; ir 1720 cm^{-1} (CO ester); nmr δ 1.4 (t, 6, CH_2CH_3), 2.5 (b, H>CCH_2), 3.0 (b, $-CH_2CO_2C_2H_5$), 4.45 (q, 4, CH_2CH_3).

Anal. Calcd for $C_{12}H_{26}O_4N_2Cl_2$: C, 43.4; H, 7.8; N, 8.4. Found: C, 43.5; H, 7.8; N, 8.4.

***trans*-Decahydro-1,5-naphthyridine-2,6-dione** (**24**).—**23** (150 mg) was dissolved in 5 ml of absolute ethanol, the pH was adjusted to 7.5 with potassium ethoxide, and the suspension stirred at 5° for 12 hr. The solution was filtered, the filtrate was concentrated to dryness, and the residue was sublimed at 300° and 2 μ, giving 40 mg (93%) of **24**: mp dec above 350°; ir 1655 cm^{-1} (CO); nmr δ 2.3 (m, 4, C-3 H_2 and C-7 H_2), 3.0 (m, 4, C-4 H_2 and C-8 H_2), 3.8 (m, 2, J = 10 Hz, –CH).

Anal. Calcd for $C_8H_{12}O_2N_2$: C, 57.1; H, 7.2; N, 16.6. Found: C, 57.1; H, 7.2; N, 16.9.

Diethyl *rac*-4,5-diaminosuberate dihydrochloride (**26**) was prepared following the technique described for the meso isomer **23**. From 500 mg of *rac*-2,2′-bi(pyrrolidine)-5,5′-dione (**25**) was obtained 95 mg (20%) of **26**, mp 137–140°.

Anal. Calcd for $C_{12}H_{26}O_4N_2Cl_2$: C, 43.4; H, 7.8; N, 8.4. Found: C, 43.4; H, 7.8; N, 8.3.

When equilibrated at pH 7.5 as described for **24**, **26** afforded *cis*-decahydronaphthyridinedione **21** in 95% yield.

Ethyl 3-Amino-6-oxohexahydropyridine-4-propionate Hydrochloride (27).—Bislactam **10** (300 mg) was dissolved in 5 ml of 6 *N* hydrochloric acid and the solution heated under reflux for 24 hr. The same technique described previously for the synthesis of **23** was then followed and 225 mg (50%) of **27** was obtained: mp 134–136°; ir 1690 (CO), 1740 cm^{-1} (CO ester); nmr δ 1.4 (t, CH_2CH_3), 2.2 (b, C-5 H_2), 2.7 (m, $CH_2CH_2CO_2Et$), 3.7 (b, C-2 H_2), 4.4 (q, CH_2CH_3).

Anal. Calcd for $C_{10}H_{19}N_2O_3Cl$: C, 47.9; H, 7.6; N, 11.2. Found: C, 47.7; H, 7.6; N, 11.4.

***cis*-Decahydro-1,5-naphthyridine (28).**—*cis*-Decahydro-1,5-naphthyridine-2,6-dione (**21**) (1.7 g) was slowly added with constant stirring to a suspension of 3 g of lithium aluminum hydride in 200 ml of tetrahydrofuran. The resulting mixture was heated at reflux for 10 hr, and then 200 ml of water was added. The solution was adjusted to pH 12 with a concentrated sodium hydroxide solution and extracted with five 50-ml portions of chloroform. The extract was dried (Na_2SO_4), concentrated, and distilled giving 500 mg (50%) of **28**: bp 66° (0.25 mm) [lit.[11] bp 55° (0.1 mm)]; identical (ir, nmr, tlc) with a sample prepared by reduction of 1,5-naphthyridine.[11]

Anal. Calcd for $C_8H_{16}N_2$: C, 68.5; H, 11.5; N, 20.0. Found: C, 68.6; H, 11.5; N, 20.1.

***trans*-Decahydro-1,5-naphthyridine (29)** was obtained following the procedure described for the synthesis of **28**. From 560 mg of **24** was obtained 210 mg (45%) of **29**: mp 176–177° (lit.[11] mp 177–178°); identical (ir, tlc, melting points, nmr) with a sample prepared by reduction of 1,5-naphthyridine.[11]

Registry No.—**2**, 3469-64-5; **3**, 27017-56-7; **4**, 27017-57-8; **5**, 27017-58-9; **6**, 27017-59-0; **7**, 27017-60-3; **8**, 27017-61-4; **9**, 27017-62-5; **10**, 27022-27-1; **12**, 27017-63-6; **13**, 27017-64-7; **14**, 27017-65-8; **15**, 27017-66-9; **16**, 27017-67-0; **17**, 7689-62-5; **18**, 27017-69-2; **20**, 27017-70-5; **21**, 27022-28-2; **23**, 27022-29-3; **24**, 27022-30-6; **26**, 27022-31-7; **27**, 27017-71-6.

Further Evidence as to the Nature of the Transition State Leading to Decarboxylation of 2-Pyridinecarboxylic Acids. Electrical Effects in the Transition State

ELLIS V. BROWN* AND RUSSELL J. MOSER

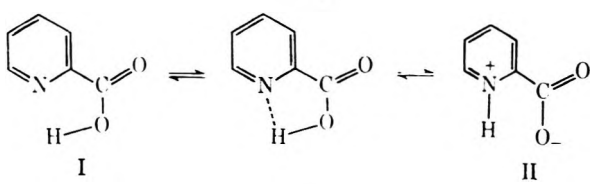
Department of Chemistry, University of Kentucky, Lexington, Kentucky 40506

Received July 10, 1970

The rates of decarboxylation of 6-nitro-2-pyridinecarboxylic, 6-chloro-2-pyridinecarboxylic, 6-bromo-2-pyridinecarboxylic, 2-pyridinecarboxylic, 6-acetamido-2-pyridinecarboxylic, 6-methyl-2-pyridinecarboxylic, 6-methoxy-2-pyridinecarboxylic, and 6-amino-2-pyridinecarboxylic acids in 3-nitrotoluene were determined. The $\Delta G^{\pm}$, $\Delta H^{\pm}$, and $\Delta S^{\pm}$ were then calculated. An examination of a linear free-energy plot of relative rates *vs.* the σ' constants suggested that the electron density on the ring nitrogen affects the $\Delta G^{\pm}$ of the reaction. The observation that 6-methoxy and 6-acetamido groups decrease the rate of decarboxylation by a factor of 4 and 10, respectively, as compared to 6-amino and 6-methyl groups was indicative of a steric effect by the larger substituents. A mechanism is suggested which is consistent with the available data.

Preliminary work has been done on the decarboxylation of 2-pyridinecarboxylic acid in various solvents.[1-4] All of these investigators have looked at the transition state and tried to deduce the structure of the intermediate leading to the transition state. Different methods must be used to study the distribution of reactant other than those used to deduce the structure of the transition state. Thus, we have not tried to postulate that either I or II is the principal reactant but assumed that both are present and that a rapid equilibrium exists between the two reactants (Scheme I).

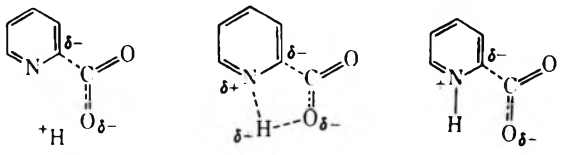
SCHEME I



I II

Irrespective of which reactant leads to which transition state, there are a total of three possible transition states, III, IV, or V (Scheme II). The electrical effects

SCHEME II



III IV V

in the three possible transition states are quite different. If transition states III or V lead predominantly to decarboxylation, one would predict that electron-withdrawing effects would stablize the transition state and lead to larger rate constants.

If transition state IV were the one leading to products, one would argue that there are opposing effects. In one case electron withdrawal should increase the rate constants and in the other case decrease the rate constants. On close examination of IV, it can be seen that two events are occurring: (1) NH bond formation, and (2) CC bond cleavage. With these two events three possibilities exist: (a) CC bond cleavage is leading NH bond formation resulting in a developing negative charge on C-2 in the transition state, (b) CC bond cleavage is lagging behind NH bond formation resulting in a developing positive charge on the ring nitrogen in the transition state, or (c) CC bond cleavage has progressed at an even rate with NH bond formation, resulting in no overall charge being developed on the ring in the

(1) L. W. Clark, *J. Phys. Chem.*, **66**, 125 (1962).
(2) L. W. Clark, *ibid.*, **69**, 2277 (1965).
(3) N. H. Cantwell and E. V. Brown, *J. Amer. Chem. Soc.*, **74**, 5967 (1952).
(4) N. H. Cantwell and E. V. Brown, *ibid.*, **75**, 4466 (1953).

transition state. Only if b exists will the information obtained in this study indicate that IV is the best representation of the transition state. Theoretically, there is a second possibility if b exists. If it were assumed that the transition state for decarboxylation was the formation of the zwitterion, which then rapidly decomposes, then the ring, in the transition state, would have a developing positive charge. This argument is dismissed for two reasons: (1) it is difficult to explain why an acid–base reaction should have a higher activation energy than a CC bond cleavage reaction, and (2) amino acids are known to exist as zwitterions, and they are quite stable.

Since the decarboxylation of 2-pyridinecarboxylic acid in various solvents has thrown little light on the nature of the transition state, the next step is to study the effects of substituents on the rate of decarboxylation. After eliminating a vicinal relationship between the substituent (R) and the carboxyl function (Y), the following cases should be considered: 4-R-2-Y, 5-R-2-Y, and 6-R-2-Y. In the first of a series of papers we have chosen to study the 6-substituted 2-pyridinecarboxylic acids.

If the electron density on the ring nitrogen is changed (without changing anything else) by substituents, one should see a rate change if the NH bond is forming in the transition state. It has already been shown that the electron density on the ring nitrogen can be controlled by ortho substituents. Ortho-substituted pyridines in which the ring nitrogen atom is not the reaction site show a linear relation with σ_p; however, the electrical effect exerted by ortho substitutents on reactions involving the lone-pair electrons on the ring nitrogen atom in pyridine is best represented by σ_I.[5] The σ' constants are almost the same as the σ_I constants, and it would be expected that much of the field effect present in the σ_I constants is eliminated in the σ' constants.[6]

To determine if sterically hindering the lone electron pair on the ring nitrogen would retard the rate of decarboxylation, we decided to look at 6-acetamido- and 6-methoxy-2-pyridinecarboxylic acids. The acetamido group was chosen because it was intuitively felt that it was large enough to prevent the NH bond from forming when one considers the volume swept out by rotation about its bonds. It is believed that this rotation must be considered, since an acid proton which starts to bond to the ring nitrogen would be pushed away by the rotation of the substituent. These rotations are many times faster than the rates of decarboxylation. The methoxyl group was chosen because it was felt that this group was large enough to prevent the NH bond from forming.

Results and Discussion

The 6-substituted 2-pyridinecarboxylic acids, 6-nitro-2-pyridinecarboxylic, 6-chloro-2-pyridinecarboxylic, 6-bromo-2-pyridinecarboxylic, 2-pyridinecarboxylic, 6-acetamido-2-pyridinecarboxylic, 6-methyl-2-pyridinecarboxylic, 6-methoxy-2-pyridinecarboxylic, and 6-amino-2-pyridinecarboxylic acids, were synthesized and their rates of decarboxylation in 3-nitrotoluene were determined in the manner described in the Experimental Section. The rate constants are in Table I, and the activation parameters are in Table II. The coefficient of variation for the data has been calculated in each case. This value is used as a measure of the relative variability of the data. In all cases it is less than 5%.

TABLE I

APPARENT FIRST-ORDER RATE CONSTANTS FOR THE DECARBOXYLATION OF 6-SUBSTITUTED 2-PYRIDINECARBOXYLIC ACIDS IN 3-NITROTOLUENE

Acid	Temp, °C	Rate constant × 10^4 sec^{-1}	Coefficient variation	Standard deviation
6-Nitro-2-pyridinecarboxylic acid	189.9	0.53	3.76	0.009
	195.0	0.78	1.26	0.003
	199.7	1.47	1.82	0.008
	200.0	1.33[a]		
	204.8	2.16	4.10	0.016
	210.1	2.99	2.02	0.010
6-Bromo-2-pyridinecarboxylic acid	190.2	1.25	0.56	0.002
	194.5	2.02	1.24	0.007
	200.0	2.97[a]		
	200.6	2.63	3.78	0.016
	205.0	4.83	3.47	0.023
	209.6	6.78	2.08	0.016
6-Chloro-2-pyridinecarboxylic acid	190.3	0.93	0.70	0.003
	194.6	1.74	2.24	0.013
	200.0	2.36[a]		
	200.4	2.12	4.04	0.026
	205.3	3.71	1.08	0.004
	210.9	6.39	2.17	0.012
2-Pyridinecarboxylic acid	158.5	0.57	3.51	0.006
	163.6	1.22	4.31	0.016
	169.8	1.92	1.21	0.007
	175.0	2.96	1.73	0.008
	179.5	4.49	1.14	0.008
	200.0	26.5[a]		
6-Acetamido-2-pyridinecarboxylic acid	185.2	0.79	0.44	0.001
	190.3	1.25	0.62	0.002
	194.5	1.89	1.50	0.006
	199.7	2.78	1.95	0.009
	200.0	3.01[a]		
	204.0	4.50	1.00	0.005
6-Methyl-2-pyridinecarboxylic acid	161.2	0.59	3.28	0.008
	164.6	0.76	1.66	0.005
	170.1	1.62	2.58	0.012
	174.8	2.31	1.54	0.008
	180.2	4.26	2.53	0.012
	200.0	28.8[a]		
6-Methoxy-2-pyridinecarboxylic acid	200.0	0.33[a]	3.91	0.009
	204.5	0.47	3.91	0.009
	210.6	1.23	3.95	0.012
	213.5	2.03	1.01	0.005
	218.2	2.60	0.89	0.003
	224.8	4.85	0.37	0.002
6-Amino-2-pyridinecarboxylic acid	195.0	0.70	1.53	0.004
	200.0	1.23[a]		
	200.2	1.21	0.80	0.003
	204.6	2.28	1.15	0.006
	209.8	3.32	0.45	0.002
	215.4	4.55	1.92	0.007

[a] Calculated from rate constants at other temperatures.

Hammett Plot.—Table II shows that, as the electron-withdrawing ability of the substituent increases, the activation energy ($\Delta G^{\pm}$) increases. The last three compounds in Table II do not fit into this generalization. They will be discussed later. Figure 1 shows

(5) M. Charton, *J. Amer. Chem. Soc.*, **86**, 2033 (1964).

(6) E. M. Kosower, "Physical Organic Chemistry," Wiley, New York, N. Y., 1968, p 49.

TABLE II

ACTIVATION PARAMETERS FOR THE DECARBOXYLATION OF 6-SUBSTITUTED 2-PYRIDINECARBOXYLIC ACIDS IN 3-NITROTOLUENE

Acid	$\Delta G_{200}^{\ddagger}$, kcal/mol	E_{act}, kcal/mol	$\Delta H_{200}^{\ddagger}$, kcal/mol	$\Delta S_{200}^{\ddagger}$, cal/deg/mol	Coefficient varation	Standard deviation
6-Nitro-2-pyridinecarboxylic acid	(36.53)[a]		(38.60)	(+4.38)		
	36.52	39.54	37.66	+2.39	0.98	0.088
6-Chloro-2-pyridinecarboxylic acid	(35.99)		(38.72)	(+5.78)		
	35.99	39.66	37.78	+3.79	1.47	0.123
6-Bromo-2-pyridinecarboxylic acid	(35.77)		(36.89)	(+2.37)		
	35.77	37.83	35.95	+0.39	1.27	0.103
2-Pyridinecarboxylic acid	(33.71)		(35.60)	(+3.99)		
	33.71	36.54	34.66	+2.00	1.14	0.098
6-Methyl-2-pyridinecarboxylic acid	(33.63)		(40.34)	(+14.18)		
	33.63	41.28	39.40	+12.19	0.77	0.068
6-Acetamido-2-pyridinecarboxylic acid	(35.76)		(38.36)	(+5.50)		
	35.76	39.30	37.42	+3.51	0.46	0.039
6-Amino-2-pyridinecarboxylic acid	(36.59)		(41.73)	(+10.85)		
	36.60	42.67	40.79	+8.86	1.45	0.124
6-Methoxy-2-pyridinecarboxylic acid	(37.84)		(51.84)	(+29.61)		
	37.83	52.87	51.90	+27.62	1.99	0.173

[a] The quantities in parentheses are based on first-order kinetics (*i.e.*, $\Delta H^{\ddagger} = E_{act} - RT$). The quantities not in parentheses are based on apparent first-order kinetics (*i.e.*, $\Delta H^{\ddagger} = E_{act} - 2RT$).

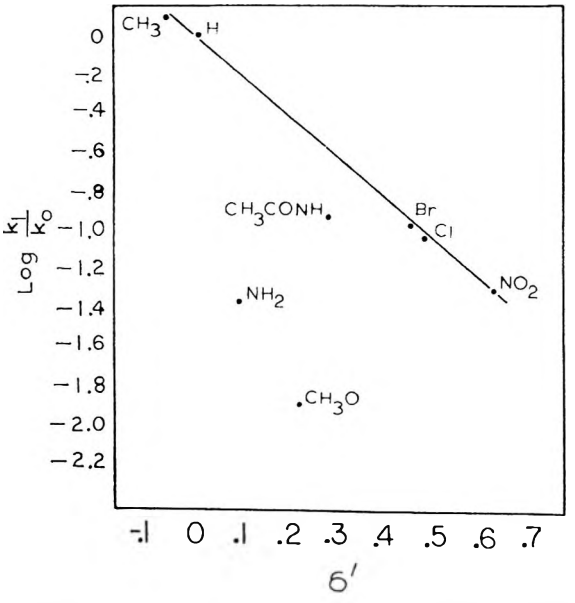


Figure 1.—A plot of σ' *vs.* log k_1/k_0 for the calculated rates of decarboxylation of 6-substituted 2-pyridinecarboxylic acids at 200°.

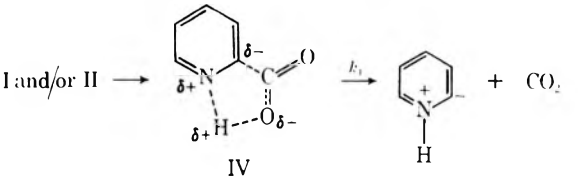
that a linear relation exists between the σ' values of CH_3, H, Br, Cl, and NO_2 and their relative rate constants. The slope of this line is −1.92. With a ρ value as large as this, it must indicate that a very large positive charge is developing in the transition state. This indicates that if IV is the transition state, then NH bond formation is slightly ahead of CC bond cleavage.

One of the results of a Hammett $\sigma\rho$ plot is that all compounds which fall on the plotted line must be decarboxylating by the same mechanism if the $\Delta S^{\ddagger}$ is relatively constant. We propose that 2-pyridinecarboxylic acid has the same transition state and feels the same electrical effects in the transition state as 6-methyl-, 6-chloro-, 6-bromo-, and 6-nitro-2-pyridinecarboxylic acids. The fact that the methyl group lies on the line may be fortuitous since the $\Delta S^{\ddagger}$ for this group is larger than for the other substituents. This proposed transition state is shown in Scheme III.

It must be pointed out that possibly these data could

SCHEME III

SUGGESTED INTERMEDIATES AND TRANSITION STATES FOR DECARBOXYLATION OF 2-PYRIDINECARBOXYLIC ACIDS



IV

be explained by kinetics of complex mechanisms involving equilibria. There are two reasons why the authors have not developed this idea further: (1) there are no data to support the idea that the equilibrium between the zwitterion and neutral molecule is affected by substitution on 2-pyridinecarboxylic acid in 3-nitrotoluene, and (2) if it can be assumed that the rate of approach to equilibrium is rapid as compared to the rate of decarboxylation, then the position of equilibrium between zwitterion and neutral molecule will have relatively no effect on which intermediate decarboxylates. However, further work is needed in these areas.

The 6-amino substituent does not fall on the straight line in Figure 1. Since the amino group is such a strong electron-releasing group by resonance, this could be used to explain its effect. However, if the effect of resonance could be simplified to only how much electron density the amino group donated to the ring nitrogen, then we would expect it to lie on the straight line similar to the methyl group. Since it does not, and the rate of decarboxylation of 6-amino-2-pyridinecarboxylic acid is slower than expected, resonance must have an opposing effect. At the present time this is not understood; however, it has already been pointed out that the 2-amino substituent does not correlate well with σ_I in the ionization of 2-substituted pyridines in water either.[5]

Sterically Hindered Decarboxylation.—Table II and Figure 1 show that 6-acetamido- and 6-methoxy-2-pyridinecarboxylic acids do not behave as the other substituted acids do. Taft has pointed out that failure of the Hammett equation for a particular substituent (or type of substituent) may result in a change in reac-

tion mechanism.[7] Both compounds have a much slower reaction rate than expected. Thus, the rotation of the substituent must be preventing the ring nitrogen and acid proton from interacting easily.

Kaneda and Hara have found that 2-pyridinecarboxylic acid and 2,6-pyridinedicarboxylic acid both decarboxylate at similar rates and the rate data do not fit equations for consecutive reactions.[8] Although they did not interpret it as such, this could be used as further evidence that transition state IV does lead to decarboxylation. An acid function at the 6 position would be expected to slow the rate of decarboxylation of the acid function at the 2 position as the 6-nitro group does, but, since there are two acid functions present in 2,6-pyridinedicarboxylic acid, either one can decarboxylate. Statistically then the rates of decarboxylation of 2-pyridinecarboxylic and 2,6-pyridinedicarboxylic acids could be equal. We would expect to observe no steric effect with the diacid since, when either proton was in the vicinity of the ring nitrogen, that particular acid function would decarboxylate.

Experimental Section

Starting material, unless otherwise specified, is 6-amino-2-methylpyridine purchased from Reilly Tar and Chemical Corp., Chicago, Ill. All of the compounds had satisfactory C, H, and N analyses and these are reported only for the new compounds. All melting points are uncorrected.

Preparation of 6-Nitro-2-pyridinecarboxylic Acid.—This compound was prepared as described in the literature[9] and has mp 168° (lit.[10] mp 168°).

Preparation of 6-Chloro-2-pyridinecarboxylic Acid.—This compound was prepared *via* diazotization[11] followed by oxidation[9] and has mp 190° (lit.[10] mp 190°).

Preparation of 6-Bromo-2-pyridinecarboxylic Acid.—This compound was prepared by M. B. Shambhu *via* diazotization[12] followed by oxidation[13] and had mp 189° (lit.[10] mp 189–190°).

Preparation of 2-Pyridinecarboxylic Acid.—This compound was prepared from 2-methylpyridine *via* oxidation[14] and had mp 131° (lit.[10] mp 132–133°).

Preparation of 6-Methyl-2-pyridinecarboxylic Acid.—This compound was prepared by Brown and Cantwell and is reported in the literature.[3] It had mp 128° (lit.[10] mp 129°).

Preparation of 6-Acetamido-2-pyridinecarboxylic Acid.—This compound was prepared by acetylation[15] followed by oxidation[16] and had mp 220–221° (lit.[10] mp 227–229°).

Preparation of 6-Methoxy-2-pyridinecarboxylic Acid.—This compound was prepared by M. B. Shambhu from 6-bromo-2-pyridinecarboxylic acid[17] and had mp 130°.

(7) R. W. Taft, in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, Chapter 13.

(8) T. Hara and A. Kaneda, *Sci. Eng. Rev. Doshisha Univ.*, **7** (4), 172 (1967).

(9) E. V. Brown, *J. Amer. Chem. Soc.*, **76**, 3167 (1954).

(10) E. P. Oliveto in "Heterocyclic Compounds," E. Klingsberg, Ed., Interscience, New York, N. Y., 1962, Chapter 10.

(11) E. V. Brown, *J. Amer. Chem. Soc.*, **79**, 3565 (1957).

(12) C. F. Allen and J. R. Thirtle, *Org. Syn.*, **26**, 16 (1946).

(13) H. Gilman and S. M. Spatz, *J. Org. Chem.*, **16**, 1485 (1951).

(14) G. Black, E. Depp, and B. B. Carson, *ibid.*, **14**, 14 (1949).

(15) S. M. McElvain, "The Characterization of Organic Compounds," Revised ed, Macmillan, New York, N. Y., 1964, pp 210–221.

(16) G. Ferrari and E. Marcon, *Farmaco, Ed. Sci.*, **14**, 594 (1959); *Chem. Abstr.*, **54**, 6709*a* (1960).

(17) R. Adams and T. Govindachari, *J. Amer. Chem. Soc.*, **69**, 1806 (1947).

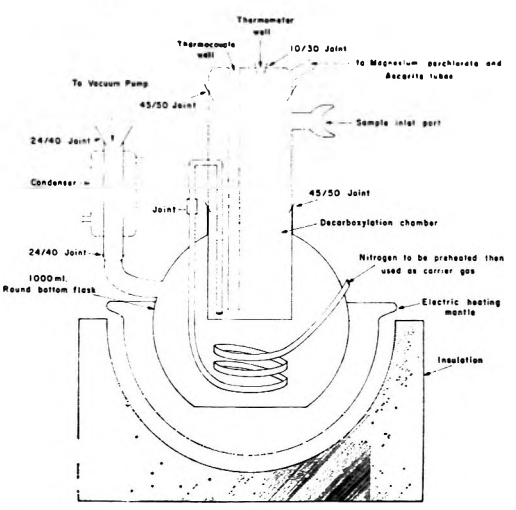


Figure 2.—A modified version of the decomposition apparatus described by E. G. Prout and F. C. Tomplins [*Trans. Faraday Soc.*, **40**, 488 (1944)] was used in this study. The round-bottomed flask contains any suitably boiling solvent, usually methyl salicylate, 1,4-dicyanobutane, or *p*-cymene.

Anal. Calcd for $C_7H_7O_3N$: C, 54.8; H, 4.6; N, 9.2. Found: C, 54.4; H, 4.5; N, 8.9.

Preparation of 6-Amino-2-pyridinecarboxylic Acid.—This compound was prepared from 6-acetamido-2-pyridinecarboxylic acid[16] and had mp 320° (lit.[10] mp 317–319°).

Procedure.—In each experiment 80 ml of 3-nitrotoluene were poured into the decarboxylation chamber (Figure 2). The heating mantle, vacuum pump, and carefully regulated stream of nitrogen carrier gas were turned on. The boiling point of the refluxing liquid was adjusted to the desired temperature by manipulation of the rheostat governing the heating mantle and manostat governing the pressure above the refluxing liquid. This took about 2.5 hr. When the thermometer and thermocouple both measured the desired temperature, the magnesium perchlorate drying tube and ascarite tubes connected to a three-way stopcock were arranged in two sets to alternate. The two ascarite tubes were filled with ascarite and weighed about 25 g each. Nitrogen was allowed to pass through each ascarite tube about 20 min, and then each ascarite tube was weighed on an analytical balance. Enough acid was weighed out in a glass boat to deliver about 0.0500 g of carbon dioxide. The boat and sample were then pushed into the sample inlet port and allowed to fall into the hot 3-nitrotoluene. The weighing of the first ascarite tube was always taken 10 min after the sample was dumped into the solvent. This was taken as zero time, and then the ascarite tubes were weighed alternately. The carbon dioxide absorbed every weighing was subtracted from that known to have been present in the acid at zero concentration. The logarithm of the decrease of carbon dioxide *vs.* time was plotted and a straight line was obtained. On the average, six readings were taken for each experiment and, in most cases, the reaction was allowed to proceed to greater than 50% completion. Reaction rates were taken for each acid over a 20° range at approximately 5° intervals.

Registry No.—6-Nitro-2-pyridinecarboxylic acid, 26893-68-5; 6-bromo-2-pyridinecarboxylic acid, 21190-87-4; 6-chloro-2-pyridinecarboxylic acid, 4684-94-0; 2-pyridinecarboxylic acid, 98-98-6; 6-acetamido-2-pyridinecarboxylic acid, 26893-72-1; 6-methyl-2-pyridinecarboxylic acid, 934-60-1; 6-methoxy-2-pyridinecarboxylic acid, 26893-73-2; 6-amino-2-pyridinecarboxylic acid, 23628-31-1.

Direct Conversion of *N*-Methylindoles into Indoxyl, Oxindole, and Dioxindole *O*-Benzoates*

YUICHI KANAOKA, MASATO AIURA, AND SACHIKO HARIYA

Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo, Japan

Received July 9, 1970

Benzoyl peroxide in benzene solution at room temperature converts indoles into indoxyl, oxindole, and dioxindole *O*-benzoates. The mono- and di-*O*-benzoates of 1-methylindoxyl, 1,2-dimethylindoxyl, 1,3-dimethyloxindole, and 1-methyldioxindole were prepared from the corresponding *N*-methylindoles by this convenient one-step procedure in yields of 10–80% depending on the ratio of substrate to reagent. The mechanism is discussed in terms of both homolytic and heterolytic cleavage of the reagent.

Oxidative transformations of the pyrrole moiety of indoles involve both the 2 and 3 positions, leading to oxindoles and indoxyls, respectively. In 1952 Witkop, *et al.*, investigated and reviewed *in vitro* and *in vivo* oxidation of indole compounds with emphasis on natural substrates and biologically important substances, such as tryptophan and its derivatives.[1]

Oxindoles can be directly obtained from indoles. Witkop oxidized certain 3-substituted indoles to the corresponding oxindoles either by hydrogen peroxide in acetic acid or by *N*-bromosuccinimide.[2] The same conversion is possible by chlorination or bromination and subsequent hydrolysis.[3] The oxidation of indole is difficult to arrest at the indoxyl stage, because it is so sensitive to autoxidation. The only known *direct* synthesis of indoxyl acetate from indole proceeds by 3-iodination of indole followed by solvolysis.[4] Dioxindoles can be obtained by oxidation of 3-alkylated oxindoles or indoles.[5] The present paper describes the direct formation of indoxyl, oxindole, and dioxindole *O*-benzoates by oxidation of indoles with benzoyl peroxide.

Thermal decomposition of diacyl peroxide provides a convenient source of aryl radicals for the arylation of aromatic substrates.[6a,7a] For example, thermolysis of benzoyl peroxide **1** yields two benzoyloxy radicals **2**, some of which, by loss of carbon dioxide, yield phenyl radicals **3** which participate in the arylation reaction, usually by way of a σ complex **5** with radical character, to give phenyl products **7**. Alternatively, benzoyloxy radical **2** also reacts with aromatic substrates to give esters by way of a related σ complex **4**, which loses a hydrogen atom in the presence of appropriate hydrogen acceptors to form benzoyloxy products **6**. In homolytic substitution of aromatics with benzoyl peroxide, usually phenylation to **7** is a major reaction accompanied by benzoyloxylation to form **6** as a side reaction. Benzoyloxylation increases with the reactivity of the aromatic substrates toward homolytic attack.[6b] For example, with reactive substrates, such as naphthalene[8,9] and other polynuclear aromatics,[9,10] benzoyloxylation becomes an important pathway. Appreciable benzoyloxylation is also observed with anisole[11] and trimethoxybenzene.[12]

Excess 1-methylindole **8** was heated with benzoyl peroxide **1** at 80° for 17 hr following a standard procedure of aromatic phenylation.[6a,7b] Phenylated indoles expected from "normal" homolytic aromatic substitution with **1** were not detected. Instead, the only isolable product (56% yield) arising from **8** was a crystalline ester of benzoic acid with an indole chromophore of the composition $C_9H_8N + C_7H_5O_2$, *m/e* 251, a 1:1 reaction product. Structure **9**, 1-methylindoxyl benzoate, was supported by the nmr data [δ 7.4 (1 H), singlet, $CDCl_3$; 2 H of indole] and the ir spectrum (1720 cm^{-1}, ester). The assignment was confirmed by an independent synthesis, *viz.*, thermal cyclization of *N*-methyl-*N*-(α-carboxyphenyl)glycine (**11**) in the presence of benzoic anhydride, an adaptation of the known synthesis of its acetyl analog.[13] Benzoyloxylation of indole itself was difficult to control and the results were inconclusive. Apparently the abstraction of H· from the free NH group of indole leads to side reactions. When aromatic hydrocarbons react with benzoyl peroxide, benzoyloxylation usually supervenes at lower temperature, where the benzoyloxy radicals decarboxylate more slowly. When the reaction of **8** with **1** was repeated in benzene solution at room temperature, preparative tlc gave a small amount (4%) of a new crystalline product in addition to a lower yield of **9** (Table I). Elemental analysis and mass spectrometry (*m/e* 371) established formula $C_{23}H_{17}NO_4$, *i.e.*, a 1:2 ratio for this new reaction product. In support of the structure of 1-methyldioxindole dibenzoate, the nmr spectrum of **10** lacked the characteristic signals of the 2- and 3-indole protons.[14] Since oxindole benzoate was not detected in the reaction mixture, the formation of **10** may be explained by subsequent benzoyloxylation of initially formed **9**. In fact, **9** was directly converted into **10** in 8% yield on treatment with **1**. When an equimolar mixture of **8** and **1** was allowed to react at room temperature for 2 days, **9** was produced in 21% yield based on the starting indole. Benzoyloxylation at 50° slightly raised this yield. Yields of up to 64% of **9** were obtained when pyridine was used as a solvent. The results are summarized in Table I.

* Correspondence should be addressed to Dr. Bernhard Witkop, Public Health Service, National Institutes of Health, Bethesda, Md. 20014.

(1) A. Ek, H. Kissman, J. B. Patrick, and B. Witkop, *Experientia*, **8**, 36 (1952), and papers cited therein.

(2) B. Witkop, *Justus Liebigs Ann. Chem.*, **558**, 98 (1947); W. B. Lawson and B. Witkop, *J. Org. Chem.*, **26**, 263 (1961).

(3) W. B. Lawson, A. Patchornik, and B. Witkop, *J. Amer. Chem. Soc.*, **82**, 5918 (1960).

(4) R. D. Arnold, W. M. Nutter, and W. L. Stepp, *J. Org. Chem.*, **24**, 117 (1959).

(5) E. C. Kendall and A. E. Osterberg, *J. Amer. Chem. Soc.*, **49**, 2047 (1927).

(6) (a) G. H. Williams in "Homolytic Aromatic Substitution," Pergamon Press, London, 1960, p 34; (b) p 116.

(7) (a) W. A. Pryer in "Free Radicals," McGraw-Hill, New York, N. Y., 1966, p 253; (b) p 91.

(8) R. L. Dannley and M. Gippin, *J. Amer. Chem. Soc.*, **74**, 332 (1952).

(9) D. E. Davies, D. H. Hey, and G. H. Williams, *J. Chem. Soc.*, 1878 (1958).

(10) I. M. Roit and W. A. Waters, *ibid.*, 2695 (1952).

(11) B. M. Lynch and R. B. Moore, *Can. J. Chem.*, **40**, 1461 (1962).

(12) P. L. Pauson and B. C. Smith, *J. Org. Chem.*, **18**, 1403 (1953).

(13) L. Ettinger and P. Friedländer, *Ber.*, **45**, 2074 (1912).

(14) L. A. Cohen, J. W. Daly, H. Kny, and B. Witkop, *J. Amer. Chem. Soc.*, **82**, 2184 (1960).

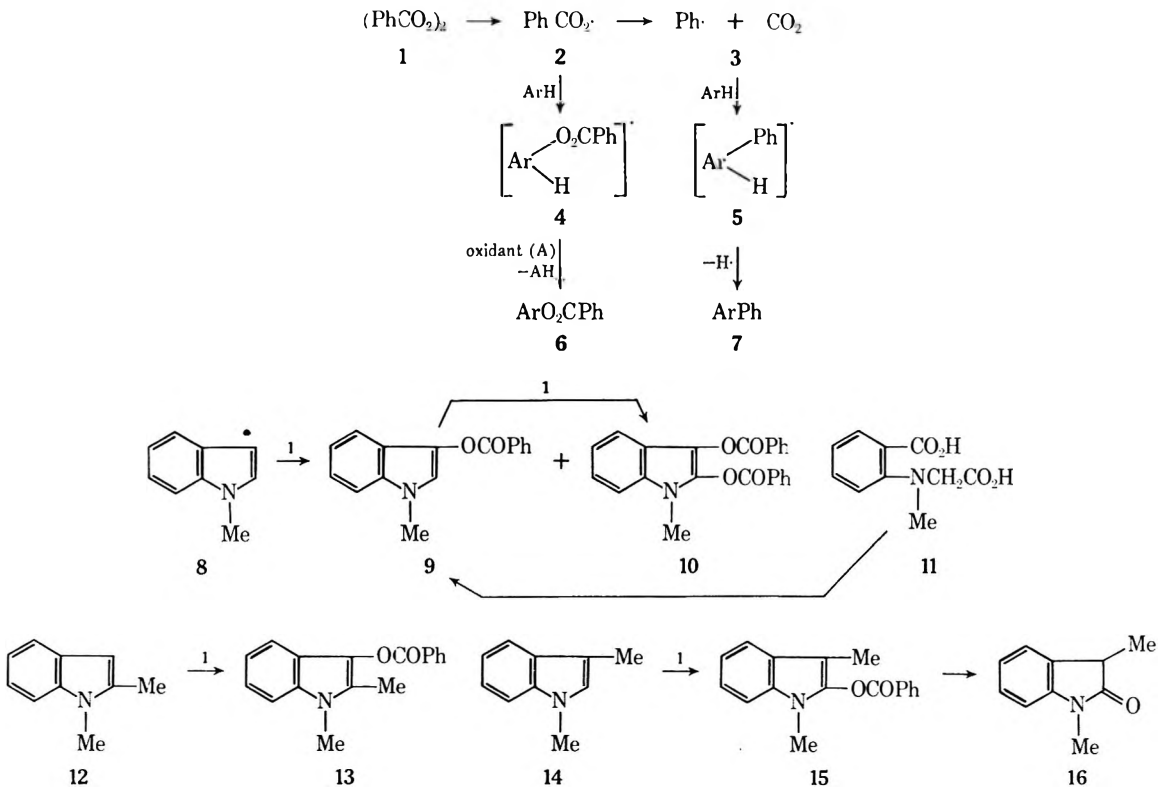


TABLE I
BENZOYLOXYLATION OF INDOLES

Expt no.	Substrate	Ratio[a]	Solvent[b]	Temp,[c] °C	Time, hr	Product,[d] yield[e] 2-OBz	3-OBz	2,3-(OBz)2	Benzoic acid
1	8	8		80	17		56		94
2	8	5	B	R	24		33	4	136
3	8	1	B	50	77		27	15	106
4	8	1	B	R	48		21	10	125
5	8	1	P	R	24		64	5	123
6	12	8		65	1.5		60		63
7	12	5	B	R	2		81		106
8	12	1	B	R	1		50		88
9	14	5	B	R	5	43			128
10	14	1	B	R	3	28			112
11	14	1	B[f]	R	4	15			152
12	14	1	P	R	5	62			156
13	9	1	B	R	96				158

[a] Substrate *vs.* reagent (mole). [b] B, benzene; P, pyridine; the atmosphere is nitrogen, unless otherwise stated. [c] R, room temperature. [d] Bz, benzoyl. [e] Mole per cent based on **3**. [f] Oxygen was bubbled through the reaction mixture.

The oxidation of 1,2- and 1,3-dimethylindole, **12** and **14**, was next examined to study the influence of alkyl substituents on benzoyloxylation. When **12** reacted with **1** at 65°, the expected 1,2-dimethylindoxyl *O*-benzoate **13** was isolated as the sole nitrogen-containing product. Elemental analysis, spectral data, the parent molecular ion (*m/e* 265), ir (1735 cm^{-1}, ester), and nmr spectra (no signal for 3 H) supported structure **13**. At room temperature the yield was raised to 81% based on the amount of **1**. An experiment with an equimolar mixture of substrate and reagent gave the indoxyl **13** in 50% yield based on the starting indole **12**.

When a benzene solution of **14** reacted with **1** at room temperature, the 1:1 reaction product **15** was obtained in moderate yield. Structure **15** was supported by analytical data and mass (*m/e* 265) and ir (1750 cm^{-1}, ester) spectra. Alkaline hydrolysis liberated authentic 1,3-dimethyloxindole (**16**).[15] With 1 equiv of **1** the indole **14** was converted to the oxindole **15** in 28% yield. When pyridine was employed as a solvent, oxindole **16** was obtained as the major product apparently as the result of hydrolysis of the benzoate **15** in the course of work-up.

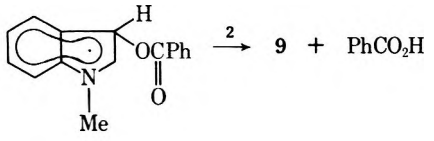
Certain diacyl peroxides have recently found application as oxygenating agents of aromatic substrates particularly in conjunction with another oxidant. The prototype of this reaction is the formation of alkenyl benzoates from olefins with **1** and copper salts.[16] Kovacic, *et al.*, have developed a diisopropyl peroxydicarbonate–aromatic–cupric chloride system as an effective oxy-

(15) P. L. Julian, J. Pikl, and D. Boggess, *J. Amer. Chem. Soc.*, **56**, 1797 (1934).

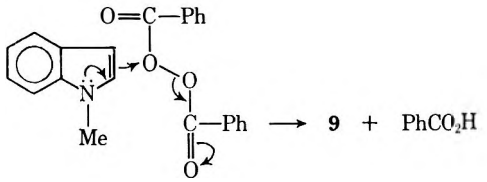
(16) M. Kharasch and A. Fono, *J. Org. Chem.*, **24**, 606 (1956); J. K. Kochi, *J. Amer. Chem. Soc.*, **84**, 1572 (1962).

genating agent.[17] A related aromatic–benzoyl peroxide–iodine system has been proposed for aromatic benzoyloxylation.[18,19]

Probably benzoyloxy radical 2 is the species which accepts a hydrogen radical from an intermediate **17**. This inference is supported by good recovery of benzoic acid (Table I), which may arise both from 2 by abstraction of a hydrogen atom from **17** and by heterolytic cleavage of **18** → **9**. Studies on the mechanism of these



17



18

reactions are in progress. Since this benzoyloxylation procedure affords a simple, one-step method for preparation of oxygenated indoles in acceptable yields, this may open a new route to hydroxyindoles. The scope of these reactions is currently under investigation.

Experimental Section[20]

1-Methylindoxyl *O*-Benzoate (9) (Expt 1, at 80°).—A mixture of 1-methylindole (**8**) (4.2 g, 32 mmol) and **1** (1.0 g, 4 mmol) was heated at 80° for 17 hr in an atmosphere of N_2. After cooling, benzene was added to the mixture, which was extracted with a saturated aqueous solution of $NaHCO_3$ to remove benzoic acid. On acidification of the aqueous layer benzoic acid (460 mg) was obtained. The organic layer was washed with water, dried (Na_2SO_4), and concentrated *in vacuo* to leave **9** as colorless needles (180 mg). The filtrate was evaporated *in vacuo* and the residue was distilled *in vacuo* to remove unreacted **8** (3.2 g). When ether was added to the residue, a second crop of **9** (270 mg) was isolated. The residue obtained on removal of ether was subjected to preparative tlc (benzene–hexane, 1:1). With the isolation of an additional fraction of **9** (120 mg), the total yield of **9** was 570 mg or 56%. Recrystallization from ethyl acetate gave colorless needles: mp 133–133.5°; uv λ_{max} (CH_3CN) 226 mμ (log ε 4.64), 277 (shoulder, 3.85), 283 (3.88), 290 (shoulder, 3.87).

Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.47; H, 5.22; N, 5.57. Found: C, 76.40; H, 5.34; N, 5.68.

1-Methyldioxindole Dibenzoate (10) and 1-Methylindoxyl *O*-Benzoate (9) (Expt 2, at Room Temperature).—A solution of **8** (2.0 g, 15 mmol) in benzene (3 ml) was mixed with **1** (740 mg, 3 mmol) at room temperature and the mixture stirred in an atmosphere of N_2 for 24 hr. The reaction mixture was washed with aqueous $NaHCO_3$ to remove benzoic acid (450 mg). The organic layer was washed with water, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was distilled *in vacuo* to remove unreacted **8** (1.4 g). The residue, after preparative tlc (benzene), gave **8** (250 mg) and **10** (40 mg). The latter was recrystallized from benzene–hexane to give almost colorless fine prisms: mp 155–155.5°; uv λ_{max} (CH_3CN) 229 mμ (log ε 472), 279 (4.03); ir ν_{max}^{Nujo} 1740, 1755 cm^{-1} (ester); nmr (CCl_4) no indolic 2 H and 3 H; mass spectrum *m/e* 271.

Anal. Calcd for $C_{23}H_{17}NO_4$: C, 74.38; H, 4.61; N, 3.17. Found: C, 74.40; H, 4.65; N, 3.92.

In expt 3 and 4, 1-methylindole (**8**, 400 mg, 3 mmol) was reacted with **1** (740 mg, 3 mmol) in benzene (3 ml) solution, at 50° and at room temperature, respectively. The organic layer was washed with water, dried (Na_2SO_4), and evaporated *in vacuo*. The residue after preparative tlc (benzene) yielded **9** and **10**. In expt 5, after the evaporation of pyridine *in vacuo* and the addition of benzene, the work-up was as above.

Independent Synthesis of 1-Methylindoxyl *O*-Benzoate (9).—*N*-Methyl-*N*-(α-carboxyphenyl)glycine (**11**), prepared as described in the literature,[13] formed colorless plates from water, mp 180–185° (lit.[13] mp 189°). A mixture of **11** (209 mg, 1 mmol), benzoic anhydride (2.3 g, 10 mmol), and sodium benzoate (144 mg, 1 mmol) was heated at 190° (bath temperature) for 4 hr. After cooling, dichloromethane was added and the solution was washed with aqueous $NaHCO_3$ and water, dried (Na_2SO_4), and evaporated *in vacuo*. Distillation *in vacuo* removed excess benzoic anhydride, and the residue, after preparative tlc (benzene–hexane, 2:3), gave **9** as colorless needles from ethyl acetate, mp 133–133.5°. This sample showed no depression of melting point on admixture with the compound obtained in expt 1. Their ir spectra were superimposable.

1,2-Dimethylindoxyl *O*-Benzoate (13). **A** (Expt 6, at 65°).—1,2-Dimethylindole (**12**) (1.16 g, 8 mmol) was melted at 50° and to the melt **1** (242 mg, 1 mmol) was added portionwise (N_2). A vigorous reaction took place. The mixture was heated at 65° (bath temperature) for 4 hr. Ether was added and the mixture extracted with aqueous $NaHCO_3$ to remove benzoic acid (77 mg). The organic layer was washed with water, dried (Na_2SO_4), and evaporated. After tlc (benzene–hexane, 1:1), **13** was obtained as colorless prisms (160 mg) from ethyl acetate: mp 135.5–136.5°; uv λ_{max} (CH_3CN) 229 mμ (log ε 4.68), 277 (shoulder, 3.89), 283.5 (3.93), 292 (shoulder, 3.88); ir ν_{max}^{Nujol} 1735 cm^{-1} (ester); nmr, no 3 H of indole; mass spectrum *m/e* 265.

Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.83; H, 5.66; N, 5.27.

B. At Room Temperature (Expt 7).—To a solution of **12** (2.2 g, 15 mmol) in benzene (3 ml) was added **1** (740 mg, 3 mmol) with stirring at room temperature in an atmosphere of N_2. A slightly exothermic reaction took place. After stirring for 2 hr the mixture was washed first with aqueous $NaHCO_3$ to remove benzoic acid (380 mg) and then with water and dried (Na_2SO_4). After removal of the solvent distillation *in vacuo* gave unreacted **12** (1 g). The resultant residue was recrystallized from dichloromethane–hexane to give **13** (470 mg). Additional **13** (170 mg) was obtained from the mother liquor by tlc, total yield 640 mg. Experiment 8 was performed in a similar manner.

1,3-Dimethyloxindole Benzoate (15) (Expt 9).—To a solution of **14** (2.2 g, 15 mmol) in benzene (3 ml) was added **1** (740 mg, 3 mmol) with stirring at room temperature for 5 hr. The reaction mixture was worked up as in expt 2. After tlc (benzene), **15** was obtained as colorless crystals (340 mg) from benzene–hexane: mp 105–106°; uv λ_{max} (CH_3CN) 230 mμ (log ε 4.67), 278–280 (3.94), 290 (shoulder, 3.85); ir ν_{max}^{Nujol} 1755 cm^{-1} (ester); nmr, no 2 H of indole; mass spectrum *m/e* 265.

Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 77.11; H, 5.77; N, 5.25.

Experiments 10 and 11 were performed similarly except that vacuum distillation to recover starting material was unnecessary. Experiment 12 was performed as expt 5 to give **15** (110 mg) and **16** (230 mg).

Hydrolysis of 15 to 1,3-Dimethyloxindole (16).—To a solution of **15** (93 mg) in a mixture of methanol (0.9 ml) and tetrahydrofuran (0.3 ml) was added dropwise 0.35 *N* NaOH–methanol (1 ml) with stirring. After the addition, formic acid was immediately added to neutralize excess alkali. The mixture was evaporated *in vacuo* to remove methanol. Ether was added and the organic layer was washed with water, dried (Na_2SO_4), and evaporated (the residue after tlc (dichloromethane) gave **16** as colorless oil (33 mg) (the ir spectrum of this sample was superimposable with that of an authentic specimen): bp 133–135° (11 mm) [lit.[14] bp 136–138° (11 mm)]; ir λ_{max}^{neat} 1720 cm^{-1} (carbonyl of oxindole); mass spectrum *m/e* 161.

Registry No.—**9**, 26595-98-2; **10**, 26595-99-3; **13**, 26596-00-9; **15**, 26596-01-0.

(17) (a) P. Kovacic and M. E. Kurz, *Tetrahedron Lett.*, 2689 (1966); (b) M. E. Kurz, P. Kovacic, A. K. Bose, and I. Kugajevsky, *J. Amer. Chem. Soc.*, **90**, 1818 (1967); (c) P. Kovacic, C. G. Reid, and M. E. Kurz, *J. Org. Chem.*, **34**, 3302 (1969).

(18) R. Perret and R. Perret, *Helv. Chim. Acta*, **28**, 558 (1945).

(19) S. Hashimoto, W. Koike, and M. Yamamoto, *Bull. Chem. Soc. Jap.*, **42**, 2733 (1969).

(20) Melting and boiling points are uncorrected. Preparative thin layer chromatography (tlc) was performed on silica gel.

New Synthesis of 4-Aryl-2,3-dihydro- and 2,3,4,5-Tetrahydro-2(1*H*)-benzazepines and Corresponding 1,3-Diones

GORDON N. WALKER* AND DAVID ALKALAY

Research Department, CIBA Pharmaceutical Company, Inc., Division of CIBA Corporation, Summit, New Jersey 07901

Received May 28, 1970

Phthalaldehydic acid condenses with arylacetonitriles in the presence of sodium methoxide to give, after acidification, cyanostilbene acids, **1**. These and corresponding products **2** of hydrogenation (Pd) are cyclized respectively to seven-membered imides **3** and **4**. These two imide types, as well as their respective *N*-alkyl analogs **5** and **6**, were interrelated and their structures proven by hydrogenations **3** → **4** and **5** → **6**; hydride reductions of various alkylated imides were also carried out, giving a variety of new, 2- and 4-substituted 2,3,4,5-tetrahydro-2(1*H*)-benzazepines. Basic, solvolytic ring opening of the two novel imide systems, affording additional evidence of structure, is discussed briefly.

Owing to the frequently predominant formation of tetrahydro-1-benzazepin-2-ones in either Schmidt or Beckmann expansions of α-tetralones, 2,3,4,5-tetrahydro-2(1*H*)-benzazepin-1-ones are not often readily available by such routes.[1,2] Whereas various 1,4-naphthoquinone-derived azides have been expanded similarly in both possible directions, only the 1-benzazepine-2,4,5-triones survive the conditions of the reaction, the 2-benzazepine-1,3,5-triones collapsing to ylidenephthalimidines or -phthalides.[3,4] Although a few synthetic approaches, other than ring expansion, to tetrahydro-2-benzazepines and corresponding ones are now known,[5-7] they do not appear to be general, and thus a new route to 2-benzazepines would be potentially valuable. Such a route is described in this paper.

Phthalaldehydic acid is comparable to acid chlorides in its ease of reaction with nucleophiles,[8] including carbanions.[9] We explored, among other things, condensation of phthalaldehydic acid with phenylacetonitriles, a previously unreported reaction (see Scheme I). Sodium methoxide was used to generate the arylacetonitrile anion, no stronger bases appearing to be required or to serve our purpose as well. In its first stages, this facile reaction, like others of the type, apparently is reversible. Several experiments in which manipulations under various conditions were tried led, in one instance upon neutralization of the reaction mixture, to isolation of a phthalide corresponding to the intermediate aldol (see Scheme I), and in other instances wherein work-up involved basic, aqueous conditions, to regeneration of much phenylacetonitrile. However, if reaction solutions, after condensation, were acidified *before* water was introduced, good yields of cyano acids **1a–f** were obtained.

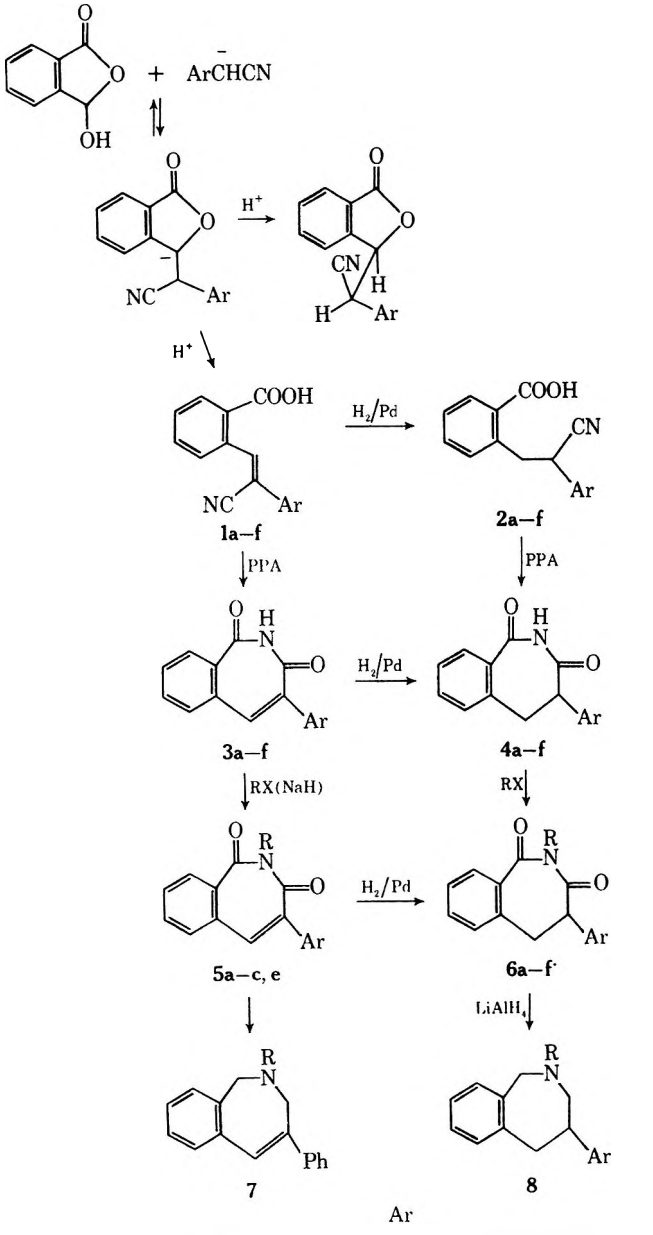
These compounds were reduced smoothly in the presence of palladium/charcoal to cyano acids **2a–f**. Preliminary experiments with acetic anhydride on **2a** yielded only the anhydride corresponding to **2a**, and there was neither internal acylation of the methine adjacent to CN nor imide formation The conversion of benzamide-2-thioacetic acid to 1,4-benzthiazepine-3,5-dione with acetic anhydride[10] or thionyl chloride,[11] as well as the formation of thianaphthenones from benzoic acid–2-thioacetamides with acetic anhydride and bases,[10] have been reported, but such reactions are not prone to occur in compounds **2**. However, polyphosphoric acid cyclization at 100° was found to convert cyano acids **2** readily to 2,3,4,5-tetrahydro-2(1*H*)-benzazepine-1,3-diones, **4**. Evidence, in addition to spectra, in agreement with the cyclic imide structure was soon forthcoming. Compounds **4** had, like phthalimide, an acidic imide proton, and in the presence of such bases as sodium hydride or potassium *tert*-butoxide were alkylated readily with iodomethane and other halides, giving *N*-alkylimides **6**, and these in turn were readily reduced with lithium aluminum hydride to the cyclic amines, 2,3,4,5-tetrahydro-2(1*H*)-benzazepines, **8**. A number of compounds, **2**, **4**, **6**, and **8**, Ar being various substituted phenyl groups and pyridyl as indicated in Scheme I, and R being H, CH_3, benzyl, other aralkyl, CH_2COOR, and β- or γ-dialkylaminoethyl or -propyl groups, were easily prepared.

Cyano acids **1** were also found to by cyclized with PPA at 100°. The results were gratifying, not only inasmuch as they constituted a direct route to 2-benzazepine-1,3-diones and another route to **4**, **6**, and **8**, but also because they afforded desired indication of the stereochemistry of **1**. Heating **1a** with PPA gave **3a** with properties very similar to those of **4a**. Hydrogenation (Pd) of **3a** gave **4a**, just as **1** had given **2**. Moreover, N-methylation of **3a** to **5a** and reduction of the latter gave **6a**, identical with that from methylation of **4a**. This sequence, together with the fact that **5a** was reduced with lithium aluminum hydride to **7a**, dispelled any remaining doubts concerning the seven-membered imide structures.

The cyclization **1** → **3** demonstrates rather conclusively that cyano acids **1** are *trans*-stilbenes (*cis*-cinnamonitriles), *i.e.*, have that geometry which permits the benzoic acid group to rotate into proximity with the nitrile. This was not unexpected, since *trans*-stilbenes are normally the products of base-catalyzed condensations in which aldols or aldolates are intermediates;[12]

(1) J. A. Moore and E. Mitchell, *Heterocycl. Compounds*, **9**, 224 (1967).
(2) L. H. Werner, S. Ricca, A. Rossi, and G. de Stevens, *J. Med. Chem.*, **10**, 575 (1967).
(3) H. W. Moore and H. R. Shelden, *J. Org. Chem.*, **32**, 3603 (1967).
(4) H. W. Moore and H. R. Shelden, *Tetrahedron Lett.*, 5431 (1968); 1243 (1969).
(5) M. H. Sherlock, U. S. Patents 3,225,031 (1965); 3,242,164 (1966).
(6) H. Fujimura and M. Hori, U. S. Patent 3,409,607 (1968).
(7) I. MacDonald and G. R. Proctor, *J. Chem. Soc.*, 1321 (1969); 2481 (1968).
(8) D. D. Wheeler, D. C. Young, and D. S. Erley, *J. Org. Chem.*, **22**, 547 (1957).
(9) R. C. Elderfield, *Heterocycl. Compounds*, **2**, 68 (1951).
(10) E. W. McClelland, M. J. Rose, and D. W. Stammers, *J. Chem. Soc.*, 81 (1948).
(11) R. Ponci, A. Baruffini, and F. Gialdi, *Farmaco, Ed. Sci.*, **19**, 515 (1964).
(12) See G. N. Walker, *J. Med. Chem.*, **8**, 583 (1965), and references therein.

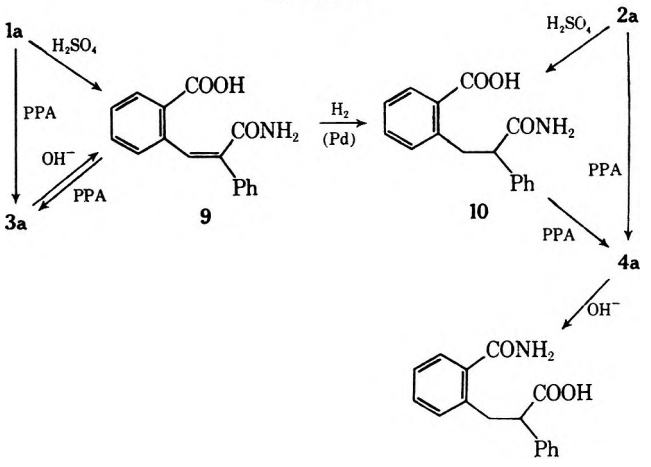
SCHEME I



furthermore, other investigators have prepared *cis*-cinnamonitrile having an *o*-carboxylic group by ring expansion of nitrosonaphthol,[13] and this acid nitrile subsequently was reported to be converted (PCl_5) to 3-chloro-2(1*H*)-benzazepin-1-one.[14]

Further evidence for structures of imides **3** and **4** and a clearer idea on mechanism of their formation from **1** and **2**, respectively, were obtained through some work with related acid amides. Treatment of **1a** with concentrated sulfuric acid did not give **3a** but rather an acid amide **9** (Scheme II). The same **9** was obtained by ring opening of imide **3a** by the action of aqueous bases stronger than sodium bicarbonate. On hydrogenation, **9** gave **10**; identical acid amide **10** and not **4a** was obtained through the action of concentrated sulfuric acid on **2a**. Base-catalyzed, hydrolytic ring opening of **4a**, however, did not give **10** but a different acid amide **11**. The saturated imides **4** thus open in a different sense than do the unsaturated imides **3**, pointing up the fact that phenylacetic acid derivatives are more liable to nucleophilic attack than are stilbene-α-carboxylic acid derivatives. While **9** and **10** were reclosed with PPA to respective imides as shown, compound **11** was not. Clearly the success of the seven-membered imide syntheses encountered here is owing to generation of a benzoylium ion from a benzoic acid moiety and its further, direct attack on nitrogen of a nitrile or carboxamide group, in molecules so constituted as *not* to present any opportunity for collapse under acidic conditions of the compounds into five- or six-membered rings.

SCHEME II



Experimental Section[15]

α′-Cyano-*trans*-stilbene-2-carboxylic Acid (1a).—To a solution of 12.6 g of sodium in 450 ml of methanol was added 64.5 g of phenylacetonitrile and then, 10–20 min later at room temperature, 75 g of phthalaldehydic acid. The solution was boiled 0.5–1.0 hr on a steam cone, allowing 50–75% of the solvent to escape. The chilled solution was neutralized by adding glacial acetic acid, acidified strongly with concentrated HCl and poured into ice water (2 l.). Alternatively, the reaction solution was poured directly into 2 l. of ice and water containing 75 ml of concentrated HCl. The colorless, very voluminous crystals were collected, washed with water, pressed dry on the filter, and then dissolved in EtOAc. The organic solution upon drying ($MgSO_4$) and evaporating gave 101 g (81%) of **1a**: mp 175–176°, raised on recrystallization (EtOAc) to mp 178–180°; ir 4.47 and 5.91 μ; uv 302 nm (ε 14,450).

Anal. Calcd for $C_{16}H_{11}NO_2$: C, 77.09; H, 4.45; N, 5.62. Found: C, 77.14; H, 4.62; N, 5.66.

Unless the cooled reaction solution was acidified, as described, before adding water, lower yields of **1a** were obtained and much phenylacetonitrile was recovered, owing to hydroxide-catalyzed, reverse aldol reaction. In one experiment the reaction mixture was neutralized soon after addition to water, and from an ether-washed, aqueous $NaHCO_3$ extract of crude product on careful treatment with dilute acid there was isolated crystalline **3-(α-cyano-α-phenylmethyl)phthalide**, mp 207–209°, after recrystallization from EtOAc: ir 4.45 and 5.69 μ; uv 280 and 302 nm (ε 4540 and 4410); nmr ($CDCl_3$) *J* (of the two benzhydryl protons) was 4 Hz, indicating threo form. On treatment with hydrochloric acid this compound gave **1a**.

Anal. Calcd for $C_{16}H_{11}NO_2$: C, 77.09; H, 4.45; N, 5.62. Found: C, 77.37; H, 4.31; N, 5.62.

(13) J. A. Elvidge and D. E. H. Jones, *J. Chem. Soc.*, 2059 (1967).
(14) G. Simchen, *Angew. Chem.*, **80**, 484 (1968).

(15) Melting points were obtained using a calibrated, Thomas–Hoover stirred silicone oil bath. Infrared spectra (Nujol mulls, unless otherwise noted) were taken on a Perkin-Elmer double beam instrument, ultraviolet spectra (methanol solutions) with a Cary recording spectrophotometer, and nmr spectra using a Varian A-60 apparatus with TMS internal standard.

TABLE I

ACID NITRILES

Acid	Mp, °C	Ir, λ, μ	Uv, λ_{max}, nm (ε)	Recrystn solvent[a]	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1b	191–193	4.49, 5.95	309 (17,070)	a	77.55	4.98	5.32	77.55	4.69	5.06
1c	193–195	4.49, 5.94	321 (16,850)	a	73.11	4.69	5.02	73.02	4.54	4.74
1d	210–212	4.49, 5.92	302 (14,300), 284	a	71.90	3.77	5.24	72.17	3.69	5.41
1e	232–234	4.48, 5.91	330 (14,290), 248 (13,260)	b	69.89	4.89	4.53	69.84	4.72	4.35
1f	255–257	4.50, 5.95	298 (14,820), 238 (11,630)	c[b]	71.99	4.03	11.20	72.10	3.99	11.19
2b	125–127	4.44, 5.96	272 (1530)	d	76.96	5.70	5.28	76.67	5.68	5.08
2c	115–118	4.44, 5.96	275 (3050), 282 (2780)	d	72.58	5.37	4.98	72.56	5.42	4.92
2d	157–158	4.46, 5.95	269 (2010)	d	71.36	4.49	5.19	71.63	4.33	5.23
2e	176–178	4.45, 5.92	279 (4940), 285 (4380)	a	69.44	5.50	4.50	69.70	5.57	4.41
2f	238–240	4.46, 5.95	261 (3870), 267 (3140)	b[b]	71.41	4.80	11.11	71.04	4.61	10.88

[a] Recrystallized from (a) EtOAc, (b) MeOH, (c) EtOH, (d) ether. [b] Mp dec.

Following essentially the same procedure as for **1a**, other α′-cyanostilbene-2-carboxylic acids **1b–f**, listed in Table I, were prepared from phthalaldehydic acid and appropriate, commercially available phenylacetonitriles, in yields of about 80–90%. Compounds **1e** and **1f** formed exceptionally insoluble sodium salts which were readily isolated. Neutralization (HCl) of a hot water solution of the sodium salt of **1f** gave crystalline **1f**.

The nmr spectra of cyano acids **1a–f** had *inter alia* δ *ca.* 7 ppm (s, 1) signals, characteristic of the *trans*-stilbene proton.

The methyl ester corresponding to **1e** was prepared by 3-hr reflux of a solution of **1e** (26 g) in saturated, methanolic HCl (1.5 l.). The neutral product (13 g) on recrystallization from methanol gave pale yellow needles: mp 132–133.5°; ir 4.48 and 5.86 μ; uv 331 (ε 14,320) and inflection 248 nm (ε 14,130).

Anal. Calcd for $C_{19}H_{17}NO_4$: C, 70.57; H, 5.30; N, 4.33. Found: C, 70.68; H, 5.15; N, 4.22.

o-(2-Cyano-2-phenylethyl)benzoic Acid (2a).—Hydrogenation of a solution of 11.1 g of **1a** in 300 ml of EtOAc in the presence of 4 g of 10% Pd/C catalyst at 3 atm and 60° for 40 min until uptake ceased or slowed abruptly gave, after filtration and evaporation of solvent, a quantitative yield of **2a**: crystals from ether; mp 122–124°; ir 4.50 and 5.92 μ; uv 278 nm (ε 1370) with lesser maxima at 257, 263, and 286 nm (ε 930, 980, and 1020, respectively).

Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.47; H, 5.22; N, 5.57. Found: C, 76.50; H, 5.16; N, 5.55.

On a larger scale, the sodium salt of **1a** in water (ten parts) was hydrogenated similarly at room temperature, and **2a** was obtained from the filtered solution on acidification.

The anhydride of **2a** was obtained when 5 g of **2a** was refluxed 1.5 hr with 100 ml of acetic anhydride; evaporation and recrystallization of the residue from EtOAc gave crystals, mp 176–178°, ir 4.48 and 5.64 μ.

Anal. Calcd for $C_{32}H_{24}N_2O_3$: C, 79.32; H, 4.99; N, 5.79. Found: C, 79.45; H, 4.89; N, 5.78.

The corresponding diacid, **o-carboxy-2-phenylhydrocinnamic acid**, was obtained by concentrated HCl–glacial HOAc hydrolysis (3.5-hr reflux) of **2a** and was recrystallized from ether (Norit), mp 193–195°, ir 5.86–5.92 μ.

Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.10; H, 5.07.

Cyano acids **2b–f** (Table I) were prepared by hydrogenation of **1b–f**, as for **2a**. Compound **2e** was difficult to obtain in large amounts owing to low solubility of **1e** in both organic solvents and aqueous bases.

The methyl ester corresponding to **2e** was obtained by similar hydrogenation of the methyl ester of **1e**: colorless crystals from ether; mp 100–102°; ir 4.47 and 5.82 μ; uv 280 nm (ε 4800) and infl 284 (4360).

Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.40; H, 6.02; N, 4.20.

4-Phenyl-2,3-dihydro-2(1*H*)-benzazepine-1,3-dione (3a).—A mixture of 30 g of **1a** and 500 g of polyphosphoric acid was heated at 100° with stirring for 2.5 hr. The cooled, brown solution was hydrolyzed with ice and water (2 l.), and the suspension of crystals was stirred at room temperature 1–2 hr. The product was collected, washed with several portions of water, and then triturated thoroughly with 5% sodium bicarbonate solution, again collected, washed with water, and dried, yield 23 g (76.5%), mp 207–209°. Recrystallization (ethyl acetate) gave colorless crystals: mp 211–213°; ir 3.16, 3.27 (bonded NH) and 6.06 with lesser peaks 5.92, 6.18, and 6.28 μ; uv 227 and 316 nm (ε 37,600 and 11,410) with inflections at 256 and 324 (12,080 and 11,310); nmr (DMSO) δ 11.4 (s, 1, D_2O exchanged, NH), 8.4 (m, 1, peri aromatic proton), 7.9–7.2 (m, 9, aromatic and vinyl H).

Anal. Calcd for $C_{16}H_{11}NO_2$: C, 77.09; H, 4.45; N, 5.62. Found: C, 77.20; H, 4.29; N, 5.45.

The imide was soluble in 5–10% sodium hydroxide solution and dissolved more slowly in potassium carbonate solution. On acidification of resulting solutions, there was obtained ***trans*-stilbene-2-carboxylic acid α′-carboxamide (9)**: mp 195–196° (solvated) after recrystallization from methanol–ether, and mp 184–186° after drying *in vacuo* (65°); ir 2.87 and 2.97 (intense, NH peaks), 5.85–5.91, 6.02, 6.17, and 6.32 μ; uv 254 nm (ε 10,490); nmr (DMSO) three D_2O-exchangeable protons. Treatment with PPA at 100° regenerated **3a**.

Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.90; H, 4.94; N, 5.11.

This same acid amide was obtained when 4 g of **1a** was dissolved in 100 ml of concentrated H_2SO_4; the solution was let stand 7 hr and hydrolyzed (ice), and the crystalline product recrystallized from EtOAc: mp 184–185°; mmp (with sample from imide) 184–185° (undepressed); and ir spectra the same.

By the same general procedure of action of PPA on cyano acids **1**, there were also obtained the following imides **3**.

Compound 3b was obtained from 15 g of **1b** with 500 g of PPA in 10.5 g yield and crystallized from ethyl acetate as colorless crystals: mp 198–200°; ir bonded NH and 6.09 μ (sharp, intense, with shoulder 6.05 μ and lesser peaks 6.22 and 6.28 μ); uv 225 and 327 nm (ε 58,080 and 12,660).

Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.29; H, 4.86; N, 5.36.

Compound 3c was similarly recrystallized from EtOAc as yellow crystals: mp 208–210°; ir 3.00, 5.96 and 6.03 μ; uv 228, infl 268, and 338 nm (ε 45,080, 10,340, and 12,120).

Anal. Calcd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 73.4; H, 4.4; N, 4.90.

Compound 3d was obtained as colorless crystals from EtOAc: mp 196–197°; ir 3.14 (bonded), 5.94 and 6.05 μ; uv 226 nm (ε 38,080), infl 256 (12,710), and 316–324 (11,900).

Anal. Calcd for $C_{16}H_{10}FNO_2$: C, 71.90; H, 3.77; N, 5.23. Found: C, 72.2; H, 3.59; N, 5.08.

Compound 3e was obtained as light greenish yellow, dense crystals, from EtOAc: mp 223.5–226°; ir 3.19, 3.31, 5.96, 6.06, 6.15, and 6.26 μ; uv 224 nm (ε 37,810), 262–272 (12,850), 330 (9280), and infl 344 (8990); nmr (DMSO) δ 11.3 (broad s, 1, D_2O exchanged, NH), 8.3 (m, 1, peri aromatic H), 7.8–6.8 (m, 7, aromatic and vinyl H), and 3.8 (s, 6, methoxyl CH_3).

Anal. Calcd for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 69.66; H, 4.86; N, 4.43.

Compound 3f.—After heating 10.3 g of **1f** and 74 g of PPA at 100° for 3 hr, addition of water to the cooled solution gave a very voluminous, colorless solid (9 g), mp >320°, which appeared to be a phosphate salt of **3f**. Treatment of this solid with saturated $NaHCO_3$ solution, followed by warm methanol trituration of the collected washed and dried crystals, and finally recrystallization from ethanol or methanol, gave colorless crystals: mp 249–251°; ir 5.93 and 6.08 μ; uv 228 nm (ε 30,460) and 306 (12,840) with infl 256 (14,590).

Anal. Calcd for $C_{15}H_{10}N_2O_2$: C, 71.99; H, 4.03; N, 11.20. Found: C, 71.62; H, 4.20; N, 11.20.

2-(β-Phenylethylbenzoic acid)-β-carboxamide (10). A.—Sulfuric acid (100 ml, concentrated) solution of **2a** (10 g) after standing overnight was poured over ice, and the crystalline, bicarbonate-soluble product was collected, washed with water, dried, and recrystallized from ethyl acetate: colorless crystals; mp 203–205°; ir 2.93, 3.14, and 5.94–6.03 μ (doublet); uv 278 nm (ε 1440).

Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.13; H, 5.72; N, 5.09.

B.—Hydrogenation of 3 g of *trans*-stilbene-2-carboxylic acid α′-carboxamide in the presence of 2 g of 10% Pd/C catalyst in 275 ml of EtOAc and 10 ml of MeOH for 2 hr at 3 atm and 70° gave, on evaporation of the filtered solution, 2.6 g of crystals, mp 204–207°, mixture melting point with A product undepressed, and ir spectra identical.

A hemimethanolate of the acid amide, mp 208–210°, was obtained when the compound was recrystallized from methanol–ethyl acetate and dried *in vacuo* at 80°.

Anal. Calcd for $C_{16.5}H_{17}O_{3.5}N$: C, 69.46; H, 6.01; N, 4.91. Found: C, 69.29; H, 6.41; N, 4.99.

Cyclization of the acid amide with PPA at 100° gave **4a**.

4-Phenyl-2,3,4,5-tetrahydro-2(1*H*)-benzazepine-1,3 dione (4a). A. By Cyclization.—A suspension of 50 g of **2a** in 650 g of PPA was heated to 95–100° and stirred for 2.5 hr. Hydrolysis of the cooled solution with ice water (2 l.) gave the crude solid which was collected, washed with water, stirred 0.5 hr with 300 ml of *ca.* 2% sodium bicarbonate solution, and again filtered, washed with water, and dried; yield of the crude imide was 35 g. Recrystallization from ethyl acetate afforded 30 g of colorless crystals: mp 175–177°, raised on further recrystallization to mp 180–182°; ir 3.15 (bonded NH) and intense, sharp peak 6.01 μ with satellite peaks 5.90, 5.95, and 6.07 μ; uv 238 nm (ε 10,980) and 284 (1750); nmr (DMSO) δ 10.9 (s, broad, 1, D_2O exchanged, NH), 7.9 [m, 1, peri (9) proton], 7.5–7.0 (m, 8, aromatic protons), 4.2 (1, doubled doublet, X of ABX, 4 proton), and *ca.* 3.3 (m, 2, poorly resolved quartet of doublets, AB of ABX, 5-methylene protons).

Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.47; H, 5.22; N, 5.57. Found: C, 76.74; H, 5.10; N, 5.46.

By acidification of bicarbonate wash solution from this experiment, as well as from separate, base-promoted hydrolyses of **4a**, there was obtained **2-(β-phenylethylbenzamide)-β-carboxylic acid** (11), crystallizing from methanol as colorless crystals: mp 231–232°; ir 2.90, 3.02, 3.14, 5.80, 6.09, and 6.18–6.26 μ (doublet); uv 258 nm (ε 730) with infl 220 (15,220).

Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.49; H, 5.35; N, 4.97.

B. By Hydrogenation of Unsaturated Imide 3a.—A solution of **3a** (1–5 g) in EtOAc with 10% Pd/C (0.5–3 g) was shaken under 3 atm of H_2 at 70° for 3–4 hr and filtered. The solution evaporated and the residue recrystallized from EtOAc to give colorless crystals: mp 179–181°; mixture melting point with product A undepressed; ir and uv spectra identical.

By methods A or B, there were prepared in addition the following imides **4**.

Compound 4b, preferably prepared from **3b** by method B and also obtained in low yield by cyclization of **2b,** was crystallized from EtOAc: mp 206–208°; ir 3.18–3.30, 5.89–6.00–6.09 (triplet); uv 272 and 282 nm (ε 1720 and 1770) and infl 235 (11,480),

Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.96; H, 6.0; N, 5.15.

Compound 4c, obtained from **3c** by method B, was recrystallized from EtOAc: mp 158–160°; ir 3.15–3.27 (bonded NH), 5.88 and 6.06 μ; uv 225 nm (ε 23,442), 276 (3054), 282 (2995), and infl 244 (11,597).

Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.66; H, 5.58; N, 4.90.

Compound 4d, obtained from **2d** by method A in 70% yield, was recrystallized from EtOAc: mp 180–181°; ir 3.15–3.26, 5.88, and 5.99–6.06 μ; uv 238 nm (ε 11,140), 270 (2060), and 282 (1770).

Anal. Calcd for $C_{16}H_{12}FNO_2$: C, 71.36; H, 4.50; N, 5.19. Found: C, 71.22; H, 4.62; N, 4.83.

Compound 4e was obtainable only by reduction of **3e** (method B) and, owing to sparing solubility of **3e** in EtOAc and other solvents, it was practical to reduce only *ca.* 3–4 g per run (in *ca.* 300 ml of EtOAc) using the standard Parr shaker, at 70°; on occasion the Pd/C catalyst had to be renewed and the reaction time prolonged (4–5 hr). Recrystallization from ethyl acetate gave colorless needles: mp 130.5–132.5°, still slightly solvated (nmr, EtOAc) after prolonged drying at 80°; ir 3.15–3.26 (bonded NH), 5.78–5.85 (doublet) and 6.05 μ; uv 230 nm (ε 17,200) and 279 (4230); nmr ($CDCl_3$) δ 8.6 (s, 1, slowly D_2O exchanged, NH), 8.1 (m, 1, peri 9 proton), 6.5–7.5 (m, 6, aromatic protons), 4.0 (m, 1, methine 4 proton), 5.19 and 5.22 (singlets, 3 each, methoxyl CH_3), 2.9–3.4 (m, 2, methylene protons), and EtOAc fingerprint.

Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.27; H, 5.94; N, 4.20.

Compound 4f was prepared by PPA (150 g) cyclization of **2f** (5 g) following method A. The phosphoric acid solution obtained on treatment of the reaction mixture with water was treated with $NaHCO_3$ to precipitate the product which was collected, washed with water, dried (yield, 4.4 g), and recrystallized from EtOAc: colorless crystals; mp 220–222°; ir 5.92 and 6.00 μ and bands indicating zwitterionic transfer of imide proton to pyridyl N; uv 242 nm (ε 12,370), 282 (1750), and infl 267 (3790).

Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.41; H, 4.80; N, 11.11. Found: C, 71.71; H, 4.68; N, 11.14.

2-Methyl-2,3-dihydro-4-phenyl-2(1*H*)-benzazepine-1,3-dione (5a) (**R = CH_3**).—A solution of 10 g of **3a** in 80 ml of DMF was treated with 1.9 g of 56% sodium hydride (oil); after stirring a few minutes at ambient temperature, there was added 45 ml of iodomethane. The mixture was stirred 5 hr. About half of the DMF was removed *in vacuo*, and the residue was treated with cold water. Ether extract of the organic material was washed thrice (water), dried ($MgSO_4$), and evaporated. The residue on trituration with ether gave 8.9 g of colorless crystals, mp 125–127°. A sample, recrystallized from ether, had mp 126.5–127.5°; ir 5.95, 6.07, and 6.15 μ; uv 233 nm (ε 32,630) and 306 (11,720); nmr ($CDCl_3$) δ 8.26 (m, 1, peri 9 proton), 7.3–7.75 (m, 8, remaining aromatic protons), 7.23 (sharp s, 1, vinyl proton), and 5.27 (s, 3, methoxy CH_3).

Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.29; H, 4.67; N, 5.31.

Potassium *tert*-butoxide instead of NaH, with *tert*-butyl alcohol in place of DMF, were used with equal success in the above procedure.

2-Methyl-4-phenyl-2,3,4,5-tetrahydro-2(1*H*)-benzazepine-1,3-dione (6a) (**R = CH_3**). **A.**—Alkylation of **4a** (5 g) with iodomethane (20 ml) in the presence of NaH (0.95 g, 56% in oil) in DMF (30 ml), following the procedure of the preceding experiment, gave 2.6 g of colorless crystals: mp 132–134°, raised on recrystallization (ether) to mp 135–136°; ir 5.88 and 6.05 μ; uv benzenoid.

Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.95; H, 5.45; N, 5.18.

B.—Hydrogenation of **5a** (R = CH_3) (4.4 g) in glacial acetic acid in the presence of 2 g of 10% Pd/C at 3 atm and 70° for 2 hr, evaporation of the filtered solution, and recrystallization of the product (3.8 g) from ether gave colorless crystals: mp 135–136°; mmp (with A imide) 135–136°; ir and uv spectra identical.

Other *N*-alkylimides **5** and **6**, listed in Table II, were prepared following procedures exemplified by the preceding experiments. The NaH in DMF method served well in alkylating **4** in general and **5** with basic halides (β- and γ-dimethylaminoethyl- and -propyl chlorides). In the latter *ca.* 2–3 molar equiv of chloroamine per mol of imide, and the ether-extracted products (after washing) were dried over K_2CO_3. None of the resulting imides **6** having R = $(CH_2)_{2-3}NMe_2$ were crystalline, nor could well-characterized hydrochlorides, picrates, or methiodides be obtained from many of them, and therefore in each case crude, basic side-chain substituted compounds **6** were reduced with $LiAlH_4$ according to standard methods, and the resulting dibasic amines **8** [R = $(CH_2)_{2-3}NMe_2$] characterized as corresponding dipicrates or bismethiodides, purified by recrystallization from methanol or ethanol and also listed in Table II.

Alkylation of **3** with the higher molecular weight halides was best carried out using a slight excess of the appropriate bromide or iodide, and potassium *tert*-butoxide in *tert*-butyl alcohol as basic agent and solvent, respectively, at ambient temperatures or with a brief period of gentle warming (*ca.* 40–50°) following addition of the halide. Products **5** are also listed in Table II.

Compound **6e**, R = CH_3, was obtained by hydrogenation of **5e**, R = CH_3. Compound **8a** (R = CH_2CH_2OH) was obtained from $LiAlH_4$ reduction of crude, noncrystalline **6a** (R = CH_2COOEt).

Lithium Aluminum Hydride Reduction of Imides. General Procedure.—In 600 ml of dry ether (for neutral compound) or tetrahydrofuran (for basic imides), 20 g of $LiAlH_4$ was stirred and

TABLE II

N-ALKYLIMIDES 5 AND 6 AND REDUCTION PRODUCTS 7 AND 8[a]

Compd	R	Mp, °C	Formula
5a	$CH_2C_6H_5$	111–112	$C_{23}H_{17}NO_2$
	CH_2COOEt	104–106	$C_{20}H_{17}NO_4$
5b	CH_3	74–76	$C_{18}H_{15}NO_2$
5c	CH_3	122–124	$C_{18}H_{15}NO_3$
5e	CH_3	149–151	$C_{19}H_{17}NO_4$
6a	$CH_2C_6H_5$	99–100	$C_{23}H_{19}NO_2$
	$(CH_2)_2C_6H_5$	96–97	$C_{24}H_{21}NO_2$
	CH_2CN	123–124	$C_{18}H_{14}N_2O_2$
	$(CH_2)_2NMe_2 \cdot MeI$	191–195 dec	$C_{21}H_{27}IN_2O_3$
6b	CH_3	140–141	$C_{18}H_{17}NO_2$
6d	CH_2	122–123	$C_{17}H_{14}FNO_2$
6e	CH_3	116–118	$C_{19}H_{19}NO_4$
6f	CH_3	171–172	$C_{16}H_{14}N_2O_2$
	$CH_3 \cdot MeI \cdot {}^1/_2H_2O$	176–178	$C_{17}H_{18}IN_2O_{2.5}$
7a	$CH_3 \cdot HCl$	242–244 dec	$C_{17}H_{18}ClN$
8a	$CH_3 \cdot HCl$	218–219 dec	$C_{17}H_{20}ClN$
	$CH_2C_6H_5$	130–131	$C_{23}H_{23}N$
	$(CH_2)_2C_6H_5$	98–99	$C_{24}H_{25}N$
	$(CH_2)_2C_6H_5 \cdot HCl$	271–275 dec	$C_{24}H_{26}ClN$
	$(CH_2)_2OH \cdot$ picrate	150–151	$C_{24}H_{24}N_4O_8$
	$(CH_2)_2OH \cdot HCl$	186–188	$C_{18}H_{22}ClNO$
	$(CH_2)_3OC_6H_5$	79–80.5	$C_{25}H_{27}NO$
	$(CH_2)_3OC_6H_5 \cdot HCl$	153–155	$C_{25}H_{28}ClNO$
	$(CH_2)_2NMe_2 \cdot$ picrate	220–221 dec	$C_{32}H_{32}N_8O_{14}$
	$(CH_2)_3NMe_2 \cdot$ picrate	203–205 dec	$C_{33}H_{34}N_8O_{14}$
	$(CH_2)_3NMe_2 \cdot MeI$	261–263 dec	$C_{23}H_{34}I_2N_2$
8b	$CH_3 \cdot HCl \cdot H_2O$	173–174	$C_{18}H_{22}ClN \cdot H_2O$
	$(CH_2)_3NMe_2 \cdot$ picrate	198–200 dec	$C_{34}H_{36}N_8O_{14}$
8c	$(CH_2)_3NMe_2 \cdot$ picrate	198–200 dec	$C_{34}H_{36}N_8O_{15}$
8d	$(CH_2)_3NMe_2 \cdot$ picrate	189–191 dec	$C_{33}H_{33}FN_8O_{14}$
8e	CH_3	104–105	$C_{19}H_{23}NO_2$

[a] Satisfactory analytical values (±0.35% for C, H, and N) were reported for all compounds: Ed.

to the suspension was added 10 g of imide as a concentrated THF solution. Refluxing and stirring were continued 6–7 hr, and the cooled, stirred suspension was treated gradually with 100 ml of water, stirred 1 hr, and filtered. The solvent was evaporated, the residue dissolved in ether, and the ether solution dried (K_2CO_3) and evaporated to give crude 2,3,4,5-tetrahydro-2(1*H*)-benzazepines which were either recrystallized from ether or ethanol or converted to suitable derivatives (Table II) by standard methods.

Compound 8a, R = H, from $LiAlH_4$ (13.5 g) reduction of **4a** (6.8 g) in THF (300 ml) was obtained as a crude oil (6 g) and was converted to the corresponding hydrochloride (2.8 g): hygroscopic, colorless crystals from ethanol–ether; mp 242–243° dec; ir devoid of peaks indicating carbonyl or conjugated groups; uv 257 nm (ε 540).

Anal. Calcd for $C_{16}H_{17}N \cdot HCl$: C, 73.97; H, 6.98; N, 5.39. Found: C, 73.88, 73.63; H, 6.89, 7.07; N, 5.32.

An attempt was made to reduce **3a** to **7a** (R = H), but the resulting base was unstable to air and to acids and was not characterized.

Registry No.—**1a**, 26926-14-7; **1b**, 26926-15-8; **1c**, 26926-16-9; **1d**, 26926-17-0; **1e**, 26926-18-1; methyl ester of **1e**, 26932-25-2; **1f**, 26926-19-2; **2a**, 26926-20-5; anhydride of **2a**, 26926-21-6; **2b**, 26925-62-2; **2c**, 26925-63-3; **2d**, 26925-64-4; methyl ester of **2e**, 26925-65-5; **2f**, 26925-66-6; **3a**, 26925-67-7; **3b**, 26925-68-8; **3c**, 26925-69-9; **3d**, 26925-70-2; **3e**, 26925-71-3; **3f**, 26963-62-2; **4a**, 26925-72-4; **4b**, 26925-73-5; **4c**, 26925-74-6; **4d**, 26925-75-7; **4e**, 26925-76-8; **4f**, 26925-77-9; **5a** (R = CH_3), 26925-78-0; **5a** (R = $CH_2C_6H_5$), 26925-79-1; **5a** (R = CH_2COOEt), 26925-80-4; **5b** (R = CH_3), 26925-81-5; **5c** (R = CH_3), 26925-82-6; **5e** (R = CH_3), 26925-83-7; **6a** (R = CH_3), 26925-84-8; **6a** (R = $CH_2C_6H_5$), 26925-85-9; **6a** [R = $(CH_2)_2C_6H_5$], 26925-86-0; **6a** (R = CH_2CN), 26925-87-1; **6a** [R = $(CH_2)_2NMe \cdot MeI$], 26925-88-2; **6b** (R = CH_3), 26925-89-3; **6d** (R = CH_3), 26925-90-6; **6e** (R = CH_3), 26925-91-7; **6f** (R = CH_3), 26925-92-8; **6f** (R = $CH_3 \cdot MeI$), 26925-93-9; **7a** (R = $CH_3 \cdot HCl$), 26925-94-0; **8a** (R = H) hydrochloride, 26932-26-3; **8a** (R = $CH_3 \cdot HCl$), 26925-95-1; **8a** (R = $CH_2C_6H_5$), 26925-96-2; **8a** [R = $(CH_2)_2C_6H_5$], 26925-97-3; **8a** [R = $(CH_2)_2C_6H_5 \cdot HCl$], 26925-98-4; **8a** [R = $(CH_2)_2OH \cdot$ picrate], 26925-99-5; **8a** [R = $(CH_2)_2OH \cdot HCl$], 26926-00-1; **8a** [R = $(CH_2)_3OC_6H_5$], 26926-01-2; **8a** [R = $(CH_2)_3OC_6H_5 \cdot HCl$], 26926-02-3; **8a** [R = $(CH_2)_2NMe \cdot$ picrate], 26926-03-4; **8a** [R = $(CH_2)_3NMe \cdot$ picrate], 26926-04-5; **8a** [R = $(CH_2)_3NMe \cdot MeI$], 26926-05-6; **8b** (R = $CH_3 \cdot HCl$), 26963-63-3; **8b** [R = $(CH_2)_3NMe \cdot$ picrate], 26926-06-7; **8c** [R = $(CH_2)_3NMe \cdot$ picrate], 26963-64-4; **8d** [R = $(CH_2)_3NMe \cdot$ picrate], 26926-07-8; **8e** (R = CH_3), 26932-17-2; **9**, 26932-18-3; **10**, 26932-19-4; **11**, 26932-20-7; *threo*-3-(α-cyano-α-phenylmethyl)phthalide, 26932-27-4; *o*-carboxy-2-phenylhydrocinnamic acid, 26925-61-1.

Acknowledgment.—We are indebted to Mrs. Angela Aretakis for literature search work, to Mr. Louis Dorfman, Miss Ruth Behnke, and Miss Natalie Cahoon for spectra and aid in interpretation thereof, to Mr. George Robertson and Mr. Rudolf Oeckinghaus for microanalytical data, to Mr. Shyam Sunder for some technical assistance, and to Mr. Robert Dziemian and Miss Ann Smith for large-scale preparation of certain intermediates.

Synthesis of 5-Oxo-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-10-carboxylic Acids, Corresponding Nitriles, and Related Bridged Lactones, Hemiketals, Lactams, Amines, Amidoximes, and Amidines (5,10-Epoxymethano and 5,10-Iminomethano Compounds)

GORDON N. WALKER,* DAVID ALKALAY, ALLAN R. ENGLE, AND ROBERT J. KEMPTON

Research Department, CIBA Pharmaceutical Company, Inc., Division of CIBA Corporation, Summit, New Jersey 07901

Received June 12, 1970

Cyclization of cyano acid chlorides **2** gives novel dibenzsuberone nitriles **5**, hydrolyzed to corresponding keto acids **8** and converted by standard methods into amides **4**, **7**, and **11**, and acids **12**. Borohydride reduction of **5** and **8** gives *via* corresponding hydroxy nitriles and hydroxy acids, respectively, iminolactone **9**, previously alluded to as a borohydride conjugate reduction product of **6**, and bridged lactone **13**. Known compounds **6**, **14**, and **15** were prepared independently and points of identity correlating the new synthesis with known routes were established with compounds **6** and **12**. Bridged lactam **23** (giving derived compounds **24**) was prepared by hydrogenolysis of **22**, obtained by reaction of lactone **13a** with H_2NOH in refluxing glycol. Another route to bridged lactam, *via* internal displacement of chloroamide **20**, proved to be not general. Bridged keto amidoximes **27** were synthesized from keto nitriles, **5** and **26**, and Ni hydrogenolysis of **27** gave bridged keto amidines **28**. Hydroxy nitriles **31** and hydroxy amides **33**, from borohydride reduction of substituted keto nitriles **26** and corresponding bridged keto amides **30**, respectively, on treatment with concentrated HCl gave bridged lactams **32**, while lactones **36** were formed from **33** in the presence of more dilute acids or nitrous acid. Bridged amines (5,10-iminomethano compounds) **25** and **34** were prepared by borane or $LiAlH_4$ reduction of lactams. Bridged ethers (5,10-epoxymethano compounds) **18** and **35**, through appropriate hydride reductions, and a bridged hemiketal **40**, *via* keto ketal Grignard product **39**, were also prepared. Polyphosphoric acid cyclization of *o*-[2-cyano-2-(3,4-dimethoxyphenyl)]benzoic acid (**1e**) gives dibenzsuberone amide **4e**, an exception to the closures of other cyano acids **1** to 2,3,4,5-tetrahydro-2(1*H*)-benzazepine-1,3-diones.

The study of linear tricyclic psychopharmacological compounds[1-4] has progressed in two decades from the phenothiazines[1] through iminodibenzyls[5] and dibenzo[*a*,*d*]cycloheptenes[6-8] to a number of related, tricyclic systems (thioxanthenes and dibenzo and pyrido oxepins, thiepins, azepines, diazepines, thiazepines, etc.) bearing basic side chains,[9-24] and with it have been developed the techniques for synthesis of a number of interesting intermediate dibenzo seven-membered cyclic compounds. One must forego here any attempt to review critically this large and interesting area (the citations given here are intended only to convey an idea of the importance of the field and indicate the volume and scope of chemistry done), and merely say that, while this field of work which began with imipramine[5] and amitriptyline[6-8] is still avidly pursued in many quarters, one of the most intriguing chemical aspects recently is perhaps the synthesis of *bridged* dibenzsuberans (dibenzo bicyclic compounds)[25-27] and hydroanthracenes.[28]

Thus, some time ago it was realized that in the

(1) K. Stach and W. Pöldinger in "Arzneimittelforschung," Vol. 9, E. Jucker, Ed., Birkhäuser Verlag, Basel, 1966, pp 129–190.

(2) M. Gordon in "Psychopharmacological Agents," Vol. 2, M. Gordon, Ed., Academic Press, New York, N. Y., 1967, Chapter 1 and pp 305–518.

(3) F. Häfliger and V. Burckhardt, *ibid.*, Vol. 1, 1964, Chapter 3.

(4) S. J. Childress and J. H. Biel, *Annu. Rep. Med. Chem.*, **1**, 16 (1965); **4**, 11 (1966). I. J. Pachter and A. A. Rubin, *ibid.*, 1 (1967); 1 (1968). M. A. Davis, *ibid.*, 14 (1967); 13 (1968).

(5) W. Schindler and F. Häfliger, *Helv. Chim. Acta*, **37**, 472 (1954); U. S. Patent 2,554,736 (1951).

(6) S. O. Winthrop, M. A. Davis, G. S. Myers, J. G. Gavin, R. Thomas, and R. Barber, *J. Org. Chem.*, **27**, 230 (1962).

(7) R. D. Hoffsommer, D. Taub, and N. L. Wendler, *ibid.*, **27**, 4134 (1962); **28**, 1751 (1963). E. L. Engelhardt, *et al.*, *J. Med. Chem.*, **8**, 829 (1965).

(8) F. J. Villani, U. S. Patent 3,409,640 (1968); 3,301,863 (1967); 3,419,565 (1968).

(9) P. V. Petersen, N. Lassen, T. Holm, R. Kopf, and I. M. Nielsen, *Arzneim. Forsch.*, **8**, 395 (1958).

(10) V. Mychajlyszyn and M. Protiva, *Collect. Czech. Chem. Commun.*, **24**, 3955 (1959). M. Protiva, *et al.*, *J. Med. Pharm. Chem.*, **4**, 411 (1961). V. Seidlova, M. Protiva, *et al.*, *Monatsh. Chem.*, **96**, 182, 650 (1965); *Collect. Czech. Chem. Commun.*, **32**, 1747, 2826, 3186, 3448 (1967); **34**, 468, 2258 (1969).

(11) C. van der Stelt, A. F. Harms, and W. Th. Nauta, *J. Med. Pharm. Chem.*, **4**, 335 (1961); *Arzneim. Forsch.*, **16**, 1342 (1966); U. S. Patent 3,358,027 (1967).

(12) S. O. Winthrop, M. A. Davis, F. Herr, J. Stewart, and R. Gaudry, *J. Med. Pharm. Chem.*, **5**, 1199, 1207 (1962); **6**, 130 (1963). M. A. Davis, *et al.*, *ibid.*, **6**, 251, 513 (1963); **9**, 860 (1966); **10**, 627 (1967).

(13) R. Jacques, A. Rossi, E. Urech, H. J. Bein, and K. Hoffmann, *Helv. Chim. Acta*, **42**, 1265 (1959).

(14) C. I. Judd, A. E. Drukker, and J. H. Biel, U. S. Patent 2,985,660 (1961).

(15) F. J. Villani, C. A. Ellis, C. Teichman, and C. Bigos, *J. Med. Pharm. Chem.*, **5**, 373 (1962); F. J. Villani, C. A. Ellis, R. F. Tavares, and C. Bigos, *J. Med. Chem.*, **7**, 457 (1964).

(16) A. E. Drukker, C. I. Judd, and D. D. Dusterhoft, *J. Heterocycl. Chem.*, **3**, 206 (1966); **2**, 276 (1965); U. S. Patent 3,316,245, 3,316,246 (1967).

(17) G. Stille, *Arzneim. Forsch.*, **14**, 534 (1964); **16**, 255 (1966). G. Stille, H. Lauener, E. Eichenberger, F. Hunziker, and J. Schmutz, *ibid.*, **15**, 841 (1965). J. Schmutz, F. Kunzle, F. Hunziker, O. Schindler, and A. Bürki, *Helv. Chim. Acta*, **47**, 1163 (1964); **48**, 336 (1965); **49**, 244, 1433 (1966); U. S. Patent 3,367,930 (1968). H. Gross and E. Langner, *Arzneim. Forsch.*, **16**, 316 (1966). J. Schmutz, F. Hunziker, and F. M. Kunzle, U. S. Patent 3,454,561 (1969).

(18) W. Pöldinger, *et al.*, *Arzneim. Forsch.*, **17**, 1133 (1967); **19**, 492 (1969); **16**, 650 (1966).

(19) A. M. Monroe, R. M. Quinton, and T. I. Wrigley, *J. Med. Chem.*, **6**, 255 (1963).

(20) B. M. Bloom and J. F. Muren, U. S. Patent 3,310,553 (1967); *J. Med. Chem.*, **13**, 14, 17 (1970). B. M. Bloom and J. R. Tretter, U. S. Patent 3,420,851 (1969).

(21) H. A. Pfenninger, U. S. Patent 3,424,749 (1969); K. J. Doebel and H. A. Pfenninger, U. S. Patent 3,300,504 (1967).

(22) J. C. L. Fouché, U. S. Patent 3,462,436, 3,476,761, 3,476,758, 3,479,356, 3,480,624 (1969).

(23) F. Hoffmeister, *Arzneim. Forsch.*, **19**, 808 (1969); G. Aichinger, S. Schutz, and F. Hoffmeister, U. S. Patent 3,431,257 (1969).

(24) M. Takeda, M. Matsubara, and H. Kugita, *J. Pharm. Soc. Jap.*, **89**, 158 (1969).

(25) T. A. Dobson, M. A. Davis, A.-M. Hartung, and J. M. Manson, *Tetrahedron Lett.*, 4139 (1967); *Can. J. Chem.*, **46**, 2843 (1968); **47**, 2826 (1969); U. S. Patents 3,406,186, 3,361,767, 3,412,085, 3,418,339 (1968); 3,426,015, 3,458,518, 3,462,457 (1969).

(26) S. J. Cristol, R. M. Sequeira, and C. H. DePuy, *J. Amer. Chem. Soc.*, **87**, 4007 (1965). S. J. Cristol and B. B. Jarvis, *ibid.*, **88**, 3095 (1966); **89**, 401, 5885 (1967). S. J. Cristol, R. M. Sequeira, and G. O. Mayo, *ibid.*, **90**, 5564 (1968). S. J. Cristol, G. O. Mayo, and G. A. Lee, *ibid.*, **91**, 214 (1969). S. J. Cristol and G. O. Mayo, *J. Org. Chem.*, **34**, 2363 (1969).

(27) P. W. Rabideau, J. B. Hamilton, and L. Friedman, *J. Amer. Chem. Soc.*, **90**, 4465 (1968); E. Ciganek, *ibid.*, **88**, 2882 (1966).

(28) R. Blaner, P. Imfeld, and O. Schindler, *Helv. Chim. Acta*, **52**, 2197 (1969).

10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene ring system there is present a fairly ideal, steric template for one- and two-atom bridging reactions between positions 5 and 10. Some of the many 10,5-iminomethano compounds prepared by the Dobson–Davis group (from 10,11-epoxy-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-carboxylic acid and its derivatives)[25] are also available through newer applications[29] of the classical isopavine synthesis,[30] and 5,10-epoxy compounds closely related to amitriptyline, as well as other 5,10-epoxy-11-oxo and 5,10-ethano and methano compounds of the same class, have been reported.[31]

It occurred to us 2 years ago that the hitherto unknown and inaccessible 5,10-epoxymethano- and 5,10-iminomethano-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptenes, and thus an entire, new area of compounds with possible value as drugs, might be made accessible if 5-oxo-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-10-carboxylic acids (or corresponding derivatives) could be prepared (Scheme I, **8**). Although corresponding dehydro keto acids **15** are known,[32-34] the hiatus between them and **8** would appear to be owing to difficulty in reduction of **15** and related compounds, as well as to the fact that keto nitrile **6** can neither be reduced selectively to **5** nor hydrolyzed (without rearrangement) to **15**.

In a formal sense, there have been two reports verging closely on what we are about to describe: one concerning the condensation of phthalaldehydic acids with *N*-methyloxindoles and PPA cyclization of the products thereof to 6*H*-benzo[5,6]cyclohept[1,2,3-*c*,*d*]indoline-1,6-diones (lactams of 1-amino-5-oxo-5*H*-dibenzo[*a*,*d*]-cycloheptene-11-carboxylic acids),[35] and the other describing closure with PPA of certain benzylhomophthalic acids and phthalides (having suitably placed aromatic methoxyl groups) to 2,3-dialkoxy-5-oxo-10,11-dihydrodibenzo[*a*,*d*]cyclohepene-10-carboxylic acids.[36] Neither route is general for preparation of keto acids **8** or **15**.

Another paper[37] from our laboratory reports synthesis of a number of cyano acids **1a–e** (Scheme I) *via* condensation of phthalaldehydic acid with various arylacetonitriles and reduction. These acid nitriles, with one exception reminiscent of the Indian work[36] as described below, did not give dibenzsuberone nitriles when cyclized with PPA but rather formed 2-benzazepine-1,3-diones.[37] However, after converting cyano acids **1** by PCl_5 to corresponding acid chlorides **2**, cyclization of **2a**, **b**, and **e** with Lewis acids did give respective keto nitriles **5**. In this closure, $AlCl_3$ in *sym*-tetrachloroethane[38] at 100° served well for the unsubstituted (**2a**) and *p*-methyl (**2b**) nitrile acid chlorides, and $SnCl_4$ was employed in the case of **2e** to avoid demethylation. Acid hydrolysis (HCl and HOAc) of keto nitriles **5** readily gave corresponding keto acids **8**. With these intermediates at hand in quantity, one could foresee many possible ways in which to elaborate bridged compounds.

Polyphosphoric acid cyclization of the dimethoxy cyano acid **1e**, in which there is an activating effect of *p*-methoxyl group on the benzene position capable of being electrophilically attacked internally, afforded specifically keto amide **4e** rather than 4-(3,4-dimethoxyphenyl)-2,3,4,5-tetrahydro-1*H*-2-benzazepine-1,3-dione.[37] This was evident from spectra and the fact that acid hydrolysis of **4e** gave keto acid **8e**, identical with that prepared by hydrolyzing keto nitrile **5e**. Keto acids **8** could also be converted to respective amides **4** *via* corresponding (crystalline) keto acid chlorides. Presumably because of the electrophilicity-enhancing effect of the R′ = OCH_3 group on the 5 ketone, compounds **4e** and **8e**, as well as the acid chloride corresponding to **8e**, tended to exist in the bridged (ψ) form to an extent somewhat greater than that displayed by other (**a**, **b**) corresponding members of the series, *e.g.* the acid chloride corresponding to **8a** existed only in the open form. In keto amides related to **4a**, it was observed, however, that the *N*-methyl amide specifically appeared to be partly ψ while other amides (N-substituted **4a**) were in the open form (for relevant ir and uv spectra, see Experimental Section).

Further evidence for structures **4**, **5**, and **8** was forthcoming in reductions of those ketones. Sodium borohydride reduction of keto amide **4e** gave hydroxy amide **7e**, and acid-catalyzed, palladium hydrogenolysis of **4e** or **7e** gave amide **11e**. Similar hydrogenolysis of keto acid **8a** gave acid **12**. Amide **11a** was also obtained from acid **12** as shown.

Sodium borohydride reduction of keto nitrile **5a** and keto acids **8** led, respectively, to bridged iminolactone **9** and bridged lactones **13**. In the **5a** reduction, the crude product contained a certain amount of noncrystalline material, evidently the *trans*-hydroxy nitrile **10**, but in the reduction of **8a** the product, after acidification, was essentially all lactone **13a**. Treatment of **9** with dilute acids at room temperature gave **13a**, thus (together with spectra) excluding a bridged lactam structure for **9**.

Iminolactone **9**, we suspected, was that very briefly mentioned "tetracyclic compound obtained instead" (of the expected hydroxy nitrile) by Gootjes, *et al.*,[34] in their work, *inter alia* on reduction of the dehydro keto nitrile **6**. It was of interest to settle this point, and at the same time provide additional proof of structure of the new keto nitriles and keto acids by relating them to known 5*H*-dibenzo[*a*,*d*]cyclohepten-5-ones. Therefore, we synthesized the 10-bromo ketone **16**[32-34] *via* 10,11-dibromo ketone from the dibenzsuberone and enone[39] and converted it by the reported methods,[32-34] as indicated in Scheme I, to **6**, **14**, and **15**. Sodium borohydride reduction of **6** did indeed give the same mixture of **9** and **10** as obtained from **5a**, the isolated

(29) J. H. Russel, British Patent 1,146,109 (1969); French Patent 6143M (1969); *Chem. Abstr.*, **71**, 30370 (1969).

(30) A. R. Battersby and D. A. Yeowell, *J. Chem. Soc.*, 1988 (1958).

(31) M. E. Christy, C. C. Boland, J. G. Williams, and E. L. Engelhardt, *J. Med. Chem.*, **13**, 191 (1970); Merck and Co., Belgian Patent 712,259; 712,160 (1968); *Chem. Abstr.*, **72**, 121245 (1970).

(32) W. Tochterman, U. Walter, and A. Mannschreck, *Tetrahedron Lett.*, 2981 (1964).

(33) F. Hoffmann-La Roche, Belgian Patents 659,599 and 659,786 (1965); *Chem. Abstr.*, **64**, 5023 (1966).

(34) J. Gootjes, A. B. H. Funcke, and W. Th. Nauta, *Arzneim. Forsch.*, **19**, 1936 (1969).

(35) J. Plostnieks, U. S. Patent 3,393,208 (1968).

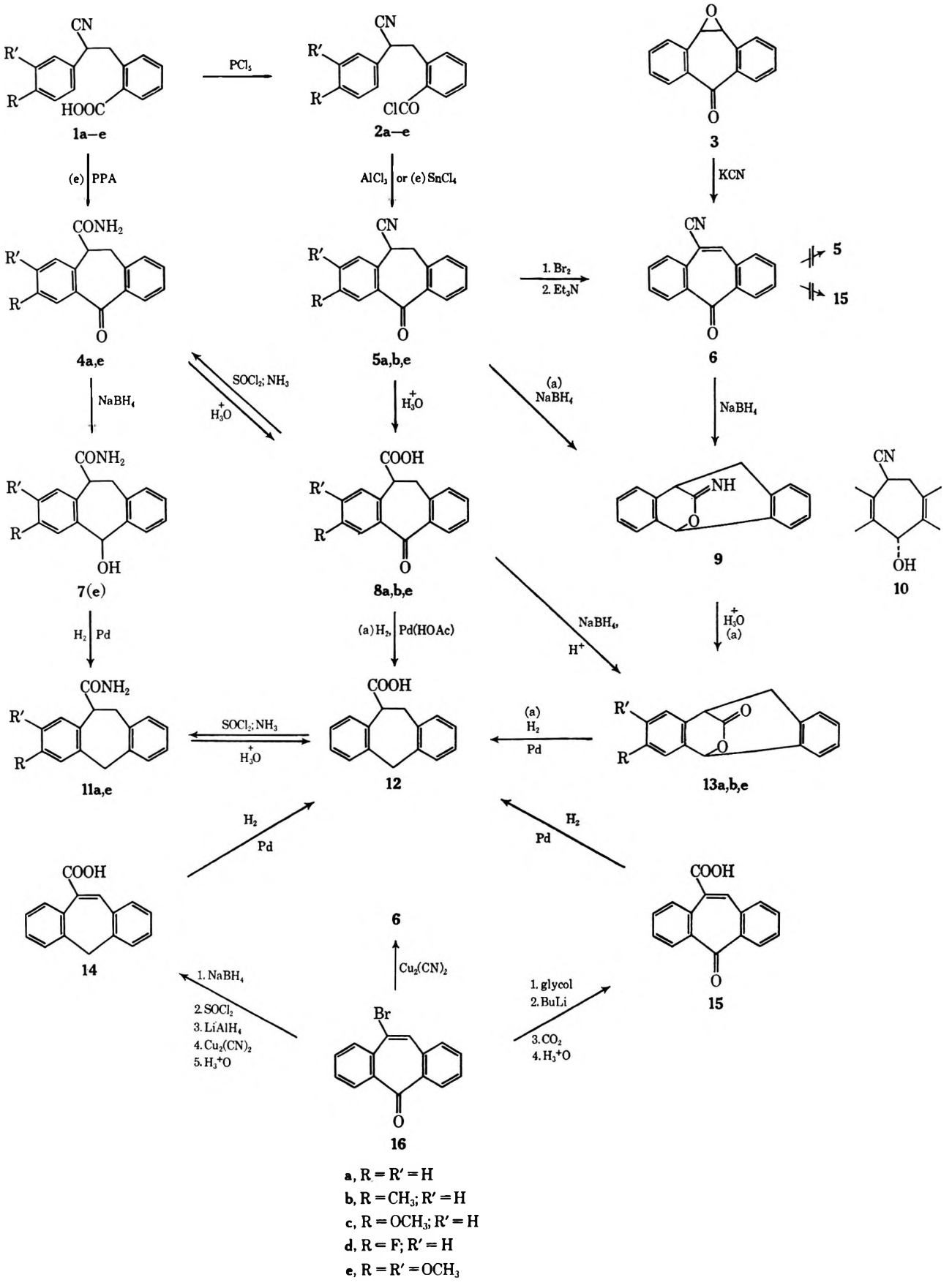
(36) J. N. Chatterjea and H. Mukherjee, *Experientia*, **16**, 2773 (1960); *J. Indian Chem. Soc.*, **37**, 379 (1960).

(37) G. N. Walker and D. Alkalay, *J. Org. Chem.*, **36**, 461 (1971).

(38) P. Kranzlein, *Ber.*, **70**, 1952 (1937).

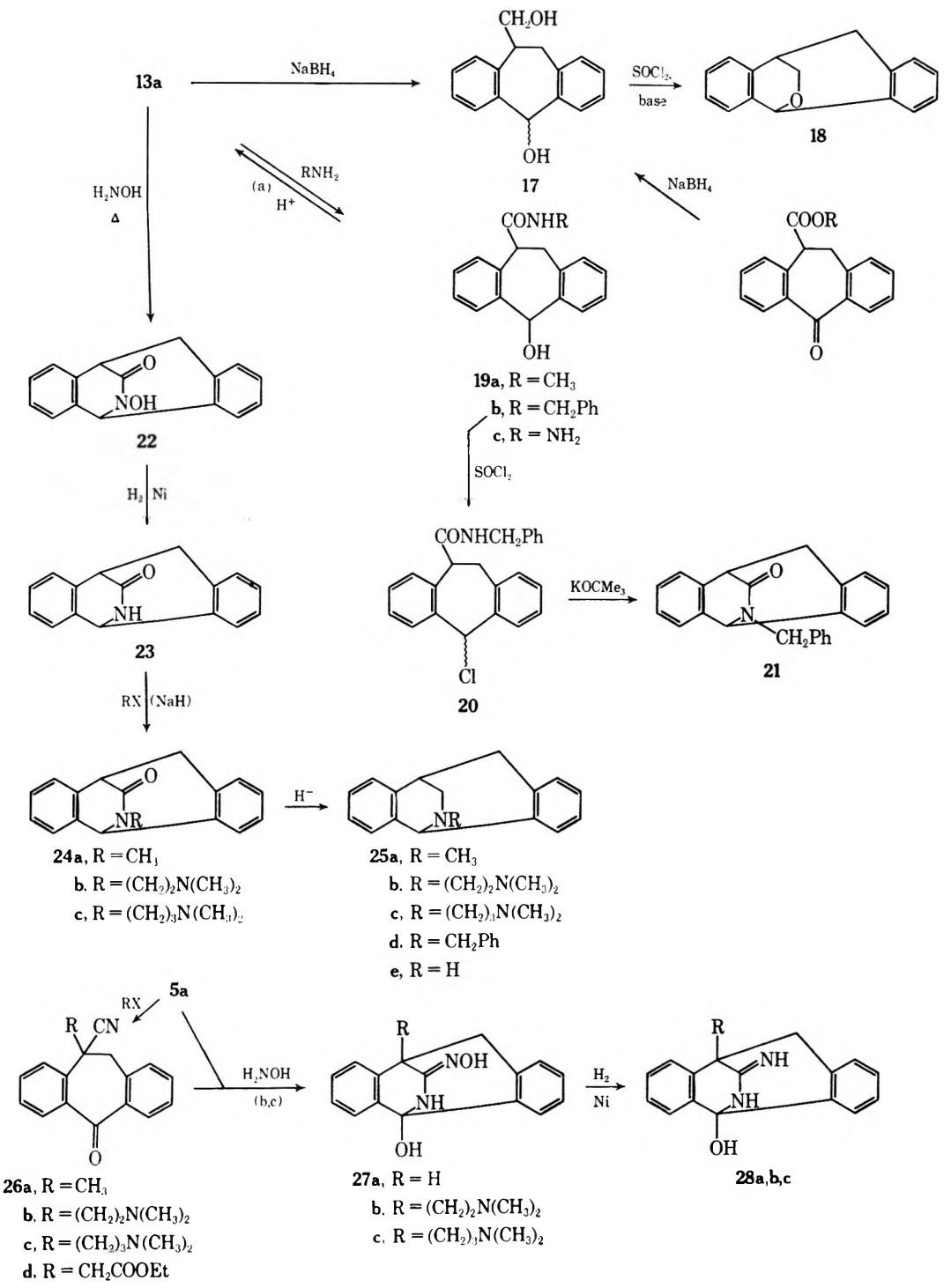
(39) S. Wawzonek, *J. Amer. Chem. Soc.*, **62**, 745 (1940); W. Treibs and H. J. Klinkhammer, *Ber.*, **84**, 671 (1951); A. C. Cope and S. W. Fenton, *J. Amer. Chem. Soc.*, **73**, 1668, 1673 (1951).

SCHEME I



iminolactone **9** being identical with that prepared from **5a**. Then, several additional and more direct correlations of **5a** and **8a** with known compounds were also made. Keto nitrile **6** was the product resulting from bromination of **5a** and dehydrobromination[39] of the resulting crude bromo nitrile with Et_3N, and was identical, not only with the sample of **6** from **16** with $Cu_2(CN)_2$ but also with that prepared in another novel way,

SCHEME II



the action of cyanide on known epoxy ketone **3**.[40] From hydrogenations[41] (Pd) of **14** (good yield) and of **15** (less efficacious, glacial acetic acid), there was obtained acid **12**, identical with that from **8a**. Thus there are now no less than three routes to **6** and four methods (including Pd hydrogenolysis of lactone **13a**, which was also done) for preparing **12**, but it is obvious that our new route is to date the only one leading to **5** and **8**. Synthesis of **12** from **8a** also is considerably more facile in practice, especially on moderate or large scale, than is preparing it from **14** or **15**.

(40) F. Hoffmann-La Roche, Netherlands Appln. 6,600,200 (1966); *Chem. Abstr.*, **65**, 15297 (1966).

(41) J. D. Loudon and L. A. Summers, *J. Chem. Soc.*, 3809 (1957).

Further work (Scheme II) with the promising **5**, **8**, and **13**, directed toward other, more elaborate, bridged compounds was undertaken. *A priori*, it seemed that it should be an easy matter to arrive at bridged lactams, but until several idiosyncratic aspects of the chemistry involved were fully understood, the goals eluded us. Esters (and the **4a** amide) from **8a** were expected to reduce with $NaBH_4$ to corresponding 5-hydroxy compounds, but when this was tried the product was instead diol **17** and gave bridged ether **18** on treatment with $SOCl_2$. Indeed, when lactone **13a** itself was reduced with $NaBH_4$ in excess, diol **17** and from it ($SOCl_2$) ether **18** again were formed. The lactone **13a** is quite unreactive to ammonia but could be made to react by heating

with primary amines (methylamine, benzylamine, H_2NNH_2) giving hydroxy amides **19a**, **b**, and **c**, respectively. Interestingly, **19a** reverted rather easily through loss of CH_3NH_2 (heat, or acids) to lactone **13a**, although **19b** and **c** were more stable.

From **19b** with $SOCl_2$ it was possible to prepare the 5-chloro amide **20**. On treatment with potassium *tert*-butoxide, **20** underwent internal displacement[42] of the very reactive benzhydryl chloride, forming *N*-benzyl bridged lactam **21**. Unfortunately, this route is not a general one to bridged lactams and amines of the type; after reduction of **21** to corresponding amine **25d**, attempted hydrogenolysis (or other cleavage) of the *N*-benzyl group resulted in ring opening (*i.e.*, rupture of the benzhydryl N bond) as well.

At this point a notable feature of dibenzsuberone nitriles **5** should be mentioned. With bases such as NaH, $NaNH_2$, potassium *tert*-butoxide, and even with various amines (pyrrolidine, piperidine), solutions of **5a** become lastingly very deep purple. Not only is the **5a** anion obviously an electron-delocalized chromophore like anions of other phenylacetonitriles, particularly those having *o*- or *p*-nitro or carbonyl substituents, but also it is quite reactive; *i.e.*, after generation it is held well and may react smoothly. Thus alkylations of **5a** with neutral and basic alkyl halides and with α-bromo esters, etc., in the presence of NaH in DMF and toluene, were found to proceed very well, giving a variety of substituted keto nitriles **26**. The keto acid corresponding to **26a**, like **8a**, gave corresponding bridged lactone **36** (R = CH_3) when reduced with $NaBH_4$ and acidified.

Thinking initially that reduction of oximes corresponding to keto acids, nitriles, esters, or amides might serve to place an amino substituent at position 5, we also explored reaction of various 5-keto compounds with hydroxylamine. Here again, evidence was found to indicate relatively high reactivity centering around the 10-cyano group and an expected, relative inertness of the 5-keto group. Keto acid **8a** and its corresponding esters and amide did not form oximes, or in fact react at all, with hydroxylamine under the usual conditions. The nitrile **5a**, however, reacted rather readily with H_2NOH; so also did several of the substituted keto nitriles **26b** and **c**. The products, **27**, all gave strong ferric chloride tests and thus logically were construed as being amidoximes. However, in none of these compounds was there the usual uv [270 mμ (ϵ ~14,000)] band characteristic of the conjugated 5 ketones; thus it was evident that the keto amidoximes existed virtually completely in the ring tautomeric form as shown in **27**. Further proof of the presence of an N–OH bond in the weakly basic **27a** as well as in the strongly basic **27b** and **c**, and a good synthesis for the equally ring-tautomeric (uv), corresponding ψ-keto amidines **28a–c**, was found in nickel-catalyzed hydrogenolysis of **27a–c**. However, further hydrogenolysis of **28** (Pd/C) again led to benzhydryl N-bond cleavage as in **25**.

Returning to the lactam problem *per se*, we capitalized on foregoing facts and found that lactone **13a** also reacted with hydroxylamine, provided the temperature was high enough (refluxing glycol). From this reaction was isolated the *N*-hydroxy lactam (bridged cyclic hydroxamic acid) **22** in high yield. Hydrogenolysis (nickel) of **22** then proceeded well, giving lactam **23**, after which straightforward alkylations (NaH) gave *N*-alkyl lactams **24**, in turn reduced with $LiAlH_4$ or borane to bridged amines **25**.

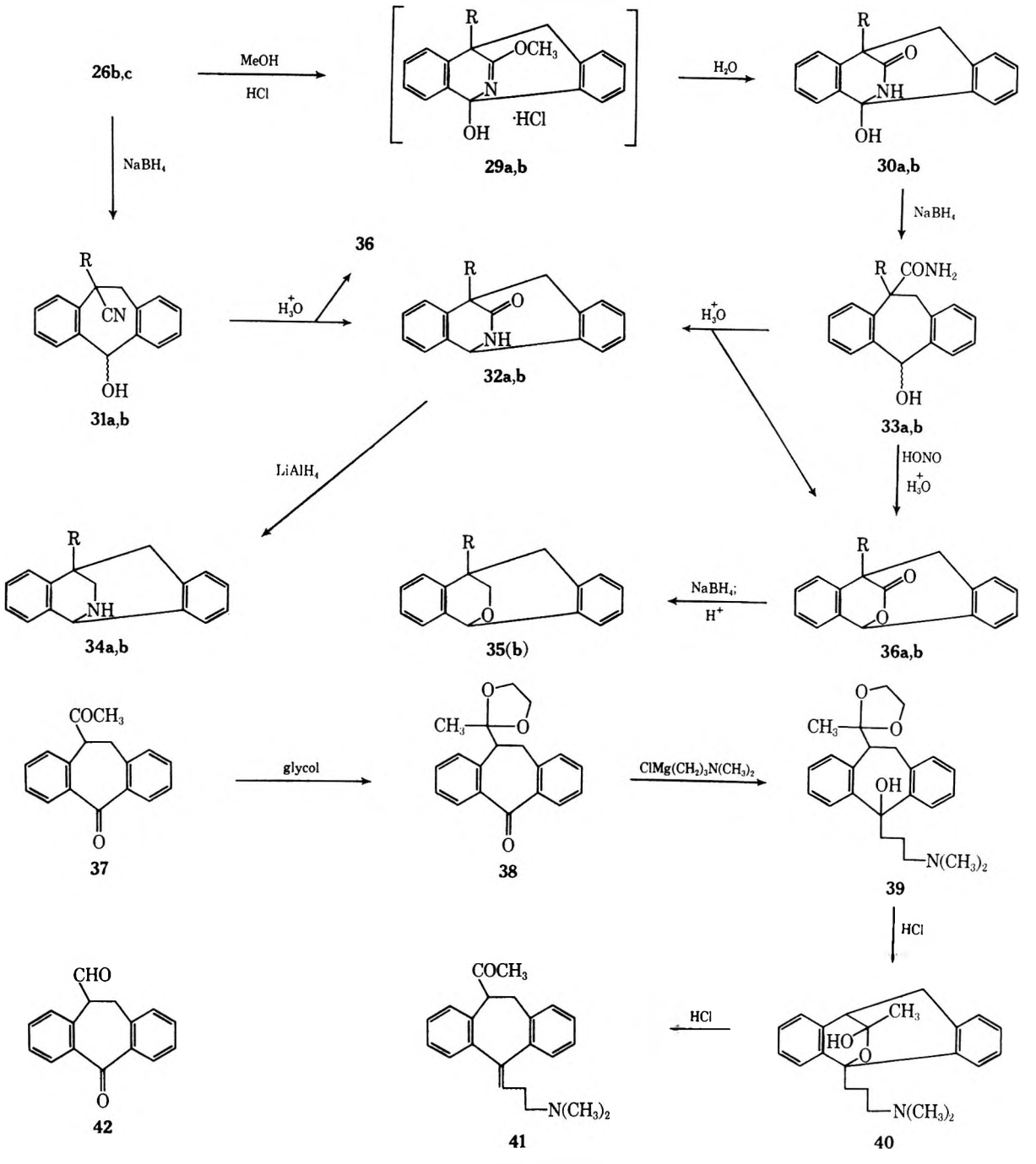
Synthesis of the projected, simpler, bridged heterocyclic compounds having been disposed of, there then remained the problem of synthesizing bridged lactones and lactams from 10-substituted keto nitriles **26**. It was evident in initial, exploratory work that a different approach to synthesis of, *e.g.*, **32** and **36** might be required, for on $NaBH_4$ reduction of **26b** and **c** little or no evidence of spontaneous iminolactone closure was found. Rather, from **26b** and **c** with borohydride (Scheme III) an isomeric mixture of hydroxy nitriles **31** in each case was formed. Also, caution in the amount of reagent used in these reactions was required, for (unlike **9**) there was both a tendency toward overreduction (benzhydrol hydrogenolysis) and, at least with **31b**, a tendency for ill-defined formation of anthracenes (*via* ring opening and reclosure, or other type of rearrangement) to occur in the presence of excess $NaBH_4$. One isomer of **31a** was eventually obtained crystalline; **31b** was not separated into its components but was characterized as a corresponding methiodide. Crude **31b**, and either crude **31a** mixture or its crystalline fraction, on boiling with concentrated hydrochloric acid gave principally the respective, basic, bridged lactams, **32b** and **a**. Structures **32** were particularly clear from nmr spectra, in which the benzhydryl proton doublet (δ 4.97, coupled to NH) collapsed to singlet on exchange of NH with deuterium. A marked contrast is to be seen between the **31** → **32** reactions and the formation of **9** *via cis*-hydroxy nitrile from **5a**; the nitrile group in **31** is much less reactive than in the latter case. For the most part, only when there is generated a carbonium ion from the carbinol at position 5 does CN interact, in the sense of a Ritter reaction.

The relatively unreactive nature of the nitrile group attached to the quaternary carbon atom was seen again in attempted methanolyses. Prolonged boiling of keto nitriles **26b** and **c** with methanolic HCl led to new products, thought at first to be imino ethers; however, initial analytical difficulties with these substances were resolved (nmr showed presence of extraneous methanol), and it emerged that respective bridged (uv) keto amides **30**, tending to crystallize as methanolates, were at hand. Thus the overall effect of the methanolytic reaction was partial hydrolysis, and, as in formation of **27**, nucleophilic attack on CN led to a bridged (ψ) derivative. Possibly ring tautomeric keto imino ethers **29** actually are intermediates in **26** → **30**, for it was observed that other strong acids (PPA, F_3CCOOH, concentrated HCl) did not convert **26** to **30** but gave mainly polymeric substances.

Keto amides **30** were reduced with $NaBH_4$ (again, as in **26**, with necessary circumspection) and with resulting, isomeric mixtures of hydroxy amides **33**, experiments involving treatment with acids under various conditions were tried Hot, strong, aqueous HCl again led **33** to form principally the respective lactams **32**, but refluxing **33a** with dilute HCl gave a separable mixture of lactam **32a** (mp 188°, ir 6.08 μ) and lactone **36a** (mp 163–165°, ir 5.75 μ). Similar observations were made with **33b**, reflux with 7% HCl leading almost exclusively to the lactone. Evidently, acid of low

(42) G. N. Walker and D. Alkalay, *J. Org. Chem.*, **31**, 1905 (1966).

SCHEME III



a, R = $(CH_2)_2N(CH_3)_2$
b, R = $(CH_2)_3NCH_3$

strength less efficiently converts carbinol to carbonium ion and partial or complete hydrolysis of amide may intervene, leading to lactone. There is no conversion of lactam **32** to lactone **36** under any conditions tried, including use of nitrous acid. However, a better way to proceed from hydroxy amide **33** to lactone **36** was found in nitrous acid deamination of the amide.

Hydride reduction of basic, bridged lactams **32** gave bridged amines **34**. There was also applied that which had been learned from experiments leading to **18**; after acid solvolysis of **33a** and borohydride reduction of the crude product, basic bridged ether **35b** was isolated (in low yield) as corresponding hydrochloride

Having placed appropriate (basic) side chains on the 10 carbon and the 13 atom of various, novel 5,10-bridged 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptenes, we wished to complete the work by preparing from **5a** at least one 5,10-bridged compound similarly substituted at position 5. Since organometallic reagents preferentially attacked the nitrile group of **5a** (with initial development of characteristic purple color of the anion), an inert group was needed at position 10, and, to secure it, acid chloride from **8a** was converted to diketone **37** using methylcadmium. Glycol reacted quite selectively with **37**, as expected, giving keto ketal **38**. Keto aldehyde **42** was also prepared, by Rosenmund reduction of keto acid chloride or better by Stephen reduction of the keto nitrile but was fairly unstable and could not be converted similarly to a monoacetal. Reaction of the Marxer Grignard reagent with **38** proceeded smoothly,

giving basic hydroxy ketal **39**. On treatment of **39**, under very mild conditions with HCl, glycol was removed and, not unexpectedly,[31] bridged hemiketal **40**, showing no evidence spectrally of a ketone group *per se*, emerged. Warm alcoholic HCl then led to dehydration and formation of basic, unsaturated ketone **41** (ir 5.87 μ), characterized as hydrochloride and apparently the anticipated mixture of two diastereoisomers.[6]

Experimental Section[43]

o-(**2-Cyano-2-phenylethyl**)**benzoyl Chloride** (**2a**).—To a stirred solution of 100 g of acid nitrile **1a**[37] in 2 l. of methylene chloride was added 100 g of PCl_5 in portions, during 0.5 hr. After the solution was allowed to stand for 2 hr at room temperature, it was washed with water, and then (while chilling) with 2% NaOH solution, and finally with three additional portions of water. After drying ($MgSO_4$) and evaporating solvent, the residue, triturated with ether–ligroin (bp 38–56°), afforded 98 g of colorless crystals: mp 83–86°, raised on recrystallization (ligroin) to mp 87–89°; ir 4.46 and 5.75 μ; uv (hexane) 246 nm (ϵ 10,650) and 290 (2260); nmr ($CDCl_3$) δ 8.2 (m, 1, aromatic H ortho to –COCl), 7.3–7.7 (m, 8, remaining aromatic protons), 4.15 (quartet, 1, J^{AX} = 5 Hz, J^{BX} = 10 Hz, methine proton), and 3.4 (octet, 2, J^{AB} = 13 Hz, J^{AX} and J^{BX} = 5 and 10 Hz, respectively).

Anal. Calcd for $C_{16}H_{12}ClNO$: C, 71.24; H, 4.49; N, 5.19. Found: C, 71.04; H, 4.64; N, 5.28.

The dried acid chloride was stored in desiccator or closed container at 0° until used.

Treatment of a sample of the cyano acid chloride with NH_4OH gave the corresponding amide nitrile: mp 154–155.5° on recrystallization from ethanol; ir 2.90, 3.18, 4.47, and 6.02 μ.

Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 77.06; H, 5.32; N, 11.01.

With methanol, the cyano acid chloride gave corresponding nitrile methyl ester: mp 119–121° (from ether); ir 4.47 and 5.85 μ.

Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.98; H, 5.4; N, 5.34.

Other substituted cyano acid chlorides **2** were prepared by the same procedure from previously reported cyano acids.[37]

Compound 2b gave colorless crystals from ether–EtOAc: mp 69–72°; ir 4.45 and 5.67–5.70 μ; uv 247 nm (ϵ 11,000) and 291 (2300).

Anal. Calcd for $C_{17}H_{14}ClNO$: C, 71.95; H, 4.97; N, 4.93. Found: C, 71.81; H, 5.3; N, 4.65.

Compound 2c similarly prepared had mp 119–120°; ir 4.45 and 5.69–5.75 μ; uv 227 nm (ϵ 14,690), 246 (9340), 275 (2470), 282 (2770), and inflections 250 (8990) and 294 (1990).

Anal. Calcd for $C_{17}H_{14}ClNO_2$: C, 68.11; H, 4.70; N, 4.67. Found: C, 68.4; H, 4.85; N, 4.60.

Compound 2d gave colorless crystals from ligroin (bp 39–53°): mp 84–85.5°; ir 4.45 (weak) and 5.71 μ (broad); uv 247 nm (ϵ 11,850), 269 (1980), and 290 (2440); nmr ($CDCl_3$) δ 8.3 (m, 1, aromatic H ortho to ClCO group), 6.9–7.6 (m, 7, remaining aromatic H), 4.15 (dd, 1, methine proton α to CN, J^{AX} = 5.4 Hz, J^{BX} = 10.4 Hz), and 2.93–3.66 (octet, centered δ 3.35, 2, J^{AB} = 13 Hz, J^{BX} = 10.5 Hz, J^{AX} = 5.4 Hz).

Anal. Calcd for $C_{16}H_{11}ClFNO$: C, 66.79; H, 3.85; N, 4.86. Found: C, 67.04; H, 3.83; N, 4.55.

Compound 2e was recrystallized from EtOAc: mp 99–101°; ir 4.45 and 5.68–5.72 μ; uv 230 nm (ϵ 17,250) and 280 (4690).

Anal. Calcd for $C_{18}H_{16}ClNO_3$: C, 65.55; H, 4.89; N, 4.24. Found: C, 65.63; H, 5.03; N, 4.25.

10-Cyano-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (**5a**).—A solution of 69.5 g of cyano acid chloride **2a** in 700 ml of *sym*-tetrachloroethane was treated with 120 g of anhydrous $AlCl_3$ and the mixture heated on a steam cone (air condenser) 2.5 hr with swirling or (magnetic) stirring. Evolution of HCl was copious during the first 0.5–0.7 hr, and most of the $AlCl_3$ dissolved. After pouring the chilled solution into ice and excess hydrochloric acid, adding *ca.* 2 l. of ether, and shaking, the organic layer was separated and washed with the following in sequence: two portions of water, an excess of 2% NaOH solution, and three portions of water. Evaporation of the dried ($MgSO_4$), brown solution gave an oil which was induced to crystallize (initially by scratching a sample on watch glass with ether, in later runs by seeding), and the material was triturated with ether–ligroin, to give 40 g of light tan crystals, mp 105–108°, sufficiently pure for further work. Recrystallization from methanol (or ether) gave a pure sample: mp 112–113°; ir 4.46 and 6.07 μ; uv 268 nm (ϵ 14,460) and 341 (490); nmr ($CDCl_3$) δ 8.0 (m, 2, aromatic protons peri to C=O), 7.6–7.1 (m, 6, remaining aromatic H), 4.4 (q, 1, J^{AX} = 3.8 Hz, J^{BX} = 6.5 Hz, methine H), and 3.54–3.49 (doublets, 1 each, J^{AX} and J^{BX} as for δ 4.4, but J^{AB} indiscernible).

Anal. Calcd for $C_{16}H_{11}NO$: C, 82.38; H, 4.75; N, 6.01. Found: C, 82.40; H, 4.78; N, 6.06.

The corresponding 2,4-dinitrophenylhydrazone required 1 week to precipitate when prepared in aqueous ethanolic (H_2SO_4) solution: orange crystals from ethyl acetate, mp 260–262°.

Anal. Calcd for $C_{22}H_{15}N_5O_4$: C, 63.92; H, 3.66; N, 16.94. Found: C, 64.27; H, 3.51; N, 16.69.

Keto Nitrile 5b.—Cyclization of **2b** (48 g) with $AlCl_3$ (58 g) in *sym*-tetrachloroethane (720 ml) by the same procedure gave **5b**, recrystallized from ethyl acetate–ether: mp 119–120°; ir 4.45 and 6.03 μ; uv 270 nm (ϵ 14,650); nmr ($CDCl_3$) very similar to that of **5a**.

Anal. Calcd for $C_{17}H_{13}NO$: C, 82.57; H, 5.30; N, 5.66. Found: C, 82.57; H, 5.12; N, 5.63.

Keto Nitrile 5e.—To stirred solution of 10.4 g of anhydrous stannic chloride in 40 ml of benzene was added (0.3 hr) a solution of 10 g of cyano acid chloride **2e** in 50 ml of benzene. After standing at room temperature, protected from moisture, overnight, hydrolysis with ice and HCl and further work-up as in the preceding experiments gave 6.2 g of keto nitrile, crystallizing from methanol–EtOAc: mp 136–138°; ir 4.46 and 6.15 μ (sharp, moderate–intense peaks); 224, 290, and 326 nm (ϵ 17,100, 9890, and 8020, respectively); nmr ($CDCl_3$) δ 7.77 (s, 1, peri Ar proton between MeO and C=O), 8.0 (m, 1, other Ar proton peri to C=O), 7.2–7.6 (m, 3, Ar protons), 6.95 (s, 1, peri Ar proton between MeO and CN), 4.41 (q, 1, J^{AX} = 3.5 Hz, J^{BX} = 6.5 Hz, methine H), 3.97 (s, 6, methyl of MeO groups), and 3.51 (d, 1, J = 3.5 Hz) and 3.46 (d, 1, J = 6.5 Hz) in which J^{AB} was nearly indiscernible (signals of the CH_2 group).

Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.70; H, 5.15; N, 4.78. Found: C, 73.82; H, 5.19; N, 4.81.

Hydrolysis of Keto Nitriles 5 to Keto Acids 8.—A solution of 25 g of **5a** in 200 ml of glacial HOAc and 300 ml of concentrated hydrochloric acid was refluxed 3 hr, the volume of the solution was then reduced to ~ 100 ml *in vacuo*, and the material was treated with ice water. The crude acid was collected and taken into 5% sodium bicarbonate solution, and the aqueous solution washed with ether and acidified with HCl. A washed (H_2O) and dried ($MgSO_4$) ether extract of the reprecipitated acid on evaporation gave 25 g of crystals of **8a**: mp 140–142°, raised on further recrystallization (ether) to mp 144–145°; ir 5.91 and 6.09 μ; uv 207 and 268 nm (ϵ 23,950 and 14,940, respectively).

Anal. Calcd for $C_{16}H_{12}O_3$: C, 76.18; H, 4.80. Found: C, 76.44; H, 4.73.

Derivatives of 8a.—The corresponding acid chloride was prepared using thionyl chloride: colorless crystals from ether; mp 108–110°; ir 5.59 and 6.07 μ; uv 264 nm (ϵ 14,930).

Anal. Calcd for $C_{16}H_{11}ClO_2$: C, 70.98; H, 4.10. Found: C, 71.0; H, 4.06.

The corresponding amide **4a**, from the acid chloride and NH_4OH, after recrystallization from ethanol–ether had mp 161–162°; ir 2.91, 3.02, 3.12, 6.01, 6.10, and 6.19 μ; uv 268 nm (ϵ 10,110).

Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.47; H, 5.22; N, 5.57. Found: C, 76.45; H, 4.98; N, 5.40.

The corresponding methyl ester, prepared from either acid or acid chloride and recrystallized from methanol–ether (Norit) had mp 50–52°; ir 5.74 and 6.08 μ; uv 268 nm (ϵ 14,760).

Anal. Calcd for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30. Found: C, 76.39; H, 5.24.

The corresponding *N*,*N*-diethyl amide, from acid chloride and diethylamine, was recrystallized from ether: mp 85–86°; ir 6.02 and 6.11 μ; uv 268 nm (ϵ 13,490).

(43) Melting points were obtained using Thomas–Hoover stirred silicone oil bath. Infrared spectra (Nujol mulls, unless otherwise noted) were taken on a Perkin-Elmer double beam instrument, ultraviolet spectra (methanol solutions, unless otherwise noted) with a Cary 14 recording spectrophotometer, and nmr spectra using a Varian A-60 apparatus with TMS internal standard.

Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.14; H, 6.89; N, 4.56. Found: C, 78.29; H, 6.84; N, 4.68.

The corresponding *N*-methyl amide, from acid chloride and methylamine, was recrystallized from methanol: ir 3.06, 3.25, 5.99, and 6.11 μ; uv 269 nm (ϵ 7210), indicating partially ring-tautomeric form.

Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 77.16; H, 5.49; N, 5.27.

Keto acid 8b was obtained by similar hydrolysis of **5b**, in quantitative yield and recrystallized from ether: mp 166–168°; ir 5.92 and 6.09 μ; uv 270 nm (ϵ 14,160).

Anal. Calcd for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30. Found: C, 76.97; H, 5.49.

Keto acid 8e was obtained (2.5 g) by similar hydrolysis of **5e** (4 g) and recrystallized from ether–ethyl acetate: mp 195–196°; ir (Nujol) 3.14 and 5.75 μ; ir ($CHCl_3$) little or no unbonded OH peak, 5.86 with weaker shoulder at 5.75 μ; uv 244, 291, and 330 nm (ϵ 14,640, 9750, and 7610, respectively); nmr (DMSO) δ 7.6 (s, 1, peri proton between MeO and C=O), 7.9 (m, 1, other Ar proton peri to C=O), 7.2–7.5 (m, 3, aromatic protons), 6.95 (s, 1, peri H between MeO and COOH), 4.3 (t, 1, J = 4.5 Hz, methine), 3.83 (s, 6, methoxyl CH_3), and 3.45 (d, 2, J = 4.5 Hz, methylene).

Anal. Calcd for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16. Found: C, 69.30; H, 5.18.

The corresponding acid chloride was prepared using $SOCl_2$ and recrystallized from ether: mp 130–131°; ir 5.60 and 6.10 μ; uv 242, 290, and 324 nm (ϵ 20,300, 10,190, and 7560, respectively); nmr ($CDCl_3$) δ 7.93 (m, 1, peri aromatic H adjacent to ketone on unsubstituted aryl ring), 7.78 (s, 1, peri aromatic H between MeO and ketone), 7.1–7.5 (m, 3, aromatic H), 6.6 (s, 1, peri aromatic H between MeO and COCl), 4.52 (t, 1, J = 4.5 Hz, methine), 3.9 (two singlets, 6, methoxyl CH_3) and 3.63 (d, 2, J = 4.5 Hz, methylene).

Anal. Calcd for $C_{18}H_{15}ClO_4$: C, 65.36; H, 4.57. Found: C, 65.74; H, 4.64.

Keto Amide 4e.—A mixture of 5.5 g of acid nitrile **1e** and 168 g of polyphosphoric acid was heated at 100° and stirred 1 hr. The bright red solution was cooled and stirred with ice and water; the resulting light yellow, crude crystals were collected, washed with water, and dried. After trituration with methanol, there was obtained 3.5 g of product, mp from *ca.* 220°, insoluble in dilute alkali. A pure sample was obtained by recrystallization from a relatively large volume of ethanol: colorless crystals; mp 226–229° (melt greenish); ir 2.93, 3.19, 5.96, 6.16, and 6.30 μ; uv 245, 290, and 328 nm (ϵ 15,580, 9710, and 7330, respectively); nmr (DMSO) δ 7.58 (s, 1, peri proton between MeO and C=O), 7.87 (m, 1, other proton peri to C=O), 7.1–7.5 (m, 3, aromatic H), 6.87 (s, 1, peri proton between MeO and $CONH_2$), 4.1 (t, 1, J = 5 Hz, methine), 3.82 (s, 6, methoxyl CH_3), and 3.42 (d, 2, J = 5 Hz, methylene).

Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.18; H, 5.61; N, 4.33.

Hydrolysis of this compound (1.7 g) with refluxing (4 hr) hydrochloric and acetic acids (25 ml each) gave keto acid **8e** (1.2 g), mp 196–198°, identical (mmp 194–196°, undepressed; spectra identical) with the sample of **8e** from the preceding experiment.

Hydroxy Amide 7e.—Sodium borohydride (3 g) reduction of **4e** (0.3 g, suspended in MeOH), evaporation of most of the methanol from the resulting solution, treatment with water, and ether trituration of the collected, washed, and dried solid, followed by recrystallization from ethanol and methanol, gave colorless crystals: mp 247–249° dec; ir 2.81, 2.95, 3.05, 3.13, 6.02, and 6.18–6.22 μ; uv 282 nm (ϵ 3360) with infl 240 and 288 nm.

Anal. Calcd for $C_{13}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 69.30; H, 6.02; N, 4.24.

Amide 11e.—In the presence of 10% Pd/C (1.5 g), keto amide **4e** (1.5 g) (or **7e**) in glacial HOAc (150 ml) was hydrogenated at 3 atm and 70° for 1 hr. Filtration, evaporation, and recrystallization of the residue (methanol) gave (quantitatively) bluish white crystals: mp 238–240°; ir 2.95, 3.05, 3.13, 6.02, and 6.18–6.22 μ; uv 285 nm (ϵ 3580).

Anal. Calcd for $C_{13}H_{19}NO_3$: C, 72.70; H, 6.44; N, 4.71. Found: C, 72.51; H, 6.38; N, 4.60.

10,11-Dihydro-5,10-epoxymethano-5*H*-dibenzo[*a*,*d*]cyclohepten-12-one (Lactone 13a).—A solution of 20.7 g of keto acid **8a** in 300 ml of methanol was treated with excess $NaBH_4$ (31 g) in portions, cautiously at first because of vigorous effervescence. After heating 0.5 hr on a steam cone and evaporating most of the methanol, the cooled residue was taken into water (300 ml) and the solution acidified with HCl. The collected, water-washed, and dried, voluminous crystals were dissolved in ether and the filtered solution was concentrated, to yield 14 g of lactone, mp *ca.* 148°. A sample, recrystallized from ether, had mp 153–154°; ir 5.75 μ; uv 264 nm (ϵ 500); nmr ($CDCl_3$) δ 6.9–7.4 (m, 8, aromatic H), 5.94 (s, 1, benzhydryl proton), 4.08 (t, 1, J^{AX} = J^{BX} = 4 Hz, methine H at position 10), and 3.33 (octet, 2, J^{AX} = 18 Hz; methylene).

Anal. Calcd for $C_{16}H_{12}O_2$: C, 81.34; H, 5.12. Found: C, 81.11; H, 4.82.

By the same $NaBH_4$ reduction, followed by acidification, were prepared the following compounds.

Lactone 13b, recrystallized from ether, had mp 149–151°; ir 5.78 μ; uv benzenoid; nmr similar to that of **13a**.

Anal. Calcd for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64. Found: C, 81.84; H, 5.45.

Lactone 13e, recrystallized from ether–ethyl acetate, had mp 196–197°; ir 5.77 μ; uv 210, 248, and 286 nm (ϵ 42,000, 5320, and 4810, respectively); nmr ($CDCl_3$) δ 7.4–7.0 (m, 4, aromatic protons of the unsubstituted phenyl), 6.82 (s, 2, peri protons adjacent to methoxyls), 5.88 (s, 1, benzhydryl H), 4.02 (t, 1, J^{AX} = J^{BX} = 3.5 Hz, methine H of position 10), 3.87 (s, 6, methoxyl CH_3), and 3.37 (octet, 2, J^{AB} = 18 Hz, methylene protons).

Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 73.26; H, 5.49.

10,11-Dihydro-12-imino-5,10-epoxymethano-5*H*-dibenzo[*a*,*d*]cycloheptene (Iminolactone, 9).—Solution of 5.2 g of keto nitrile **5a** in 200 ml of methanol was treated with excess $NaBH_4$ (*ca.* 8 g) in portions during 5–10 min; when the exothermic, effervescent reaction subsided, the solution was evaporated (steam cone, 15 min) to remove most of the methanol. Addition of water to the cooled material gave partly crystalline solid, which was collected, washed with water, and dried. The crude material (4.9 g) on fractional crystallization from ether afforded a total of 3.7 g of crystals, mp *ca.* 177–182°, of fairly pure iminolactone, and the remaining material (mostly **10**) was a glass. Further recrystallization from ether gave a pure sample: mp 181.5–183.5°; ir 3.12 (moderate, sharp) and 5.98 μ (intense, sharp); uv benzoid; nmr ($CDCl_3$) δ 7.0–7.4 (m, 9, aromatic H and 1 D_2O exchanged, NH), 5.73 (s, 1, benzhydryl H), 4.12 (t, 1, J^{AX} = J^{BX} = 3.5 Hz, methine), and 3.38 (octet, 2, J^{AX} = J^{BX} = 3.5 Hz, J^{AB} = 18 Hz, methylene).

Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.70; H, 5.67; N, 5.89.

On treatment with 18% hydrochloric acid at room temperature (overnight) the iminolactone gave lactone **13a**: mp 153.5–155° after recrystallization from ether; mmp (with preceding sample of **13a**) 153.5–155.5° (undepressed); ir and nmr spectra identical.

Mother liquors remaining from the purification of **9**, on standing a year (capped vial), afforded an odor of NH_3 and, on recrystallization of residue from methanol, a sample of lactone **13a**, mp 151–153°, identical with preceding specimens.

10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one-10-carboxylic Acid (12). A.—A solution of 15 g of keto acid **8a** in 200 ml of glacial HOAc with 5 g of 10% Pd/C was hydrogenated at 3 atm and 70° for 2 hr. Evaporation of the filtered solution and crystallization in presence of ether–ligroin (bp 38–56°) gave 10.5 g of product: mp 111–114°, raised on recrystallization from the same solvents to mp 120–121°; ir 5.91 μ; nmr ($CDCl_3$) δ 11.8 (s, 1, D_2O exchanged, carboxyl H), 7.1 (s, 8, aromatic protons), and 4.5–3.0 (m, 5, not first-order resolvable, methylene and methine protons).

Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92. Found: C, 80.90; H, 5.93.

B.—Hydrogenation of lactone **13a** (1.5 g) in glacial HOAc (100 ml) in the presence of 10% Pd/C (2.5 g) at 3 atm and 70° for 5 hr, filtration, evaporation, isolation of acidic material through sodium bicarbonate extraction of the crude residue and acidification, and recrystallization from ether–ligroin gave colorless crystals, mp 117–119°, mmp (with A product) 117–120° (undepressed), and ir spectra identical.

C.—A solution of 0.7 g of 5*H*-dibenzo[*a*,*d*]cycloheptene-10-carboxylic acid (**14**)[34] in 50 ml of 2% aqueous potassium carbonate[41] was stirred with 10% Pd/C under hydrogen at room temperature for 71 hr. Filtration, acidification with 2% HCl, extraction with ether, and evaporation of the washed (H_2O) and dried ($MgSO_4$) ether solution gave a colorless, glassy sample,

crystallizing immediately and completely when seeded with A or B sample: mp 118–120°; mmp (with sample A) 119–121° (undepressed); infrared and nmr spectra were identical.

D.—Hydrogenation of 0.35 g of 5*H*-dibenzo[*a*,*d*]cyclohepten-5-one-10-carboxylic acid (**15**)[33] in the presence of 1 g of 10% Pd/C in glacial HOAc at 3 atm and 70° for 3.5 hr, filtration, evaporation, and fractional crystallization of the residue (ether–ligroin) gave a sample of **12**, spectrally identical with preceding ones.

The acid chloride corresponding to **12**, prepared using $SOCl_2$, was not crystalline but was converted readily to a number of derivatives, *e.g.*, corresponding amide **11a**: mp 188–189° after recrystallization from methanol; ir 6.05 μ.

Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.94; H, 6.16; N, 5.74.

Acid 12b was prepared by hydrogenolysis of **8b** and recrystallized from methanol: mp 153–155°; ir 5.88 μ.

Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 81.20; H, 6.42.

10-Cyano-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (6). A. Bromination.—A solution of 12.7 g of keto nitrile **5a** and 12 g of bromine in 300 ml of benzene was let stand 2 days (room temperature). The ether-diluted, washed ($NaHCO_3$ solution, water) and dried solution on evaporation gave 18 g of crude bromo keto nitrile, a slightly fuming, viscous, yellow oil which did not crystallize.

B. Dehydrobromination.—On addition of excess triethylamine to crude A product, there was an exothermic reaction and rapid formation of crystals. After stirring 3 hr and adding water, the crystals were collected, washed with water, dried (yield 12.4 g), triturated with ether, and recrystallized from methanol: mp 175–176°, undepressed on admixture with an authentic sample (lit.[34] mp 171–172°) prepared by reaction of 10-bromo-5*H*-dibenzo[*a*,*d*]cycloheptene-5-one with $Cu_2(CN)_2$ in DMF[34]; ir and other spectra were the same as the latter.

The cyanoenone **6** was also obtained as follows. A. Epoxidation of 5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (11.8 g) in CH_2Cl_2 (350 ml) with 87% *m*-chloroperbenzoic acid (25 g) at room temperature overnight and isolation of epoxide **3** by evaporation of the washed (5% NaOH solution, water) and dried ($MgSO_4$) solution gave, after trituration with ether, 7.5 g of epoxy ketone **3**: mp 113–119°, raised on recrystallization (ether) to mp 127–130° (lit.[40] mp 127–130°); ir 6.01 μ; uv 211, 256, and 295 nm (ε 25,600, 9990, and 2250, respectively).

Anal. Calcd for $C_{15}H_{10}O_2$: C, 81.06; H, 4.54. Found: C, 81.38; H, 4.38.

B.—Potassium cyanide (1.2 g) and epoxy ketone (1.8 g) in water (10 ml) and ethanol (25 ml) was refluxed 1.5 hr, after which the solution was evaporated to smaller volume and treated with water, and the gummy, reddish solid was collected, washed (water), dried, and purified by recrystallization from ether: colorless crystals; mp 175–176°; mixture melting point with preceding samples undepressed; and spectra identical with latter; ir 4.47 and 6.08 μ; uv 212, 254, and 316 nm (ε 14,990, 32,240, and 15,490, respectively) with infl 244 nm.

Anal. Calcd for $C_{16}H_9NO$: C, 83.10; H, 3.92; N, 6.06. Found: C, 82.94; H, 4.04; N, 5.94.

Reduction of a sample of this cyanoenone in methanol with $NaBH_4$ by the procedure already described for preparation of **9**, gave **9**, mp 171–174°, after recrystallization from methanol. The infrared spectra of the two samples were identical.

Attempts to hydrolyze (HCl or H_2SO_4 with HOAc), methanolyze (CH_3OH + HCl), or convert the cyanoenone to corresponding amide (H_2SO_4) were unsuccessful.

Diol 17.—Lactone **13a** (1 g) in 100 ml of methanol was reduced with excess $NaBH_4$ (3 g, added in portions) while heating on a steam cone (20 min) and, after addition of water to cooled residue, neutral material was extracted with ether. The washed (water) and dried ($MgSO_4$) ether solution on evaporation gave nearly quantitative yield of crystals, mp 85–95°, apparently a mixture of diastereoisomers; recrystallization from ether gave a sample, mp 95–105°, ir 3.01 μ (broad, intense).

Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 80.26; H, 6.75.

The same material, and from it in turn the cyclic ether as described in the next experiment, was also obtained when methyl ester, amide, or *N*-methyl amide corresponding to **8a** were reduced similarly with $NaBH_4$.

Bridged Ether 18.—On treatment of 3.1 g of crude diol from preceding experiments with 20 ml of $SOCl_2$ there was rapid reaction. After 5 min, removal of excess reagent *in vacuo* (steam cone) gave a crystalline, but unstable, residue (1.6 g). The latter was treated with an excess of either concentrated NH_4OH or methanolic sodium methoxide to give, on subsequent addition of water, colorless crystals which in each case were collected, washed with water, dried, and recrystallized from methanol: mp 98–99°; ir devoid of C=O and OH bands; uv (benzenoid); nmr δ 5.42 (s, 1, benzhydryl H); and mass spectrum (*m*/*e* 222) confirming the structure.

Anal. Calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.48; H, 6.34.

Hydroxy Amide 19b.—Lactone **13a** (12.5 g) and benzylamine (25 ml) were heated together on a steam cone for 20 hr. The residue remaining after removal of excess amine *in vacuo* was taken into warm EtOAc and the solution diluted with ether. The crystalline product (12.5 g, mp 150–153°) was collected. Recrystallization from methanol gave pure material: mp 160–161°; ir 2.96, 6.03, and 6.29 μ.

Anal. Calcd for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.51; H, 6.14; N, 4.12.

Similar reaction of lactone **13a** (1.5 g) with boiling, 40% aqueous methylamine solution (80 ml) for 15 hr, evaporation of excess reagent, and one recrystallization of residual crystals from ethanol gave a sample of hydroxy amide **19a**, mp 178–181°, ir 3.07 and 6.13 μ. This compound gradually reverted to **13a**, however, on attempted further recrystallization from various solvents and drying at 80°, and a completely pure sample could not be obtained. In $SOCl_2$, the reversion to lactone **13a** was immediate.

Anal. Calcd for $C_{17}H_{17}NO_2 \cdot H_2O$: C, 71.56; H, 6.71; N, 4.91. Found: C, 72.13; H, 6.49; N, 4.5.

Hydroxy acid hydrazide 19c, obtained by heating **13a** with hydrazine at 100° overnight and recrystallized from methanol, had mp 219–221°; ir 2.81, 3.02, and 6.14–6.20 μ.

Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.85; H, 6.08; N, 10.37.

13-Benzyl-10,11-dihydro-5,10-iminomethano-5*H*-dibenzo[*a*,*d*]cyclohepten-12-one (21). A.—Chloro amide **20** was obtained by treating **19b** (5.3 g) with $SOCl_2$ (60 ml) and after standing 3 min removing excess reagent *in vacuo* while warming gently on a steam cone. Attempts to purify the glassy, somewhat unstable, residue (4.8 g) using ether or EtOAc were not successful; the crude material gave a strong Beilstein (Cu) test for chlorine.

B.—Treatment of crude A in 200 ml of *tert*-butyl alcohol with 2 g of potassium *tert*-butoxide under reflux (1 hr), followed by removal of solvent *in vacuo* and addition of water, gave crude, oily crystals. The washed (water) and dried ($MgSO_4$) ether extract afforded on evaporation 3.0 g of colorless crystals: mp 151–153°, raised on further recrystallization (ether) to mp 156–157°; ir 6.02 μ and devoid of NH or OH bands.

Anal. Calcd for $C_{23}H_{19}NO$: C, 84.89; H, 5.89; N, 4.30. Found: C, 85.09; H, 5.63; N, 4.40.

Hydrogenolysis of this lactam in glacial HOAc at 70° afforded amide **11a**, mp 189–190°, identical with authentic specimen.

Bridged Amine 25d.—Lithium aluminum hydride (8 g) reduction of **21** (6.2 g) in THF (200 ml) under reflux (5 hr), subsequent addition of water (40 ml) and ether (600 ml), filtration, and evaporation of dried (K_2CO_3) solution gave crude base which was converted by ethereal ethanolic HCl to the corresponding hydrochloride: colorless crystals from methanol–ethanol; mp 198–200°, resolidifying and melting 246–248° dec; ir devoid of OH, NH, or C=O bands; nmr (DMSO) δ 6.06 (s, 1, benzhydryl proton).

Anal. Calcd for $C_{23}H_{21}N \cdot HCl \cdot {}^1/_2H_2O$: C, 77.40; H, 6.50; N, 3.93. Found: C, 77.56; H, 6.52; N, 3.90.

Hydrogenolysis of the amine·HCl (1.25 g) in ethanol (150 ml) and methanol (50 ml) in the presence of 10% Pd/C (1.5 g) at 60° for 2 hr and recrystallization of the product (0.8 g) from ethanol gave **10,11-dihydro-10-aminomethyl-5*H*-dibenzo[*a*,*d*]cycloheptene hydrochloride**, mp 229–231°; the identically same compound (ir, nmr) was obtained by borane or $LiAlH_4$ reduction of amide **11a** and conversion of basic product to corresponding hydrochloride.

Anal. Calcd for $C_{16}H_{17}N \cdot HCl$: C, 73.97; H, 6.98; N, 5.39. Found: C, 74.30; H, 6.92; N, 5.39.

13-Hydroxy-10,11-dihydro-5,10-iminomethano-5*H*-dibenzo[*a*,*d*]cyclohepten-12-one (22).—Hydroxylamine HCl (35 g) in water (20 ml) was neutralized at 0° by slowly adding NaOH (14 g) in water (10 ml), ethylene glycol (120 ml) was added, the solution was filtered, lactone **13a** (5.25 g) was added; the solution

was refluxed 13 hr and kept at 100° for 4 days. The product, crystallized on addition of water, was collected, washed with water and ether, and dried: yield 3.75 g; mp 233–236°, raised on recrystallization from ether to mp 237–239°; ir 6.05 μ and bonded OH; nmr (DMSO) δ 5.41 (s, 1, benzhydryl proton).

Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.47; H, 5.22; N, 5.57. Found: C, 76.65; H, 4.94; N, 5.55.

The *N*-hydroxyl lactam gave a deep purple $FeCl_3$ test.

Bridged Lactam 23.—To a solution of 19.5 g of **22** in 1800 ml of ethanol was added 6 teaspoons of Raney nickel (washed with water and ethanol), and the suspension was shaken under H_2 (3 atm) at 70° for 1.5 hr. The warm suspension was filtered, the catalyst was leached with several portions of hot ethanol, and the combined filtrates were evaporated. The yield of ethanol-ether triturated, colorless crystals was 15 g: mp 226–228°, not raised on recrystallization from ethanol; ir 3.04 (moderate, broad) and 6.10 μ with subsidiary bands 5.96 and 6.2–6.25 μ; nmr (DMSO) δ 8.8 (d, 1, J = 5.5 Hz, exchange with D_2O, NH), 6.9–7.5 (m, 8, aromatic protons), 5.18 (d, 1, J = 5.5 Hz, benzhydryl proton, collapsing to s on deuteration of NH), 3.72 (t, 1, $J \simeq 4$ Hz, methine), and 3.17 (octet, 2, J^{AB} = 19 Hz, $J^{AX} = J^{BX}$ = 4 Hz, methylene).

Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.99; H, 5.45; N, 6.06.

N-Alkylation of 23.—Compound **24a**, for example, was prepared by treating 5.5 g of **23** in 400 ml of toluene with 1.15 g of NaH (56%, oil) and after 3 min with 50 ml of iodomethane. The suspension was refluxed and stirred 3.3 hr, then cooled, diluted with ether, washed with water, dried ($MgSO_4$), and evaporated to small volume; the crystals (5.6 g) were collected with the aid of ether. A sample recrystallized from ether had mp 245–246°; ir 6.07 μ; nmr ($CDCl_3$) δ 6.9–7.4 (m, 8, aromatic protons), 4.82 (s, 1, benzhydryl H), 3.9 (t, 1, J = 3.5 Hz, methine), 3.26 (octet, 2, J^{AB} = 18 Hz, $J^{AX} = J^{BX}$ = 3.5 Hz, methylene), and 3.02 (s, 3, *N*-methyl).

Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 82.20; H, 6.15; N, 5.62.

By similar procedure using 2–3 equiv of appropriate *N*,*N*-dimethyl-β- and -γ-chloroalkylamines, there were prepared the following *N*-alkyl lactams.

Compound 24b, after evaporation of dried (K_2CO_3) organic solution and recrystallization from ether–ligroin, had mp 86.5–88°, ir 6.08–6.10 μ.

Anal. Calcd for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.24; H, 7.17; N, 8.88.

Compound 24c, from ether, had mp 125.5–127°, ir 6.03 μ.

Anal. Calcd for $C_{21}H_{24}N_2O$: C, 78.71; H, 7.55; N, 8.74. Found: C, 78.67; H, 7.77; N, 8.72.

Bridged Amines 25.—Lithium aluminum hydride reduction of lactams **24** in THF as described for amine **25d** and, when appropriate, conversion of crude products to suitable derivatives by standard procedures, gave the following compounds.

Compound 25e was obtained from reduction of **24** (R = H); the hydrochloride was obtained from ethanol–ether, mp 272–274° dec.

Anal. Calcd for $C_{16}H_{15}N \cdot HCl$: C, 74.55; H, 6.26; N, 5.44. Found: C, 74.73; H, 6.05; N, 5.44.

Compound 25a was obtained as the hydrochloride, from ethanol–ether, mp 251–253°.

Anal. Calcd for $C_{17}H_{17}N \cdot HCl$: C, 75.12; H, 6.67; N, 5.15. Found: C, 75.04; H, 6.57; N, 5.26.

Compound 25b was an oil; the corresponding dipicrate was recrystallized from methanol, mp 233–234° dec.

Anal. Calcd for $C_{32}H_{30}N_8O_{14}$: C, 51.20; H, 4.03; N, 14.93. Found: C, 51.36; H, 3.84; N, 15.2.

Compound 25c, also an oil, was characterized as the dipicrate, mp 229–230° dec (from methanol).

Anal. Calcd for $C_{33}H_{32}N_8O_{14}$: C, 51.83; H, 4.22; N, 14.66. Found: C, 51.77; H, 4.60; N, 14.38.

10-Cyano-10-(β-dimethylaminoethyl)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (26b).—A swirled solution of 35.1 g of keto nitrile **5a** in 125 ml of DMF was treated with 7.2 g of NaH (56%, oil) with occasional brief cooling, 250 ml of 1.39 *M* dried toluene solution of β-dimethylaminoethyl chloride was added to the very deep purple solution, and the mixture was heated on a steam cone with stirring 2.5 hr; additional chloro amine solution (100 ml) was added after 0.8 hr. At the end of the reaction period, the deep purple color had been discharged. The deep reddish, cooled suspension was stirred into ice and water (1 l.), ether was added, the organic layer was washed (three portions of water) and dried (K_2CO_3), and the solvents were evaporated. The crude, red-brown oil was taken into 1 l. of ether, and the dried (K_2CO_3) solution filtered and treated with a slight excess of 5% ethanolic HCl to precipitate the corresponding hydrochloride: 28 g, crystallizing in ethanol–ether as a solvated form; mp 217–220° dec; after recrystallization from ethanol–ether and drying at 80° *in vacuo*, mp 204–206° dec; ir 4.45 and 6.02 μ as well as bands indicative of aminium chloride; uv 269 nm (ε 13,910).

Anal. Calcd for $C_{20}H_{20}N_2O \cdot HCl$: C, 70.47; H, 6.21; N, 8.22. Found: C, 70.32; H, 6.41; N, 8.05.

The corresponding free base, prepared from purified hydrochloride with NaOH solution, extracted with ether, dried (K_2CO_3), and isolated by evaporation, was a colorless oil, ir 6.02 μ.

Compound 26c was prepared by essentially the same procedure, from **5a** (30 g) and γ-dimethylaminopropyl chloride (50 ml) in 65 ml of DMF and 100 ml of toluene in the presence of 5.6 g of NaH (56%, oil), and also isolated as the hydrochloride (22.5 g): mp 199–201°; ir 4.47 and 6.03 μ; uv 269 nm (ε 13,870).

Anal. Calcd for $C_{21}H_{22}N_2O \cdot HCl$: C, 71.07; H, 6.53; N, 7.90. Found: C, 71.18; H, 6.91; N, 7.73.

The corresponding base was not crystalline.

Compound 26a, prepared by alkylation of **5a** in DMF with iodomethane in the presence of NaH, was an oil and was characterized by hydrolysis (HCl and HOAc, 3-hr reflux) to the corresponding keto acid: mp 142–144° (from ether); ir 5.90 and 6.06 μ; uv 268 nm (ε 12,440).

Anal. Calcd for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30. Found: C, 76.60; H, 5.08.

Sodium borohydride (12 g) reduction of this keto acid (5 g) in methanol (100 ml) under reflux (0.5 hr) and after evaporation acidification of the aqueous solution of hydroxy acid, gave the 10-methyl-substituted bridged lactone (**36**, R = CH_3): yield 5 g; colorless crystals (from ether); mp 174–175°; ir 5.78 μ.

Anal. Calcd for $C_{17}H_{14}O_2$: C, 81.6; H, 5.64. Found: C, 81.8; H, 5.71.

Compound 26d, prepared by similar alkylation of **5a** with ethyl bromoacetate and recrystallized from methanol, had mp 101.5–103.5°; ir 4.48, 5.80, and 6.05 μ; uv 269 nm (ε 12,930).

Anal. Calcd for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39. Found: C, 75.27; H, 5.24; N, 4.33.

Bridged (ψ) Keto Amidoximes 27.—Solutions of hydroxylamine, prepared from 40 g of $H_2NOH \cdot HCl$ and 16 g of NaOH in 150 ml of water at 0°, and keto nitrile **5a** (16 g) in 250 ml of ethanol were combined and refluxed 4 hr. On addition of 1.5 l. of ice and water, **27a** crystallized and was collected, washed with water, dried (yield 8 g), and recrystallized from methanol: colorless crystals; mp 182–183°; ir 2.91 and 6.01 μ; uv 266 and 274 nm (ε 2400 and 2100, respectively).

Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.29; H, 5.31; N, 10.49.

The amidoxime gave a deep red test with $FeCl_3$.

The hydrochloride of **27a**, recrystallized from ethanol–acetone, had mp 184–188° dec, and was solvated (nmr), ir 5.96 μ and NH, OH bands.

Anal. Calcd for $C_{16}H_{14}N_2O_2 \cdot HCl$: C, 63.47; H, 4.99. Found: C, 63.44; H, 5.32.

Compound 27b, prepared by 3-hr reflux of **26b** (3.75 g) with H_2NOH (from 9 g of $H_2NOH \cdot HCl$ and 4 g of NaOH) in 35 ml of water and 55 ml of ethanol and precipitated from the chilled, diluted solution by dilute NaOH, was collected, washed, dried (yield 2.8 g), and recrystallized from methanol: mp 236–238°; ir 6.04–6.10 μ and a very broad OH band; uv showing no conjugated ketone; $FeCl_3$ test wine-red.

Anal. Calcd for $C_{20}H_{23}N_3O_2$: C, 71.19; H, 6.87; N, 12.45. Found: C, 71.13; H, 6.97; N, 12.09.

Compound 27c, from 8 g of **26c**, 19 g of $H_2NOH \cdot HCl$ and 8 g of NaOH in 80 ml of water, and 100 ml of ethanol by the same procedure as in the preceding experiment, was obtained (6 g) and recrystallized from ether: mp 216–217°; ir 3.04 and 6.10 μ: uv devoid of conjugated C=O; $FeCl_3$ test deep green.

Anal. Calcd for $C_{21}H_{25}N_3O_2$: C, 71.77; H, 7.17; N, 11.96. Found: C, 72.16; H, 7.33; N, 11.74.

Bridged (ψ) Keto Amidines 28.—A solution of 3.5 g of amidoxime **27a** in 280 ml of ethanol was shaken under H_2 (3 atm) in the presence of 1 teaspoon Raney nickel at 60° for 2 hr. The catalyst was filtered and leached with five portions of ethanol, and the combined filtrates were evaporated to give 3 g of amidine **28a**: mp 261–262° dec (from ethanol); ir 2.94, 3.12, and 6.03 μ; $FeCl_3$ test negative.

Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.89; H, 5.42; N, 11.14.

The corresponding hydrochloride crystallized from ethanol as a hemihydrate: mp 284–286°; ir 3.13 (intense, broad) and 5.97 μ (sharp); uv 265 nm (ϵ 1060).

Anal. Calcd for $C_{16}H_{14}N_2O \cdot HCl \cdot {}^1/_2H_2O$: C, 64.97; H, 5.45; N, 9.47. Found: C, 64.34; H, 5.07; N, 9.21.

Hydrogenation of **28a** in glacial acetic acid in the presence of Pd/C at 70° for 4 hr resulted in hydrogenolysis and solvolysis as well, giving amide **11a** on work-up, mp 189–191°, mixture melting point with preceding sample undepressed.

Compound 28b was obtained by hydrogenation of **27b** in ethanol with Raney nickel as for **28a** and recrystallized from ethanol: colorless crystals; mp 262–264°; ir 5.98, 6.19 μ and multiple NH and OH band; $FeCl_3$ test negative.

Anal. Calcd for $C_{20}H_{23}N_3O$: C, 74.74; H, 7.21; N, 13.07. Found: C, 74.65; H, 7.49; N, 13.27.

The corresponding dihydrochloride had mp 294–296° after recrystallization from ethanol, ir 5.96 μ and very broad NH band.

Anal. Calcd for $C_{20}H_{23}N_3O \cdot 2HCl$: C, 60.91; H, 6.39. Found: C, 60.56; H, 6.70.

Compound 28c, in quantitative yield from hydrogenation (Raney nickel) of **27c**, was recrystallized from ethanol: mp 192–194°; ir 2.96, 3.12, 3.20, and 6.25 μ; uv benzenoid and end absorption.

Anal. Calcd for $C_{21}H_{25}N_3O$: C, 75.19; H, 7.51; N, 12.53. Found: C, 75.11; H, 7.25; N, 12.30.

The corresponding dihydrochloride was recrystallized from methanol–ethanol, mp 329–330° dec.

Anal. Calcd for $C_{21}H_{25}N_3O \cdot 2HCl$: C, 61.76; H, 6.67; N, 10.29. Found: C, 61.91; H, 6.65; N, 10.28.

Bridged (ψ) Keto Amides. 10-(β-Dimethylaminoethyl)-10,11-dihydro-5-hydroxy-5,10-iminomethano-5*H*-dibenzo[*a*,*d*]cyclohepten-12-one (30a).—A hydrogen chloride saturated solution of 15 g of **26b** in 1 l. of methanol was refluxed 7 hr, the solution being cooled and re-treated every 2 hr with HCl. Removal of solvent on a steam cone and (next day) trituration of the semisolid residue with methanol–ether afforded 14.3 g of **30a** hydrochloride: mp 283–286° dec, raised on recrystallization (methanol) to mp 287–289° dec; ir 3.16 and 5.97 μ; uv lacking conjugated C=O band; nmr indicated slight MeOH solvation.

Anal. Calcd for $C_{20}H_{22}N_2O_2 \cdot HCl$: C, 66.93; H, 6.46; N, 7.81. Found: C, 67.30; H, 6.38; N, 7.65.

The free base, liberated with NaOH solution, isolated by ether extraction, and recrystallized from methanol, had mp 208–209° and was also a methanolate, ir 3.13 and 5.98 μ.

Anal. Calcd for $C_{20}H_{22}N_2O_2 \cdot CH_3OH$: C, 71.16; H, 7.39; N, 7.90. Found: C, 71.60; H, 7.27; N, 7.99.

Compound 30b.—Treatment of 5 g of **26c** with methanolic HCl (8 hr) and isolation as in the preceding experiment gave 2 g of slightly discolored hydrochloride, mp *ca.* 228° dec. Recrystallization from methanol–ether gave colorless crystals: mp 245–247° dec, after drying *in vacuo;* ir 5.95–6.03 μ together with OH band; uv 266 and 274 nm (ϵ 1000 and 950, respectively).

Anal. Calcd for $C_{21}H_{24}N_2O_2 \cdot HCl$: C, 67.64; H, 6.76; N, 7.51. Found: C, 67.88; H, 6.73; N, 7.39.

The base was obtained either from pure hydrochloride or from mother liquors remaining after isolation of the sample of hydrochloride, by action of NaOH solution. The crude base, initially not crystalline after extraction with ether and evaporation of the dried (K_2CO_3) solution, was reconverted to the hydrochloride and the hydrochloride was converted again to base using K_2CO_3 solution. The crystalline residue, remaining after evaporation of the washed (H_2O) and dried (K_2CO_3) ether extract, on recrystallization from ether gave colorless crystals: mp 210–212°; ir 3.14 and 6.01μ; uv 260–268 and 274 mn (ϵ 850).

Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 75.11; H, 7.44; N, 8.29.

Hydroxy Nitriles 31.—A solution of 8 g of **26c** in methanol (100 ml) was treated with *ca.* 17 g of NaBH in portions during 5–10 min. The solution was warmed gently on a steam cone 10 min, and then cooled and diluted with ice water. The collected, washed (water), and dried product (7 g) was taken up in ether, and the dried (K_2CO_3) and filtered solution was allowed to evaporate slowly. From the residue with the aid of ether and a small amount of ethanol were obtained several crops (3.2 g) of a crystalline isomer of **31b**: mp 175–176° after recrystallization from ethanol; ir 4.47 μ and bonded OH band; uv devoid of conjugated C=O; nmr ($CDCl_3$) δ 7.0–7.6 (m, 8, aromatic protons), 5.60 (s, 1, benzhydryl H), 4.53 and 3.03 (doublets, 1 each, J^{AB} = 14 Hz, magnetically nonequivalent methylene protons), and 1.8–2.2 (m, 12, methylenes and *N*-methyl of side chain).

Anal. Calcd for $C_{21}H_{24}N_2O$: C, 78.71; H, 7.55; N, 8.74. Found: C, 78.73; H, 7.63; N, 8.80.

The material (*ca.* 4 g) remaining in the filtrates after collection of the crystalline portion was a pale yellow glass having similar spectral characteristics and may have been mainly the other isomer of **31b**.

The corresponding hydrochloride, prepared from crystalline **31b** and recrystallized from ethanol–ether, had mp 211–212° dec, ir 2.94 (broad) and 4.48 μ.

Anal. Calcd for $C_{21}H_{24}N_2O \cdot HCl$: C, 70.67; H, 7.06; N, 7.85. Found: C, 70.69; H, 7.50; N, 8.04.

Compound 31a was prepared by similar $NaBH_4$ reduction of **26b** and isolated by extraction with ether as a viscous, colorless glass or amorphous solid, apparently a mixture of isomers: ir broad, bonded OH, and 4.47 μ.

A corresponding methiodide methanolate was prepared from crude **31a** with iodomethane in ether and recrystallized from methanol–ether, mp 235–237° dec, ir 3.00 and 4.46 μ.

Anal. Calcd for $C_{21}H_{25}IN_2O \cdot CH_3OH$: C, 55.00; H, 6.09; N, 5.83. Found: C, 55.35; H, 6.18; N, 5.78.

Recrystallization from ethanol rather than methanol gave the hydrated salt, mp 241–242°.

Anal. Calcd for $C_{21}H_{25}IN_2O \cdot H_2O$: C, 54.08; H, 5.84; N, N, 6.01. Found: C, 54.18; H, 5.92; N, 5.96.

Were the borohydride reductions leading to **31** prolonged beyond 15–20 min with an excessively large amount of $NaBH_4$ present, further reduction and, in the case of **31b**, formation of anthracene (uv) by-products of undetermined structure, were encountered. In one attempted preparation of **31a** involving a large excess of $NaBH_4$ and 3 hr of heating (steam cone), there was isolated **10-cyano-10-(β-dimethylaminoethyl)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene** as the corresponding hydrochloride: mp 288–290° (from ethanol); ir 4.47 μ.

Anal. Calcd for $C_{20}H_{22}N_2 \cdot HCl$: C, 73.49; H, 7.09; N, 8.57. Found: C, 73.74; H, 7.06; N, 8.59.

Hydroxy Amides 33.—Reductions of ψ-keto amides **30** with $NaBH_4$ in methanol were carried out by the same procedure as for **31**, and the respective products were isolated by dilution with water, extraction with ether, and evaporation of the well-washed (water) and dried (K_2CO_3) solutions.

Compound 33a, a colorless glassy mixture of isomers which did not crystallize, was characterized by converting a sample to corresponding methiodide: mp 235–238° dec after recrystallization from ethanol; ir 2.96–3.14 (broad, intense) and 5.98–6.05 μ; uv devoid of conjugated C=O.

Anal. Calcd for $C_{21}H_{27}IN_2O_2$: C, 54.08; H, 5.84; N, 6.01. Found: C, 54.36; H, 5.81; N, 6.00.

Compound 33b crystallized partly, and the crystalline isomer (from ether) had mp 164.5–166°; ir 2.87, 2.98–3.18, and 5.96–5.99 μ; uv lacking conjugated C=O.

Anal. Calcd for $C_{21}H_{26}N_2O_2$: C, 74.52; H, 7.74; N, 8.28. Found: C, 74.73; H, 7.76; N, 8.20.

Bridged Lactams 32.—A solution of crude **31a** (3.5 g) in 100 ml of concentrated HCl was refluxed 3.5 hr. After removal of most of the aqueous HCl *in vacuo*, a cooled, filtered water solution of the residue was made basic with K_2CO_3 and the material extracted with ether. Evaporation of the washed (H_2O) and dried (K_2CO_3) ether solution and crystallization of the residue (ether) gave 1.3 g of **32a**: colorless crystals; mp 187.5–188°; ir 6.08 μ (shoulder, 6.01 μ); nmr ($CDCl_3$) δ 7.0–7.6 (m, 9, aromatic protons and NH), 5.0 (d, 1, J = 5.2 Hz, collapsing to s when NH deuterated, benzhydryl proton), 3.05 (q, 2, J = 17 Hz, methylene), and 2.35–2.60 (m, 10, side chain CH_2 and NMe_2).

Anal. Calcd for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.52; H, 7.33; N, 9.15.

The corresponding hydrochloride was recrystallized from ethanol–ether: mp 252–254°; ir 2.89–296, 3.06, and 6.00 μ.

Anal. Calcd for $C_{20}H_{22}N_2O \cdot HCl \cdot {}^1/_2H_2O$: C, 68.26; H, 6.88; N, 7.96. Found: C, 67.98; H, 6.61; N, 7.74.

The same **32a** was obtained by similar treatment of hydroxy amide **33a** with concentrated HCl.

Compound 32b, similarly prepared by the action (3.5 hr of reflux) of concentrated HCl (400 ml) on 7.6 g of crystalline hydroxy nitrile **31b** in 5.4 g yield, had mp 168–170°; ir 6.01 μ and a highly bonded NH band; nmr ($CDCl_3$) δ 8.0 (d, 1, exchanged with D_2O, NH), 6.8–7.5 (m, 8, aromatic protons), 4.97 (d, 1, J = 5.4 Hz, collapsed to s on deuteration of NH, benz-

hydryl proton), 2.98 (q, 2, J^{AB} = 17.7 Hz, methylene), and 1.5–2.5 (m, 12, methylenes and NCH_3 of side chain).

Anal. Calcd for $C_{21}H_{24}N_2O$: C, 78.71; H, 7.55; N, 8.74. Found: C, 78.95; H, 7.68; N, 8.79.

The corresponding hydrochloride had mp 251–252° (from ethanol–ether); ir 2.91, 3.16, and 6.02 μ.

Anal. Calcd for $C_{21}H_{24}N_2O \cdot HCl$: C, 70.67; H, 7.06; N, 7.85. Found: C, 71.04; H, 7.18; N, 7.92.

Bridged Amines 34.—Borane (50 ml, 1 *M* THF solution) reduction of **32a** (1.7 g) in 50 ml of THF under reflux (4.5 hr), treatment of the cooled solution with 25 ml of water, hydrolysis (15 ml of concentrated HCl and 30 ml of glacial HOAc, reflux 0.8 hr), and isolation of crude base (after basifying the evaporated solution with NaOH solution) by ether extraction and evaporation of the washed (water) and dried (K_2CO_3) solution gave 0.8 g of oily **34a**, characterized as the dipicrate, yellow crystals (from methanol), mp 233° dec (sintering at 147–148°).

Anal. Calcd for $C_{32}H_{30}N_8O_{14} \cdot H_2O$: C, 50.00; H, 4.20; N, 14.58. Found: C, 49.97; H, 4.40; N, 14.28.

Compound 34b.—Similar reduction of **32b** with borane, or reduction of 5.2 g of **32b** with 12 g of $LiAlH_4$ in 300 ml of THF according to usual procedure, gave 4 g of oily amine, also characterized as the dipicrate, mp 266–267° dec (from methanol).

Anal. Calcd for $C_{33}H_{32}N_8O_{14}$: C, 51.85; H, 4.22; N, 14.66. Found: C, 51.97; H, 4.09; N, 14.60.

Bridged Lactone 36a.—A solution of 5 g of hydroxy amide **33a** in 100 ml of 12% hydrochloric acid and 50 ml of methanol chilled to −10° was treated slowly with 25 g of $NaNO_2$ in 60 ml of water (0.5 hr); additional methanol (*ca.* 50 ml) was added to ensure complete solution. After standing 5 hr at −10 to 0° and overnight at room temperature, the solution was warmed 20 min on a steam cone, chilled, and made basic with K_2CO_3 solution, and the material extracted with ether. The ether solution was washed with six portions of water, dried (K_2CO_3), and evaporated. Crystals formed and were collected with the aid of ether: 2.0 g; mp 159–160°, raised on recrystallization (ether) to mp 163.5–164.5°; ir 5.75 μ; nmr ($CDCl_3$) δ 7.0–7.6 (m, 8, aromatic H), 5.95 (s, 1, benzhydryl H), 3.18 (q, 2, J^{AB} = 18 Hz, methylene), and 2.2–2.6 (m, 10, methylenes and *N*-methyl of side chain).

Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.14; H, 6.89; N, 4.56. Found: C, 78.17; H, 6.77; N, 4.40.

The corresponding hydrochloride was recrystallized from ethanol, mp 260–262° dec, ir 5.79 μ.

Anal. Calcd for $C_{20}H_{21}NO_2 \cdot HCl$: C, 69.86; H, 6.45; N, 4.07. Found: C, 69.62; H, 6.53; N, 4.25.

The same lactone was obtained as a by-product on repetition of a preparation of lactam **32a**. After 3.5 hr of reflux of a filtered solution of 7.5 g of crude hydroxy amide **33a** in 400 ml of 8% aqueous alcoholic (*ca.* 1:1) HCl and isolation of crude base (K_2CO_3) *via* ether extraction, there was obtained first 1.7 g of lactam **32a**, mp 187–189°, and, on further concentration of ether filtrates, 0.75 g of **36a**, mp 163–165°; mixture melting point with the sample from nitrous acid reaction was undepressed; ir spectra were identical. The residue (3 g) remaining from isolation of these two compounds, a yellow oil, did not afford additional crystalline material.

Lactone 36b.—Experiments similar to the foregoing ones, involving treatment of **33b** with nitrous acid and its hydrolysis with 7% hydrochloric acid, were carried out. In each case, colorless to pale yellow, oily base was isolated; ir (5.76 μ) spectra of these samples were very similar to that of **36a**. However, even after removal of any lactam **32b**, attempts (including tlc) to obtain crystalline lactone using various solvents and procedures were not successful. The hydrochloride, picrate, and corresponding methiodide (solvated, mp *ca.* 200–208°, ir 2.9 and 5.76 μ) also did not crystallize.

Bridged Ether 35b.—After hydrochloric acid–methanol (300 ml) treatment of 2.5 g of crude **33b** (reflux 8 hr), the crude, basic, oily product (2.3 g) was reduced with excess $NaBH_4$ (added in portions to a MeOH solution). Addition of water, extraction with ether, and evaporation of the dried (K_2CO_3) ether solution gave 1.2 g of oil: ir 2.8–3.0 μ (broad OH bands), and a peak 5.81 μ, indicating that the material was a mixture of the diol and hydroxy ester. An ether solution of the material, on treatment with ethanolic HCl, gave 0.55 g of **35b** hydrochloride: colorless crystals; mp 235–238°, raised on recrystallization (ethanol) to 244–245°; ir and uv devoid of carbonyl bands.

Anal. Calcd for $C_{21}H_{25}NO \cdot HCl$: C, 73.34; H, 7.62; N, 4.07. Found: C, 73.10; H, 7.49; N, 3.88.

Diketone 37.—To dimethylcadmium (from 3.3 g of Mg, iodomethane, and 26.2 g of anhydrous $CdCl_2$) in 250 ml of ether was added 18 g of **8a** acid chloride in 300 ml of dry benzene. The suspension was boiled (stirring) to remove ether and refluxed (78°) and stirred 1.5 hr. After hydrolysis (ice, water, and excess HCl) and isolation of neutral product as usual, there was obtained 6.1 g of crystals, mp 90–97°. Recrystallization from methanol (or ether) gave pure material: mp 117–118°; ir 5.86 and 6.07 μ; uv 206 and 269 nm (ε 24,860 and 14,450, respectively); nmr ($CDCl_3$) δ 8.0 (m, 2, aromatic H peri to 5-keto group), 7.0–7.6 (m, 6, remaining aromatic H), 4.17 (t, 1, J = 5.0 Hz, methine), 3.52 (d, 2, J = 5.0 Hz, equivalent methylene protons), and 1.95 (s, 3, methyl of ketone).

Anal. Calcd for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64. Found: C, 81.83; H, 5.64.

The corresponding mono-2,4-dinitrophenylhydrazone formed rapidly, crystallized in ethanol, and was recrystallized from ethanol–ethyl acetate: yellow crystals; mp 161–163°; ir 6.07, 6.17, and 6.27 μ.

Anal. Calcd for $C_{23}H_{18}N_4O_5$: C, 64.18; H, 4.22; N, 13.02. Found: C, 64.49; H, 4.00; N, 12.72.

Keto Ketal 38.—A solution of 14.6 g of **37**, 19 ml of ethylene glycol, 3 ml of $MeSO_3H$, and 500 ml of benzene was refluxed 6 hr under a Dean-Stark trap, collecting 2.5 ml of water. The cooled, washed (3% NaOH solution, water), dried ($MgSO_4$), and evaporated solution afforded 11.6 g of crystals from ether: mp 140–141°; ir 6.09 μ; uv 208 and 266 nm (ε 27,430 and 14,200, respectively).

Anal. Calcd for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.43; H, 6.22.

Basic Hydroxy Ketal 39. A.—Grignard reagent was prepared as follows. Magnesium (1.5 g) under a small amount of dry ether was first treated with 5 ml of iodomethane. After 5–10 min, when reaction had begun, the supernatant solution was decanted and replaced with 20 ml of fresh ether. Dropwise addition of a dried (CaH_2) solution of 20 ml of *N*,*N*-dimethyl-γ-chloropropylamine in 25 ml of THF was then begun immediately and carried out over the course of 1 hr, leading to smooth, mildly exothermic consumption of the magnesium.

B.—A solution of 7.3 g of keto ketal **38** in 80 ml of THF was added, and the solution (protected from moisture) was refluxed 5 hr. The cooled solution was poured into water (500 ml) containing NH_4Cl (15 g). The ether extract of the material, after washing (water) and drying (K_2CO_3), was evaporated. The resulting yellow oil crystallized in the presence of ether, giving 5.3 g of colorless crystals, mp 118–120°, soluble in dilute HCl. Recrystallization from ether gave a pure sample, mp 122–123°, ir and uv devoid of ketone absorption. First-order analysis of nmr was not possible but spectrum was in agreement with the structure.

Anal. Calcd for $C_{24}H_{31}NO_3$: C, 75.56; H, 8.19; N, 3.67. Found: C, 75.28; H, 8.18; N, 3.59.

Basic Bridged Hemiketal 40.—The usual preparation of the hydrochloride from **39**, by adding 5% ethanolic HCl to an ethereal solution of **39**, afforded a quantitative yield of colorless crystals: mp 185–188° (from ethanol–ether); ir 3.11 μ and no carbonyl peak; uv devoid of carbonyl bands.

Anal. Calcd for $C_{22}H_{27}NO_2 \cdot HCl$: C, 70.66; H, 7.55; N, 3.75. Found: C, 71.0; H, 8.0; N, 3.90.

The corresponding base, **40**, prepared by treating the hydrochloride with Na_2CO_3 solution, extracting with ether, and recrystallizing from ether, had mp 135–137°, ir (bonded OH 3.13–3.23 μ), and uv devoid of carbonyl bands.

Anal. Calcd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.07; N, 4.15. Found: C, 78.38; H, 7.68; N, 4.15.

10-Amitryptylline Methyl Ketone 41.—Either **39** or **40** (2 g) in 100 ml of 5% ethanolic HCl was refluxed 4 hr. Evaporation *in vacuo*, treatment of a water solution of the residue with K_2CO_3, extraction of base with ether, and evaporation of washed (H_2O) and dried (K_2CO_3) ether solution gave an oil (ir 5.85 μ). Reconversion to the hydrochloride and (fractional) recrystallization of the salt from acetone and ethanol–ether afforded colorless samples: mp 156–159°, mp 161–166°, and mp 164–167°; ir spectra of these (5.87 μ, C=O) were virtually identical; uv 206 and 236 nm (ε 42,420 and 12,700, respectively).

Anal. Calcd for $C_{22}H_{25}NO \cdot HCl$: C, 74.27; H, 7.36; N, 3.94. Found: C, 74.17; H, 7.39; N, 3.96.

Keto Aldehyde 42.—An ethereal (1 l.) solution of 3.2 g of keto nitrile **5a**, saturated with dry HCl and treated with 11 g of anhydrous $SnCl_2$, was allowed to stand overnight. After de-

canting the supernatant solution, the oily deposit was treated with water; the resulting, bright red material was shaken with warm, dilute hydrochloric acid and ether. The ether solution was washed with $NaHCO_3$ solution and water, dried ($MgSO_4$), and evaporated. Ether trituration of the yellow, oily residue gave colorless crystals, careful recrystallization of which (ether) afforded a pure sample: mp 84–85.5°; ir 5.81 (shoulder 5.73) and 6.04 μ; uv 204 and 270 nm (ϵ 30,270 and 14,420, respectively); nmr ($CDCl_3$) δ 9.45 (s, 1, aldehyde), 8.13 and 7.87 (multiplets, 1 each, aromatic H peri to ketone), 7.1–7.6 (m, 6, remaining aromatic H), 4.03 (t, 1, J = 4.5 Hz, methine), and 3.55 (unsymmetrical doublet of doublets, J = 4.5 Hz, methylene).

Anal. Calcd for $C_{16}H_{12}O_2$: C, 81.34; H, 5.12. Found: C, 81.53; H, 5.05.

The keto aldehyde was also obtained less pure and in lower yield by Rosenmund reduction of **8a** acid chloride. The compound was unstable to heat and to bases.

The corresponding mono-2,4-dinitrophenylhydrazone was prepared as usual and recrystallized from ethanol–ethyl acetate: yellow crystals; mp 210–211°; ir 6.11, 6.17, and 6.29 μ.

Anal. Calcd for $C_{22}H_{16}N_4O_5$: C, 63.46; H, 3.87; N, 13.46. Found: C, 63.19; H, 3.59; N, 12.95.

Registry No.—**2a,** 26899-68-3; **2a** (amide nitrile)' 26899-69-4; **2a** (nitrile methyl ester), 26899-70-7; **2b,** 26963-65-5; **2c,** 26963-66-6; **2d,** 26899-71-8; **2e,** 26899-72-9; **3,** 4444-44-4; **4a,** 26963-68-8; **4e,** 26899-73-0; **5a,** 26899-74-1; **5a** (2,4-dinitrophenylhydrazone), 26899-75-2; **5b,** 26899-76-3; **5e,** 26899-77-4; **6,** 26899-78-5; **7e,** 26899-79-6; **8a,** 26899-80-9; **8a** (acid chloride), 26899-81-0; **8a** (methyl ester), 26899-82-1; **8a** (diethyl amide), 26899-83-2; **8a** (*N*-methyl amide), 26899-84-3; **8b,** 26899-85-4; **8c,** 26899-86-5; **8e** (acid chloride), 26899-87-6; **9,** 26899-88-7; **11a,** 26899-89-8; **11e,** 26899-90-1; **12a,** 26899-91-2; **12b,** 26899-92-3; **13a,** 26899-93-4; **13b,** 26899-94-5; **13e,** 26899-95-6; **17,** 26899-96-7; **18,** 26899-97-8; **19a,** 26899-98-9; **19b,** 26899-99-0; **19c,** 26900-00-5; **21,** 26900-01-6; **22,** 26900-02-7; **23,** 26963-69-9; **24a,** 26900-03-8; **24b,** 26963-70-2; **24c,** 26900-04-9; **25a** (HCl), 26900-05-0; **25b** (dipicrate), 26900-06-1; **25c** (dipicrate), 26900-07-2; **25d** (HCl), 26900-08-3; **25e** (HCl), 26900-09-4; **26a** (keto acid), 26963-71-3; **26b** (HCl), 26900-10-7; **26c** (HCl), 26909-71-7; **26d,** 26963-72-4; **27a,** 26909-72-8; **27a** (HCl), 26909-73-9; **27b,** 26909-74-0; **27c,** 26909-75-1; **28a,** 26963-73-5; **28a** (HCl), 26909-76-2; **28b,** 26909-77-3; **28b** (2HCl) 26963-74-6; **28c,** 26909-78-4; **28c** (2HCl), 26909-79-5; **30a,** 26909-80-8; **30a** (HCl), 26909-81-9; **30b,** 26909-82-0; **30b** (HCl), 26909-83-1; **31a** (methiodide), 26909-84-2; **31b,** 26909-85-3; **31b** (HCl), 26909-86-4; **32a,** 26909-87-5; **32a** (HCl), 26909-88-6; **32b,** 26909-89-7; **32b** (HCl), 26909-90-0; **33a** (methiodide), 26963-75-7; **33b,** 26909-91-1; **34a** (dipicrate), 26909-92-2; **34b** (dipicrate), 26963-76-8; **35b** (HCl), 26909-93-3; **36** (R = CH_3), 26909-94-4; **36a,** 26909-95-5; **36a** (HCl), 26909-96-6; **36b,** 26963-77-9; **37,** 26909-97-7; **37** (2,4-dinitrophenylhydrazone), 12441-27-9; **38,** 26909-98-8; **39,** 26909-99-9; **40,** 26910-00-9; **40** (HCl), 26910-01-0; **41** (HCl), 26910-02-1; **42,** 26910-03-2; **42** (2,4-dinitrophenylhydrazone), 12441-26-8; 10,11-dihydro-10-aminomethyl-5*H*-dibenzo[*a*,*d*]-cycloheptene (HCl), 1586-15-8; *N*-cyano-10-(3-dimethylaminoethyl)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene, 26910-05-4.

Acknowledgment.—We are indebted to Mrs. Angela Aretakis for literature search work, to Mr. Louis Dorfman, Miss Ruth Behnke, and Miss Natalie Cahoon for spectra and aid in interpretation thereof, to Mr. George Robertson and Mr. Rudolf Oeckinghaus for microanalytical data, to Mr. Shyam Sunder for some technical assistance, and to Mr. Robert Dziemian and Miss Ann Smith for large-scale preparation of certain intermediates.

Sulfur Dioxide Extrusion from Substituted 1,3-Dihydro-1,3-diphenylthieno[3,4-*b*]quinoxaline 2,2-Dioxides. Substituted 6-Phenylbenzo[*b*]phenazines[1,2]

EMIL J. MORICONI,* THOMAS E. BRADY,[3] AND ROBERT E. MISNER[3]

Department of Chemistry, Fordham University, New York, New York 10458

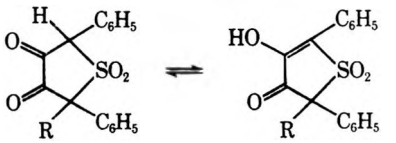
Received July 9, 1970

The extrusion of SO_2 from cis–trans mixtures of 5,8-dimethyl- (**4**), 5-methyl- (**5**), 5-methoxy- (**6**), 5-nitro- (**7**), 5-amino- (**8**), 1,3,5,8-tetramethyl- (**9**), and 1,5- (**10a**) and 1,8-dimethyl-1,3-diphenyl-1,3-dihydrothieno[3,4-*b*]-quinoxaline 2,2-dioxide (**10b**) by oxidative (alkaline hydrogen peroxide, oxygen, and peracetic acid) and reductive methods (Raney nickel and sodium borohydride) is reported. Thus, alkaline hydrogen peroxide oxidation of **4**, **5**, and **6** afforded, respectively, 2-benzoyl-3-benzyl-5,8-dimethylquinoxaline (**13**) and separable mixtures of 2-benzoyl-3-benzyl- (**14**) and 3-benzoyl-2-benzyl-5-methylquinoxaline (**15**) and 2-benzoyl-3-benzyl- (**16**) and 3-benzoyl-2-benzyl-5-methoxyquinoxaline (**17**). Similar oxidation of **8** and **10a–b**, respectively, gave mixtures of 2-benzoyl-3-benzyl- (**18**) and 3-benzoyl-2-benzyl-5-aminoquinoxaline (**19**), and 2-benzoyl-3-(α-methylbenzyl)- (**20**) and 3-benzoyl-2-(α-methylbenzyl)-5-methylquinoxaline (**21**). Diketones 5,8-dimethyl- (**26**), 5-methyl- (**27**), and 5-methoxy-2,3-dibenzoylquinoxalines (**28**) were obtained by direct oxygenation of **4**, **5**, and **6**, respectively, in KO-*tert*-Bu, *tert*-BuOH. Preformed peracetic acid oxidation of **4** and **5** afforded **13** and **14**, respectively. Oxidation of **5** with hydrogen peroxide in acetic acid gave 2-benzoyl-3-benzyl-5-methylquinoxaline 1-oxide (**24**), also obtainable by the further peracid oxidation of **14**. Raney nickel desulfurization of **4**, **5**, **6**, **8**, and **9** afforded 2,3-dibenzyl-5,8-dimethyl- (**31**), 2,3-dibenzyl-5-methyl- (**32**), 2,3-dibenzyl-5-methoxy- (**33**), 5-amino-2,3-dibenzyl- (**34**), and 5,8-dimethyl-2,3-di(α-methylbenzyl)quinoxaline (**35**). Sodium borohydride–methanol reduction was successful only with **4** and **5** affording, respectively, **31** and **32**. Cyclodehydration of **13**, **14**, **15**, and 2-benzoyl-3-(α-methylbenzyl)-5,8-dimethylquinoxaline (**22**) with concentrated sulfuric acid gave 1,4-dimethyl-6-phenyl- (**38**), 1-methyl-6-phenyl- (**39**), 1-methyl-11-phenyl- (**40**), and 1,4,11-trimethyl-6-phenylbenzo[*b*]phenazine (**45**), respectively. Similar cyclodehydration of the **16–17** mixture afforded the separable isomers 1-methoxy-6-phenyl- (**41**) and 1-methoxy-11-phenylbenzo[*b*]phenazine (**42**). $AlCl_3$ cleavage of **41** and **42** produced, respectively, 1-hydroxy-6-phenyl- (**43**) and 1-hydroxy-11-phenylbenzo-[*b*]phenazine (**44**). The results provide support for previously proposed mechanisms of SO_2 extrusion and cyclodehydration.

We recently reported on various oxidative and reductive methods of SO_2 extrusion from cis–trans mixtures of each of 1,3-diphenyl- (**1**), 1-methyl-1,3-diphenyl- (**2**), and 1,3-dimethyl-1,3-diphenyl-1,3-dihydrothieno[3,4-*b*]quinoxaline 2,2-dioxide (**3**).[4] Thus, alkaline hydrogen peroxide oxidation of **1** and **2** afforded 2-benzoyl-3-benzyl- (**11**) and 2-benzoyl-3-(α-methylbenzyl)quinoxaline (**12**), respectively. Selenium dioxide/chromic acid oxidation of **11** converted it to 2,3-dibenzoylquinoxaline (**25**). Peroxy acid oxidation of **1** led to 2-benzoyl-3-benzylquinoxaline 1-oxide (**23**) *via* its isolable precursor **11**, while **2** afforded **12**. The site of the *N*-oxide function in **23** was based on an analysis of its nmr spectrum and by cyclodehydration with concentrated sulfuric acid to 6-phenylbenzo[*b*]phenazine 12-oxide (**46**). The C-1 and C-11 protons, peri to the *N*-oxide function, are deshielded[5] [relative to the remaining benzo[*b*]phenazine (δ 8.25–7.30) and phenyl protons (δ 7.60)] and appear at δ 8.66 and 9.35, respectively.[4] Similar aromatic cyclodehydration of **11** and **12** afforded 6-phenyl- (**36**) and 11-methyl-6-phenylbenzo[*b*]phenazine (**37**). The parent phenazine (**36**) and its *N*-oxide (**46**) were interconverted *via* oxidative and reductive techniques. Sulfur dioxide extrusion from **1** and **2** under reductive conditions was achieved with sodium borohydride in methanol to give 2,3-dibenzyl- (**29**) and 2-benzyl-3-(α-methylbenzyl)quinoxaline (**30**), respectively.

In this paper we conclude our study of this sulfone system with a report on the preparation of cis–trans mixtures of two (**4**, **9**) symmetrically and five (**5–8**, **10**) unsymmetrically substituted 1,3-diphenyl-1,3-dihydrothieno[3,4-*b*]quinoxaline 2,2-dioxides and their response to similar oxidative and reductive methods of SO_2 extrusion.

Syntheses and Structure.—Inseparable cis and trans mixtures of 5,8-dimethyl- (**4**, 41%), 5-methyl- (**5**, 87%), 5-methoxy- (**6**, 97%), 5-nitro- (**7**, 64%), and 5-amino-1,3-diphenyl-1,3-dihydrothieno[3,4-*b*]quinoxaline 2,2-dioxide (**8**, 98%) were prepared by the condensation of the appropriate 3-substituted *o*-phenylenediamines and 2,5-diphenyl-3-keto-4-hydroxy-2,3-dihydrothiophene 1,1-dioxide (A).[6] Treatment of sulfone **4** with



A, R = H
B, R = CH_3

potassium *tert*-butoxide and excess methyl iodide afforded 1,3,5,8-tetramethyl-1,3-diphenyl-1,3-dihydrothieno[3,4-*b*]quinoxaline 2,2-dioxide (**9**, 80%) also as a cis–trans mixture.

In our previous work, an nmr analysis of **3** clearly established it as a cis–trans mixture,[7] which by analogy

(1) This research was supported by Public Health Service Research Grant No. 1-RO1-A108-063-01 from the National Institute of Allergy and Infectious Diseases and by the Department of the Army, U. S. Army Research and Development Command Office, Office of the Surgeon General, under Contract DA-49-193-MD-2992. This is Contribution No. 840 to the Army Research Program on Malaria.

(2) Presented before the Organic Division at the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 9–14, 1967; Abstract of Papers, O–100. From the Ph.D. Theses of T. E. Brady and R. E. Misner, Fordham University, 1968.

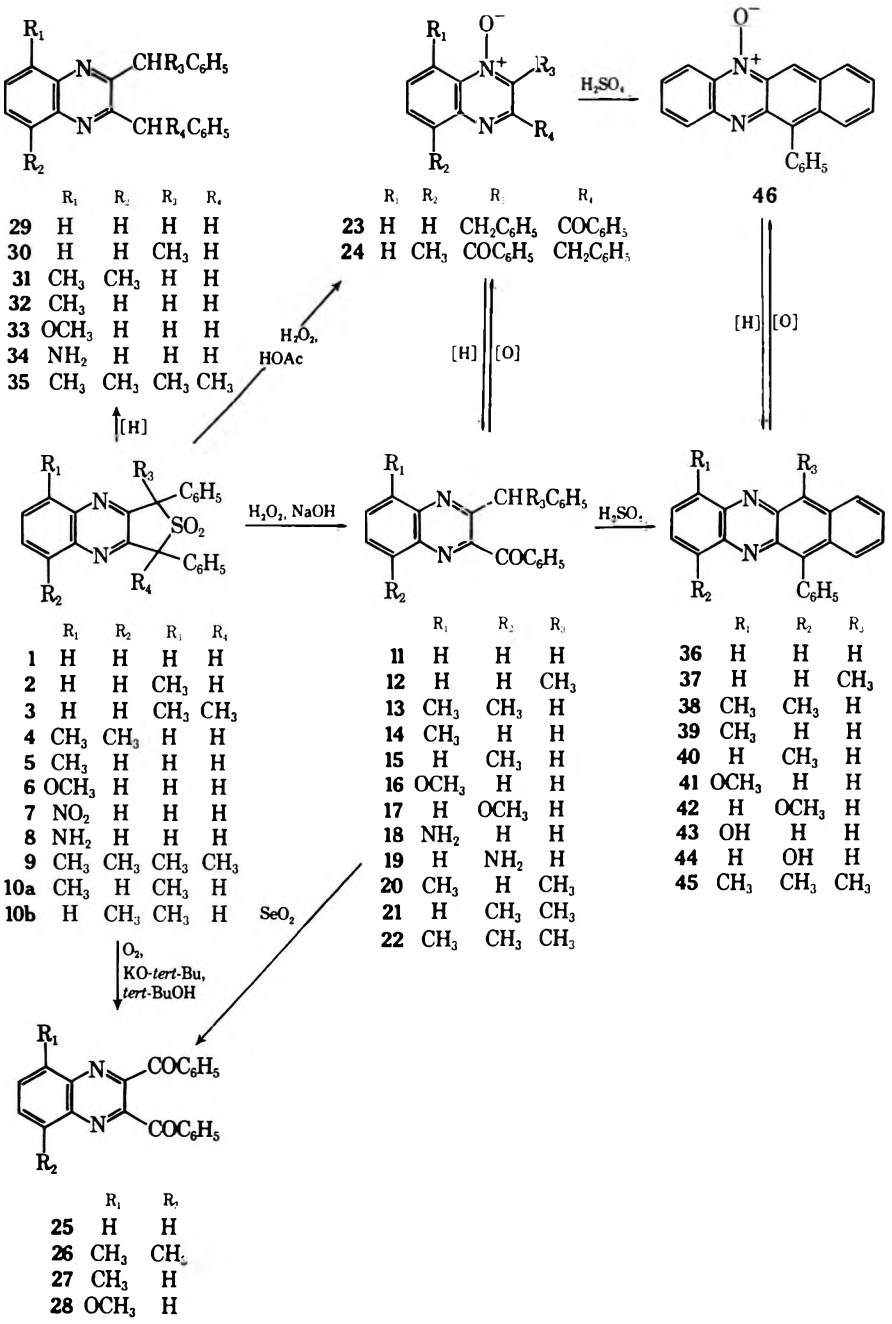
(3) Graduate Research Assistant, 1965–1968, on grants[1] supported by the NIH and WRAIR.

(4) E. J. Moriconi, R. E. Misner, and T. E. Brady, *J. Org. Chem.*, **34**, 1651 (1969).

(5) Y. Morita, *Chem. Pharm. Bull.*, **14**, 419 (1966).

(6) C. G. Overberger, S. P. Lighthelm, and E. A. Swire, *J. Amer. Chem. Soc.*, **72**, 2957 (1950).

(7) In the trans isomer the protons of each methyl group are in the shielding region of a phenyl substituent, while in the cis isomer each phenyl group shields the other.



	R_1	R_2	R_3	R_4
29	H	H	H	H
30	H	H	CH_3	H
31	CH_3	CH_3	H	H
32	CH_3	H	H	H
33	OCH_3	H	H	H
34	NH_2	H	H	H
35	CH_3	CH_3	CH_3	CH_3

	R_1	R_2	R_3	R_4
23	H	H	$CH_2C_6H_5$	COC_6H_5
24	H	CH_3	COC_6H_5	$CH_2C_6H_5$

46

	R_1	R_2	R_3	R_4
1	H	H	H	H
2	H	H	CH_3	H
3	H	H	CH_3	CH_3
4	CH_3	CH_3	H	H
5	CH_3	H	H	H
6	OCH_3	H	H	H
7	NO_2	H	H	H
8	NH_2	H	H	H
9	CH_3	CH_3	CH_3	CH_3
10a	CH_3	H	CH_3	H
10b	H	CH_3	CH_3	H

	R_1	R_2	R_3
11	H	H	H
12	H	H	CH_3
13	CH_3	CH_3	H
14	CH_3	H	H
15	H	CH_3	H
16	OCH_3	H	H
17	H	OCH_3	H
18	NH_2	H	H
19	H	NH_2	H
20	CH_3	H	CH_3
21	H	CH_3	CH_3
22	CH_3	CH_3	CH_3

	R_1	R_2	R_3
36	H	H	H
37	H	H	CH_3
38	CH_3	CH_3	H
39	CH_3	H	H
40	H	CH_3	H
41	OCH_3	H	H
42	H	OCH_3	H
43	OH	H	H
44	H	OH	H
45	CH_3	CH_3	CH_3

	R_1	R_2
25	H	H
26	CH_3	CH_3
27	CH_3	H
28	OCH_3	H

was extended to the less soluble sulfones **1** and **2**. This general insolubility and high melting point with decomposition also characterized the sulfones **4**–**10** described herein. Although vigorous efforts were made to separate each cis–trans mixture, success was partially achieved only with the separation of the trans isomer (mp 238–240°) of **9** from the mixture (mp 208–213°). The nmr of the latter was analogous to the cis–trans mixture of **3**: two phenyl proton singlets at δ 7.28 (trans) and 7.00 (cis), and two α-methyl singlets at 2.19 (cis) and 2.06 (trans). Further, since the 5,8-methyl substituents in the cis isomer of **9** reside more in the deshielding plane of the 1,3-phenyl groups,[8] these protons appear at δ 2.78 in the nmr while the less deshielded protons of the same methyls in the trans isomer appear at δ 2.71.[8b] Although the ir and uv spectra of the mixture were almost identical with that of the pure trans isomer, the nmr of the latter displayed only a six-proton singlet at δ 2.71 for the 5,8-dimethyl substituents. Both *cis–trans* sulfone mixtures, **4** and **5**, showed the two anticipated signals ascribed to methyl protons on the quinoxaline ring,[8] while the nonequivalent benzylic protons appear in both as a singlet at δ 5.83.[9]

Finally, condensation of 2,3-diaminotoluene with 4-hydroxy-3-keto-2,5-diphenyl-2-methyl-2,3-dihydrothiophene 1,1-dioxide (B)[10] afforded 1,5- (**10a**) and 1,8-dimethyl-1,3-diphenyl-1,3-dihydrothieno[3,4-*b*]quinoxaline 2,2-dioxide (**10b**) as inseparable cis–trans mixtures (four isomers) in 15% yield.

Oxidative Extrusion of SO_2.—Alkaline hydrogen peroxide oxidation of sulfone **4** afforded 2-benzoyl-3-benzyl-5,8-dimethylquinoxaline (**13**, 51%) which was

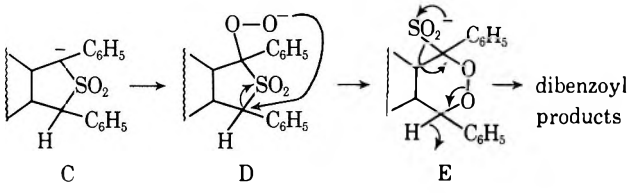
(8) (a) Dreiding models show that the phenyl groups in the cis isomer are rotationally restricted and this effect seems to be transmitted to the 5,8-quinoxaline methyls.[8b] (b) These long-range shielding effects have been observed in stilbenes [L. M. Jackman, "Applications of NMR Spectroscopy" Pergamon Press, New York, N.Y., 1959, p 126], 1,2-diphenylcyclopentanes [D. Y. Curtin, H. Gruen, and B. A. Shoulders, *Chem. Ind. (London)*, 1205 (1958)], and 1,3-diphenylisoindoles [L. A. Carpino, *J. Amer. Chem. Soc.*, **84**, 2196 (1962).

(9) Deshielded by three electronegative groups: SO_2, C_6H_5, and the quinoxaline ring.

(10) C. G. Overberger and J. M. Hoyt, *ibid.*, **73**, 3957 (1951).

further oxidized with selenium dioxide to the 2,3-dibenzoyl derivative (**26**, 68%). We have suggested that the extrusion of SO_2 from these sulfones commences with nucleophilic attack by the perhydroxyl anion on the α carbon of the sulfone.[4] The intermediacy of such an anion dictates an indiscriminate attack on both α carbons. Although symmetrical sulfones **1** and **4** expectedly afford single oxidation products, **11** and **13**, respectively, unsymmetrically substituted sulfones should yield two ketonic products in each case. This has now been realized with **5**–**8** and **10**. Thus, **5** led to a separable mixture (57%) of 2-benzoyl-3-benzyl- (**14**) and 3-benzoyl-2-benzyl-5-methylquinoxaline (**15**) (55:45 ratio, respectively), while **6** afforded a similar yield of 2-benzoyl-3-benzyl- (**16**) and 3-benzoyl-2-benzyl-5-methoxyquinoxaline (**17**). Decisive evidence for the isomeric nature of **14**–**15** and **16**–**17** was obtained from their nmr spectra, by aromatic cyclodehydration studies (*vide infra*), and by selenium dioxide oxidation of each mixture to single diketonic products, 2,3-dibenzoyl-5-methyl- (**27**) and 2,3-dibenzoyl-5-methoxyquinoxaline (**28**) in 86 and 87% yields, respectively. Similarly, alkaline hydrogen peroxide oxidation of **8** and **10a**–**b** afforded, respectively, 24% of 2-benzoyl-3-benzyl- (**18**) and 3-benzoyl-2-benzyl-5-aminoquinoxaline (**19**) and 35% (74:26 ratio) of 2-benzoyl-3-(α-methylbenzyl)- (**20**) and 3-benzoyl-2-(α-methylbenzyl)-5-methylquinoxaline (**21**). Ketone **20** was independently prepared by the alkylation of the anion of **14** with methyl iodide in DMSO. Similar treatment of **13** with sodium hydride and excess methyl iodide led to 2-benzoyl-3-(α-methylbenzyl)-5,8-dimethylquinoxaline (**22**, 52%).

Diketones **26** (33%), **27** (33%), and **28** (44%) were also prepared by direct oxygenation of sulfones **4**, **5**, and **6**, respectively, in solutions of KO-*tert*-Bu, *tert*-BuOH. In the former two cases, diketone precursors **13** (6%) and **14**–**15** (5%) could also be isolated. This reaction appears to be a precedented singlet oxygen oxidation of the generated carbanion C leading, *via* the hydroperoxide anion D, to peroxide E and ultimately to dibenzoyl products.[11] Hydride transfer (from E) to D could



C D E

initiate the ultimate formation of the benzoylbenzylquinoxaline by-products.

Oxidation of **5** with hydrogen peroxide in acetic acid also resulted in the extrusion of SO_2 to give the mono-*N*-oxide of **14**, 2-benzoyl-3-benzyl-5-methylquinoxaline 1-oxide (**24**, 33%). The consequences of a proton (C-8) peri to the anisotropic *N*-oxide linkage was again demonstrated by its appearance in the nmr at δ 8.33.[4,5] Treatment of **5** with preformed peracetic acid afforded the single product **14** which could be oxidized further to **24** (48%) with hydrogen peroxide in acetic acid and longer reaction times. Reduction of the latter with sodium hydrosulfite led to **14** (53%). Since indiscriminate attack by the peroxy molecule on both α carbons would have afforded both **14** and **15** as SO_2 extrusion products, the result supports our original mechanistic suggestion that the oxidation commences with coordination of the peroxy acid molecule to the less sterically hindered (*anti*)-quinoxaline nitrogen.[4]

Peracetic acid oxidation of **4** afforded **13** (28%),[12] while similar treatment of **6** and **7**[13] led to a complex mixture of products.[14] Sulfone **9** was unreactive to both alkaline hydrogen peroxide and peracetic acid oxidations.

Reductive Extrusion of SO_2.—The sodium borohydride–methanol reduction technique was successful only with sulfones **4** and **5**, affording the 2,3-dibenzyl-5,8-dimethyl- (**31**, 35%) and 2,3-dibenzyl-5-methylquinoxaline (**32**, 87%), respectively. Raney nickel desulfurization, however, worked with sulfones **4**, **5**, **6**, **8**, and **9**,[15] to give, respectively, **31** (59%), **32** (43%), 2,3-dibenzyl-5-methoxy- (**33**, 35%), 5-amino-2,3-dibenzyl- (**34**, 48%), and 5,8-dimethyl-2,3-di(α-methylbenzyl)quinoxaline (**35**, 47%), the last as a meso–*dl* mixture obtained from both the trans isomer and the cis–trans mixture of **9**.

6-Phenylbenzo[*b*]phenazines.—Cyclodehydration of **13** with concentrated sulfuric acid afforded 1,4-dimethyl-6-phenylbenzo[*b*]phenazine (**38**, 75%) whose nmr displayed a deshielded peri proton (R_3) at δ 8.85 and methyl protons at δ 2.90 and 2.57. The C-4 methyl protons are located in the diamagnetic shielding zone[16] of the virtually nonconjugated C-6 phenyl substituent[4] and appear 0.33 ppm upfield relative to the C-1 methyl protons.[17] Conclusive evidence for the low field assignment to the C-11 proton in **38** was obtained in the nmr spectrum of 1,4,11-trimethyl-6-phenylbenzo[*b*]phenazine (**45**) similarly prepared from **22** (60%). In **45**, the C-11 proton has been replaced by a methyl group and the effects that normally move the peri proton out of the aromatic envelope also deshield the C-11 methyl protons which now appear at δ 3.43. The 1- and 4-CH_3 protons appear at δ 2.86 and 2.50, respectively.

Cyclodehydration of **14** and **15** afforded 1-methyl-6-phenyl- (**39**, 54%) and 1-methyl-11-phenylbenzo[*b*]-

(11) R. Stewart, "Oxidation Mechanisms," W. A. Benjamin, New York, N.Y., 1964, p 122.

(12) The absence of any *N*-oxide products seems relevant here. The formation of quinoxaline mono- and di-*N*-oxides is markedly dependent on the degree and type of substitution on both carbocyclic and heterocyclic rings. 5-Substituted quinoxalines afford mono-*N*-oxides primarily and are resistant to further N oxidation: J. K. Landquist and G. J. Stacey, *J. Chem. Soc.*, 2822 (1953). Further, 5,8-dichloroquinoxaline has been prepared but its peroxy acid oxidation has not been observed: J. K. Landquist, *ibid.*, 2816 (1953). We have prepared, however, 5,8-dimethylquinoxaline and have converted it to the mono-*N*-oxide (12%) with peracetic acid under forcing conditions (see Experimental Section).

(13) Peracetic acid oxidation of **8** was not attempted since aromatic amino groups are known to be oxidized to nitro groups under such reaction conditions: W. D. Emmons, *J. Amer. Chem. Soc.*, **76**, 3470 (1954); **79**, 5528 (1957).

(14) A 10% yield of **28** could be isolated from the peracetic acid oxidation of **6**.

(15) The desulfurization of **7** over Raney Ni was unsuccessful since such nitro derivatives are known to effectively inhibit the catalytic process: H. Hauptmann, B. Wladislaw, L. Nazario, and W. Walter, *Justus Liebigs Ann. Chem.*, **576**, 45 (1952).

(16) T. H. Regan and J. B. Miller, *J. Org. Chem.*, **31**, 3053 (1966).

(17) The magnitude of the field about a benzene ring is such that appreciable effects may be observed for protons as far removed as 5–6 Å from the ring center.[8b] Dreiding models indicate the C-4 methyl protons are *ca.* 4 Å from the center of the C-6 phenyl ring. The reported shielding effect of a phenyl ring to an adjacent peri position ranges from 0.6 to 0.9 ppm.[18] There are no reported instances of a shielding effect over three fused rings, but its probability has been acknowledged.[8b]

(18) (a) T. H. Regan and J. B. Miller, *ibid.*, **32**, 593 (1967); (b) J. B. Miller, *ibid.*, **31**, 4082 (1966).

phenazine (**40**, 87%), respectively.[19a] The specific products formed verify the isomeric nature of **14** and **15** (fixing the position of the 2,3 substituents on the quinoxaline ring) and support a simple aromatic cyclodehydration mechanism for these conversions.[19b] Similarly, cyclodehydration of the **16–17** mixture afforded the separable isomers, 1-methoxy-6-phenyl- (**41**, 57%) and 1-methoxy-11-phenylbenzo[*b*]phenazine (**42**, 43%). Aluminum chloride cleavage of **41** and **42** produced 1-hydroxy-6-phenyl- (**43**, 53%) and 1-hydroxy-11-phenylbenzo[*b*]phenazine (**44**, 78%), respectively. The nmr of **41–44** all display deshielded peri protons, respectively, at δ 9.10 (C-11), 8.99 (C-6), 8.93 (C-11), and 8.91 (C-6). None of the new compounds reported herein showed any antimalarial activity in the primary mosquito and rodent screens.

Experimental Section[20]

cis- **and** *trans*-**5,8-Dimethyl-1,3-diphenyl-1,3-dihydrothieno[3,4-*b*]quinoxaline 2,2-Dioxide (4).**—A mixture of 2,3- and 2,5-dinitro-*p*-xylene[21] (15 g, 0.099 mol) in ethyl acetate was hydrogenated for 2 hr over 10% Pd/C in a Parr shaker. The solution was filtered and evaporated *in vacuo*. The residue (11.0 g, 82%) was used without further purification (*ca.* 65% of the 2,3 isomer.[21] The diamine mixture (7.15 g, 0.0053 mol) was refluxed with 14.3 g (0.0053 mol) of **A**[6] in 75 ml of absolute ethanol for 4 hr, after which it was cooled and filtered. The yellow filter cake was washed with ethyl ether to give 8.45 g (41%) of crude **4**. One recrystallization (Darco) from nitromethane gave pure **4** as a yellow powder: mp 239–240° dec; ir 7.53, 7.58, 8.53, 8.69, and 8.80 μ (SO_2); uv max (CH_3CN) 221 mμ (ε 28,200), 254 (41,400), and 327 (6100); nmr ($CDCl_3$) δ 7.54–7.23 (m, 24, aromatic), 5.83 (s, 4, CH), and 2.66 (s, 3, CH_3) and 2.61 (s, 3, CH_3).

Anal. Calcd for $C_{24}H_{20}N_2O_2S$: C, 71.97; H, 5.03; N, 6.99. Found: C, 72.01; H, 5.20; N, 7.00.

cis- **and** *trans*-**5-Methyl-1,3-diphenyl-1,3-dihydrothieno[3,4-*b*]quinoxaline 2,2-Dioxide (5).**—A solution of 12.5 g (0.042 mol) of **A**[6] in 70 ml of absolute ethanol and 5.0 g (0.042 mol) of 2,3-diaminotoluene in 30 ml of the same solvent was refluxed for 2 hr, cooled to room temperature, and filtered. The residue (14.0 g, 87%) was washed with ethyl ether and recrystallized (Darco) once from nitromethane to give **5** as a hard yellow powder: mp 230–230.5° dec; ir 7.54, 8.60, 8.78, and 8.86 μ (SO_2); uv max 220 mμ (ε 27,500), 244 (31,200), 304 (5800), and 320 (6900); nmr ($CDCl_3$) δ 8.0–7.2 (m, 14, aromatic), 5.83 (s, 4, CH), 2.71 (s, 3, CH_3), and 2.66 (s, 3, CH_3).

Anal. Calcd for $C_{23}H_{18}N_2O_2S$: C, 71.48; H, 4.69; N, 7.25. Found: C, 71.34; H, 4.88; N, 7.45.

cis- **and** *trans*-**5-Methoxy-1,3-diphenyl-1,3-dihydrothieno[3,4-*b*]quinoxaline 2,2-Dioxide (6).**—2,3-Dinitroanisole[22] (3.0 g, 0.015 mol) in ethyl acetate was hydrogenated over 10% Pd/C in a Paar apparatus. The mixture was filtered and the solvent was removed *in vacuo;* the residual oil was dissolved in 60 ml of absolute ethanol; and, after addition of 3.3 g (0.011 mol) of **A**,[6a] the solution was refluxed for 2 hr. The mixture was cooled to room temperature and filtered, and the residue was washed with ethyl ether to yield 4.3 g (97%) of crude **6**. One recrystallization (Darco) from nitromethane–ether afforded **6** as a yellow powder: mp 251.5–252° dec; ir 7.54, 8.57, and 8.80 μ (SO_2), 7.90 and 8.90 (OCH_3); uv max (CH_3CN) 221 mμ (ε 21,200), 261 (28,000), and 322 (3600).

Anal. Calcd for $C_{23}H_{18}N_2O_3S$: C, 68.64; H, 4.51; N, 6.96. Found: C, 68.51; H, 4.66; N, 7.13.

cis- **and** *trans*-**5-nitro-1,3-diphenyl-1,3-dihydrothieno[3,4-*b*]quinoxaline 2,2-dioxide (7)** (2.64 g, 64%) was prepared in a similar manner by refluxing (4 hr) 1.53 g (0.01 mol) of 3-nitro-*o*-phenylenediamine and **A**[6] (3.0 g, 0.01 mol) in 50 ml of glacial acetic acid. It was obtained as an orange powder: mp 280–281° dec (from nitromethane, Darco); ir 7.68 and 8.91 μ (SO_2), 6.52 and 7.44 (NO_2); uv max (CH_3CN) 218 mμ (ε 25,000), 282 (23,300), and 355 (960).

Anal. Calcd for $C_{22}H_{15}N_3O_4S$: C, 63.30; H, 3.62; N, 10.06. Found: C, 63.24; H, 3.71; N, 10.04.

cis- **and** *trans*-**5-Amino-1,3-diphenyl-1,3-dihydrothieno[3,4-*b*]quinoxaline 2,2-Dioxide (8).**—A mixture of 4.2 g (0.027 mol) of 3-nitro-*o*-phenylenediamine and 10% Pd/C in ethyl acetate was hydrogenated on a Parr apparatus until hydrogen uptake ceased. The catalyst was filtered and the solvent was removed *in vacuo*. The crude triamine in 100 ml of absolute ethanol and 6.6 g (0.022 mol, assuming 80% hydrogenation) of **A**[6] were then refluxed for 4 hr. The solution was cooled to room temperature, filtered, and washed with several volumes of ethyl ether to give 7.2 g (98%) of crude **8**. One recrystallization (Darco) from nitromethane afforded pure **8** as yellow needles: mp 265–266° dec; ir 2.90 and 2.98 μ (NH_2), 7.59 and 8.88 (SO_2); uv max 219 mμ (ε 27,000) and 282 (26,200).

Anal. Calcd for $C_{22}H_{17}N_3O_2S$: C, 68.24; H, 4.92; N, 10.79. Found: C, 68.08; H, 4.68; N, 10.71.

cis- **and** *trans*-**1,3,5,8-Tetramethyl-1,3-diphenyl-1,3-dihydrothieno[3,4-*b*]quinoxaline 2,2-Dioxide (9).**—A suspension of 2.0 g (0.005 mol) of **4** and 1.12 g (0.01 mol) of potassium *tert*-butoxide in 50 ml of anhydrous *tert*-BuOH was refluxed for 1 hr under N_2. After cooling to room temperature and the addition of 3.0 g (0.024 mol) of CH_3I, the mixture was again refluxed for 3 hr. The solution was then poured into H_2O and extracted several times with Et_2O. The combined ether extracts were washed with 10% HCl solution and the organic phase was dried (Na_2SO_4) and filtered. After removal of the Et_2O solvent *in vacuo*, the residue was deposited on a 2.5 × 25 cm Florisil column. Successive elution with 1:1 CH_2Cl_2–CCl_4 and CH_2Cl_2 afforded ultimately 1.7 g (80%) of a sulfone mixture. This solid was treated with 95% EtOH leaving 0.40 g of insoluble material.

The ethanol solution was charcoaled (Darco), filtered, and, upon addition of water, precipitated the cis–trans mixture of **9** as white needles: mp 208–213°; nmr ($CDCl_3$) δ 7.55 (s, 4, C-6,7 protons), 7.28 (s, 10, C_6H_5), 7.00 (s, 10, aromatic), 2.81 (s, 6, C-5,8 CH_3), 2.71 (s, 6, C-5,8 CH_3), 2.19 (s, 6, C-1,3 CH_3), and 2.06 (s, 6, C-1,3 CH_3).

Anal. Calcd for $C_{26}H_{24}N_2O_2S$: C, 72.87; H, 5.64; N, 6.54. Found: C, 72.61; H, 5.64; N, 6.73.

The ethanol insoluble material was recrystallized from CH_2Cl_2–hexane (Darco) to give the *trans*-**9** isomer: mp 238–240°; nmr ($CDCl_3$) δ 7.58 (s, 2, C-6,7 protons), 7.31 (s, 10, C_6H_5), 2.71 (s, 6, C-5,8 CH_3), and 2.09 (s, 6, C-1,3 CH_3).

Anal. Found: C, 72.65; H, 5.90; N, 6.56.

The ir for the cis–trans mixture and the trans isomer of **9** are similar while the uv are identical: ir 7.60 and 8.70 μ (SO_2); uv max 216 mμ (ε 37,700), 253 (71,900), and 327 (11,400).

cis- **and** *trans*-**1,5-Dimethyl- (10a) and** *cis-* **and** *trans*-**1,8-Dimethyl-1,3-diphenyl-1,3-dihydrothieno[3,4-*b*]quinoxaline 2,2-Dioxide (10b).**—A solution of 2,3-diaminotoluene (1.22 g, 0.01 mol) and **B**[10] (3.14 g, 0.01 mol) in 25 ml of glacial acetic acid was refluxed for 6 hr. The solution was cooled and poured into H_2O, and the whole mixture was extracted with Et_2O. The combined ether extracts were washed successively with H_2O and dilute $NaHCO_3$ solution, dried ($MgSO_4$), and filtered. Concentration of the filtrate accompanied by the addition of hexane afforded 0.60 g (15%) of crude **10a–b**. Recrystallization (Darco) from Et_2O gave **10a–b** as small yellow clumps: mp 203–205°; ir 7.60, 8.72, and 8.91 μ (SO_2); uv max 220 mμ (ε 23,600), 247 (36,800), and 327 (6800); nmr ($CDCl_3$) δ 8.05–7.15 (m, 26, aromatic), 5.60 (s, 2, CH), 2.83 (s, 3, C-5/8 CH_3), 2.68 (s, 3, C-8/5 CH_3), 2.38 (s, 3, C-1 CH_3), and 2.31 (s, 3, C-1 CH_3).

Anal. Calcd for $C_{24}H_{20}N_2O_2S$: C, 71.98; H, 5.03; N, 6.99. Found: C, 71.76; H, 5.26; N, 6.87.

Alkaline Hydrogen Peroxide Oxidation.—The general procedure used was as follows. To 1.0 g of the sulfone suspended in 20 ml of 95% EtOH was added 5 ml of 30% H_2O_2. The mixture was warmed (steam bath) and 5 ml of 10% NaOH was added slowly. The reaction mixture was then heated until the vigorous reaction subsided. The cooled mixture was then diluted with

(19) (a) Cyclodehydration of the **14–15** mixture led to a separable mixture of **39** (32%) and **40** (39%). (b) C. K. Bradsher, *Chem. Rev.*, **38**, 447 (1946).

(20) (a) Melting points were taken on a Koffler hot-stage apparatus and are corrected; (b) the infrared spectra were obtained on a Perkin-Elmer Model 337 grating spectrophotometer using KBr wafers unless otherwise stated; (c) the ultraviolet spectra were recorded in 95% ethanol solution, unless otherwise stated, on a Cary Model 15 dual-beam recording spectrophotometer; (d) unless otherwise stated, the nmr spectra were obtained on a Varian A-60 spectrometer using dilute solutions (*ca.* 100 mg/ml) and chemical shifts are reported in ppm downfield from tetramethylsilane.

(21) K. A. Kobe and T. B. Hudson, *Ind. Eng. Chem.*, **42**, 356 (1953).

(22) D. L. Vivian, G. Y. Greenburg, and S. L. Hartwell, *J. Org. Chem.*, **16**, 1 (1951).

H_2O and extracted with several equal volumes of 30–60° petroleum ether. The organic layer was dried (Na_2SO_4), filtered, concentrated on a steam bath, and cooled to give product. Any variations in product isolation procedures are noted.

Sulfone **4** (0.0025 mol) gave 0.45 g (51%) of **2-benzoyl-3-benzyl-5,8-dimethylquinoxaline** (**13**) as white needles, mp 111–112° (from 95% EtOH, Darco). The product was obtained directly after the addition of H_2O and no petroleum ether extraction was required: ir 5.99 μ (C=O); uv max 251 mu (ε 31,300), 259 (33,500), and 323 (7100); nmr ($CDCl_3$) δ 7.89–6.96 (m, 12, aromatic), 4.55 (s, 2, CH_2), 2.77 (s, 3, C-5 CH_3), and 2.58 (s, 3, C-8 CH_3).

Anal. Calcd for $C_{24}H_{20}N_2O$: C, 81.79; H, 5.72; N, 7.95. Found: C, 81.91; H, 5.84; N, 8.23.

Sulfone **5** (0.0026 mol) gave 0.55 g (57%) of a mixture of **2-benzoyl-3-benzyl-** (**14**) and **3-benzoyl-2-benzyl-5-methylquinoxaline** (**15**) as white needles: mp 94–99° (from 30–60° petroleum ether, Darco); ir 6.00 μ (C=O); uv max 245 mμ (ε 38,500), 253 (41,200), and 322 (11,500); nmr ($CDCl_3$) δ 7.90–7.00 (m, 26, aromatic), 4.52 and 4.50 (superimposed singlets, 4, CH_2), 2.81 (s, 3, CH_3), and 2.62 (s, 3, CH_3).

Anal. Calcd for $C_{23}H_{18}N_2O$: C, 81.63; H, 5.36; N, 8.28. Found: C, 81.81; H, 5.36; N, 8.36.

Careful fractional crystallization from 30–60° petroleum ether separated the two components of the mixture. Component **14** was obtained as white needles: mp 121–123°; ir 6.00 μ (C=O); uv max 249 mμ (ε 31,800), 254 (33,500), and 322 (8100); nmr ($CDCl_3$) δ 7.8–7.0 (m, 13, aromatic), 4.50 (s, 2, CH_2), and 2.82 (s, 3, CH_3).

Anal. Found: C, 81.83; H, 5.45; N, 8.44.

Component **15** was obtained as light yellow needles: mp 103–105°; ir 6.02 μ (C=O); uv max 244 mμ (ε 41,000), 254 (46,700), and 319 (12,850); nmr ($CDCl_3$) δ 7.95–6.95 (m, 13, aromatic), 4.54 (s, 2, CH_2), and 2.62 (s, 3, CH_3).

Anal. Found: C, 81.74; H, 5.51; N, 8.40.

Sulfone **6** (2.0 g, 0.0048 mol) gave 1.0 g (57%) of a mixture of **2-benzoyl-3-benzyl-** (**16**) and **3-benzoyl-2-benzyl-5-methoxyquinoxaline** (**17**), using Et_2O as the extractant: white needles, mp 124–127° (from CH_3OH, Darco); ir 6.01 μ (C=O); uv max 262 mμ (ε 30,100) and 323 (3100); nmr ($CDCl_3$) δ 7.80–7.10 (m, 26, aromatic), 4.68 (s, 2, CH_2), 4.54 (s, 2, CH_2), 4.16 (s, 3, CH_3), and 3.99 (s, 3, CH_3).

Anal. Calcd for $C_{23}H_{18}N_2O_2$: C, 77.95; H, 5.12; N, 7.90. Found: C, 78.22; H, 5.19; N, 7.95.

Sulfone **8** (0.0026 mol) gave 0.21 g (24%) of a mixture of **2-benzoyl-3-benzyl-** (**18**) and **3-benzoyl-2-benzyl-5-aminoquinoxaline** (**19**), using Et_2O as the extractant. The analytical sample was prepared by chromatography over Florisil, using 1:1 Et_2O–hexane as eluent. One recrystallization of the chromatographed material from aqueous EtOH gave the **18–19** mixture as yellow needles: mp 93.5–94.5°; ir 2.91 and 2.97 μ (NH_2), 5.98 (C=O); uv max 240 mμ (ε 21,700) and 281 (37,300); nmr ($CDCl_3$) δ 7.90–6.80 (m, 26, aromatic), 4.86–4.50 (m, 4, NH_2), 4.55 (s, 2, CH_2), and 4.46 (s, 2, CH_2).

Anal. Calcd for $C_{22}H_{17}N_3O$: C, 77.86; H, 5.05; N, 12.38. Found: C, 77.78; H, 5.06; N, 12.22.

Sulfone mixture **10a–b** (0.85 g, 0.021 mol) gave 0.26 g (35%) of a mixture of **2-benzoyl-3-(α-methylbenzyl)-** (**20**) and **3-benzoyl-2-(α-methylbenzyl)-5-methylquinoxaline** (**21**), using Et_2O as the extractant: white needles; mp 102–104° (from CH_3OH, Darco); ir 6.00 μ (C=O); uv max 252 mμ (ε 30,100) and 322 (7100); nmr ($CDCl_3$) δ 7.97–7.00 (m, 26, aromatic), 4.89 (q, 2, J = 7 Hz, CH), 2.91 (s, 3, CH_3), 2.65 (s, 3, CH_3), and 1.86 (d, 6, J = 7 Hz, α-CH_3).

Anal. Calcd for $C_{24}H_{20}N_2O$: C, 81.79; H, 5.72; N, 7.95. Found: C, 81.91; H, 5.69; N, 7.81.

2-Benzoyl-3-(α-methylbenzyl)-5-methylquinoxaline (**20**).—To a solution of 0.34 g (0.008 mol) of NaH (57% mineral oil dispersion) in 10 ml of dry DMSO was added, with cooling and under N_2, 1.2 g (0.0036 mol) of **14** in 20 ml of dry DMSO. After stirring at room temperature for 15 min, 1.8 g (0.014 mol) of CH_3I was added and whole mixture was stirred for an additional 16 hr. The solution was poured into H_2O, extracted with several volumes of pentane, dried (Na_2SO_4), and filtered. After reduction of the filtrate volume on a steam bath, cooling gave 0.60 g (46%) of **20**. An analytical sample was prepared by chromatography (twice) over Florisil (2.5 × 25 cm column, 1:1 CH_2Cl_2–CCl_4 eluent) followed by recrystallization (Darco) from CH_3OH: white needles; mp 110–112°; ir 5.99 μ (C=O); uv max 252 mμ (ε 35,400) and 323 (8800); nmr ($CDCl_3$) δ 7.97–6.93 (m, 13, aromatic), 4.83 (q, 1, J = 7 Hz, CH), 2.88 (s, 3, C-5 CH_3), and 1.85 (d, 3, J = 7 Hz, α-CH_3).

Anal. Calcd for $C_{24}H_{20}N_2O$: C, 81.79; H, 5.72; N, 7.95. Found: C, 81.94; H, 6.01; N, 7.92.

2-Benzoyl-3-(α-methylbenzyl)-5,8-dimethylquinoxaline (**22**).—Similar treatment of 0.34 g (0.008 mol) of NaH in 10 ml of DMSO, 1.3 g (0.0037 mol) of **13**, and 1.8 g (0.014 mol) of CH_3I to the point of addition of the reaction mixture to water, precipitated crude **22**. It was filtered, air-dried, and chromatographed (2.5 × 25 cm column packed with Woelm alumina (neutral activity I) using increasing amounts of $CHCl_3$ in CH_2Cl_2 as eluent. Evaporation of the solvent led to 0.70 g (52%) of **22** as white needles: mp 129–130° (from CH_3OH, Darco); ir 6.00 μ (C=O); uv max 257 mμ (ε 34,100) and 325 (7200); nmr ($CDCl_3$) δ 7.90–7.00 (m, 12, aromatic), 4.91 (q, 1, J = 7 Hz, CH_3), 2.86 (s, 3, C-5 CH_3), 2.61 (s, 3, C-8 CH_3), and 1.86 (d, 3, J = 7 Hz, α-CH_3).

Anal. Calcd for $C_{25}H_{20}N_2O$: C, 81.94; H, 6.05; N, 7.64. Found: C, 82.25; H, 6.28; N, 7.46.

Selenium Dioxide Oxidation.—The general procedure used was as follows. The product mixture was dissolved in 10–15 ml of glacial acetic acid to which was added freshly sublimed SeO_2. The mixture was refluxed 6 hr, after which the precipitated selenium was filtered from the hot solution. Chilling of the filtrate sufficed to precipitate **26**; a few drops of H_2O caused crystallization of diketone **27** while sufficient H_2O was added to the reaction mixture to precipitate **28**.

Thus 0.50 g (0.0014 mol) of **13** and 0.17 g (0.0016 mol) of SeO_2 gave 0.40 g (68%) of **2,3-dibenzoyl-5,8-dimethylquinoxaline** (**26**) as pale green plates: mp 183–184° (from acetic acid, Darco); ir 6.00 and 6.02 μ (C=O); uv max 276 mμ (ε 51,900) and 322 (5650) nmr ($CDCl_3$) δ 8.30–8.10 (m, 2, C-6,7 protons), 7.80–7.39 (m, 10, C_6H_5), and 2.75 (s, 6, CH_3).

Anal. Calcd for $C_{24}H_{18}N_2O_2$: C, 78.67; H, 4.95; N, 7.64. Found: C, 78.86; H, 4.72; N, 7.78.

Similarly, 0.50 g (0.0015 mol) of the **14–15** mixture or **14** alone with 0.16 g (0.0015 mol) of SeO_2 afforded 0.45 g (86%) of **2,3-dibenzoyl-5-methylquinoxaline** (**27**) as pale green needles: mp 168–169° (from CH_3OH, Darco); ir 5.98 and 6.08 μ (C=O); uv max 267 mμ (ε 48,600) and 320 (6700); nmr ($CDCl_3$) δ 8.27–7.46 (m, 13, aromatic) and 2.78 (s, 3, CH_3).

Anal. Calcd for $C_{23}H_{16}N_2O_2$: C, 78.39; H, 4.57; N, 7.95. Found: C, 78.16; H, 4.57; N, 7.78.

Finally, 0.50 g (0.0014 mol) of the **16–17** mixture and 0.17 g (0.0015 mol) of SeO_2 gave 0.45 g (87%) of **2,3-dibenzoyl-5-methoxyquinoxaline** (**28**) as pale yellow plates: mp 168–169°; ir 6.00 and 6.06 μ (C=O); uv max 248 mμ (ε 22,800) and 280 (37,100); nmr ($CDCl_3$) δ 8.25–8.00 (m, 3, C-6,7,8 protons), 7.80–7.10 (m, 10, C_6H_5), and 4.01 (s, 3, OCH_3).

Anal. Calcd for $C_{23}H_{16}N_2O_3$: C, 74.99; H, 4.38; N, 7.60. Found: C, 74.83; H, 4.49; N, 7.59.

Oxygen Oxidation.—The general procedure used was as follows. The sulfone was suspended in 50 ml of dry *tert*-BuOH to which was added 0.5 g (0.0045 mol) of solid KO-*tert*-Bu at once. The temperature was brought to 50–55° and a stream of O_2 was bubbled into the mixture for 3 hr. The mixture was poured into H_2O and extracted with Et_2O; the combined ether extracts were washed with 10% HCl, dried (Na_2SO_4), and filtered, and the filtrate was evaporated to dryness *in vacuo*. The oily residue was chromatographed over a 2.5 × 25 cm silica gel column.

Thus, 1.0 g (0.0025 mol) of **4** gave 0.05 g (6%) of **13** and 0.30 g (33%) of **26**, using CH_2Cl_2 and $CHCl_3$ as eluents. Similarly 1.0 g (0.0026 mol) of **5** afforded 0.04 g (5%) of **14–15** and 0.30 g (33%) of **27** using 1:1 CH_2Cl_2–CCl_4 as eluent. Finally, 1.0 g (0.0024 mol) of **6** gave 0.40 g (44%) of **28**, using $CHCl_3$ as eluent.

Peracetic Acid Oxidation of 5.—A mixture of 1.0 g (0.0026 mol) of **5** in 20 ml of glacial HOAc and 10 ml of 30% H_2O_2 was stirred at 50–60° for 16 hr. The solution was added to H_2O and the whole mixture was extracted with Et_2O. The combined ether extracts were washed successively with H_2O and dilute $NaHCO_3$, dried (Na_2SO_4), filtered, and evaporated *in vacuo*. The thick residue was recrystallized twice from 95% EtOH (Darco) to give 0.30 g (33%) of **2-benzoyl-3-benzyl-5-methylquinoxaline 1-oxide** (**24**) as pale yellow cubes: mp 169–171°; ir 6.00 μ (C=O); uv max 252 mμ (ε 44,200), 312 (10,250), and 322 (10,950); nmr ($CDCl_3$) δ 8.33 (m, 1, C-8 proton), 7.71–6.97 (m, 12, aromatic), 4.23 (s, 2, CH_2), and 2.82 (s, 3, CH_3).

Anal. Calcd for $C_{23}H_{18}N_2O_2$: C, 77.95; H, 5.12; N, 7.90. Found: C, 77.72; H, 5.17; N, 7.67.

Alternatively, a suspension of **5** (1.0 g, 0.0026 mol) in 25 ml of $CHCl_3$ and 5 ml (0.026 mol) of 40% CH_3CO_3H was refluxed for

16 hr. After cooling to room temperature, the solution was diluted with $CHCl_3$, washed several times with H_2O, dried (Na_2SO_4), and filtered. After evaporation of the filtrate *in vacuo*, the residue was successively recrystallized from 95% EtOH and 30–60° petroleum ether (Darco) to give 0.60 g (65%) of **14**.

Further oxidation of 0.80 g (0.0024 mol) of **14** in 25 ml of glacial HOAc with 10 ml of 30% H_2O_2 (50 hr at 50–60°) ultimately afforded 48% of **24**.

Reduction of **24** (0.40 g, 0.0011 mol) dissolved in 25 ml of 80% EtOH with 0.21 g (0.0012 mol) of sodium hydrosulfite ultimately gave 53% of **14**.

Peracetic Acid Oxidation of 4.—Similar oxidation of **4** (1.0 g, 0.0025 mol) suspended in 25 ml of $CHCl_3$ with 5 ml of 40% CH_3CO_3H (0.026 mol) ultimately gave 0.25 g of **13** (28%); 0.57 g of unreacted **4** was also recovered.

Sodium Borohydride Reduction.—Excess $NaBH_4$ was added in small portions to a suspension of 1.0 g (0.0025 mol) of **4** in 50 ml of CH_3OH, until the vigorous reaction ceased. The solution was cooled and diluted with H_2O and 30–60° petroleum ether, and the two-phase system was filtered to remove unreacted **4** (0.70 g). The organic phase was separated and the aqueous layer was extracted with several volumes of petroleum ether. The combined petroleum ether extracts were dried (Na_2SO_4) and filtered, and the volume of the filtrate was reduced to initiate crystallization. Filtration of the resulting solid gave 0.29 g (35%) of crude **2,3-dibenzyl-5,8-dimethylquinoxaline (31)**. One crystallization (Darco) from 30–60° petroleum ether afforded pure **31** as white needles: mp 131–132°; uv max 250 mμ (ε 74,300), 264 (15,500), 271 (8800), 315 (13,500), and 323 (14,850); nmr ($CDCl_3$) δ 7.43 (s, 2, C-6,7 protons), 7.25 (s, 10, C_6H_5), 4.30 (s, 4, CH_2), and 2.75 (s, 6, CH_3).

Anal. Calcd for $C_{24}H_{22}N_2$: C, 85.17; H, 6.55; N, 8.28. Found: C, 85.02; H, 6.53; N, 8.45.

Similar treatment of 1.0 g (0.0026 mol) of **5** (warmed on a steam bath) with excess $NaBH_4$ (using pentane as the extractant) led ultimately to 0.70 g (87%) of **32** as small white needles: mp 73–74° (from 30–60° petroleum ether, Darco); uv max 243 mμ (ε 54,400), 264 (6300), 271 (4500), 312 (9400), and 322 (11,650); nmr ($CDCl_3$) δ 7.78 (m, 3, C-6,7,8 protons), 7.25 (s, 10, C_6H_5), 4.29 (s, 4, CH_2), and 2.78 (s, 3, CH_3).

Anal. Calcd for $C_{23}H_{20}N_2$: C, 85.15; H, 6.21; N, 8.63. Found: C, 85.29; H, 6.27; N, 8.44.

Raney Nickel Desulfurization. 2,3-Dibenzyl-5,8-dimethylquinoxaline (31).—A suspension of 1.0 g (0.0025 mol) of **4** in 50 ml of 95% EtOH and 10 g of W-7 Raney nickel catalyst was refluxed 6 hr and filtered while hot. The filtrate was cooled (−30°) to yield 0.50 g (59%) of **31**.

2,3-Dibenzyl-5-methylquinoxaline (32).—Similar treatment of **5** (1.0 g 0.0026 mol) afforded **32** (0.35 g, 43%).

2,3-Dibenzyl-5-methoxyquinoxaline (33).—One gram (0.0025 mol) of **6** was reduced in the same manner as **4** and **5**. After filtration, the solvent was removed *in vacuo*, and the residual oil was deposited on a 2.5 × 25 cm silica gel column. Elution with 3:1 Et_2O–hexane ultimately gave 0.30 g (35%) of **33** as white needles: mp 83–84° (from 30–60° petroleum ether, Darco); uv max 257 mμ (ε 32,900) and 323 (4100); nmr ($CDCl_3$) δ 7.75–7.00 (m, 13, aromatic), 4.40 (s, 2, CH_2), 4.28 (s, 2, CH_2), and 4.06 (s, 3, OCH_3).

Anal. Calcd for $C_{23}H_{20}N_2O$: C, 81.15; H, 5.92; N, 8.23. Found: C, 81.18; H, 6.01; N, 8.25.

5-Amino-2,3-dibenzylquinoxaline (34).—Reduction of 1.0 g (0.0026 mol) of **8** ultimately gave 0.40 g (48%) of **34** as yellow needles: mp 96–98° (from 30–60° petroleum ether, Darco); ir 2.99 and 3.11 μ (NH_2); uv max 241 mμ (ε 9750), 278 (36,000), and 326 (2400); nmr ($CDCl_3$) δ 7.57–7.13 (m, 13, aromatic), *ca.* 4.93–4.71 (broad mound, 2, NH_2), 4.21 (s, 2, CH_2), and 4.18 (s, 2, CH_2).

Anal. Calcd for $C_{22}H_{19}N_3$: C, 81.20; H, 5.88; N, 12.91. Found: C, 81.34; H, 6.18; N, 12.69.

5,8-Dimethyl-2,3-di(α-methylbenzyl)quinoxaline (35).—Reduction of 1.0 g (0.0023 mol) of **9** ultimately gave 0.40 g (47%) of **35** as a meso-*dl* mixture: white needles, mp 110–112° (from 95% EtOH, Darco); uv max 249 mμ (ε 42,700), 270 (4750), 312 (6600) and 323 (7300); nmr ($CDCl_3$) δ 7.37–7.01 (m, 24, aromatic), 4.82–4.29 (q, 4, J = 7 Hz, CH), 2.80 (s, 6, *meso* C-5,8 CH_3), 2.73 (s, 6, *dl* C-5,8 CH_3), 1.78 (d, 6, J = 7 Hz, *meso* α-CH_3), and 1.58 (d, 6, *dl* α-CH_3).

Anal. Calcd for $C_{26}H_{26}N_2$: C, 85.21; H, 7.15; N, 7.64. Found: C, 85.19; H, 7.41; N, 7.40.

6-Phenylbenzo[*b*]phenazines.—The general procedure used was as follows. A mixture of the quinoxaline and 10 ml of concentrated H_2SO_4 was warmed on a steam bath for 30 min. The mixture was then poured onto ice and extracted several times with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and filtered and the solvent was removed *in vacuo*. The residue was deposited on a 2.5 × 25 cm Woelm alumina column (neutral activity I) and eluted. Evaporation of the eluent left crude product which was recrystallized.

1,4-Dimethyl-6-phenylbenzo[*b*]phenazine (38, 0.57 g, 75%) was obtained from **13** (0.80 g, 0.0023 mol) using 30% CH_2Cl_2–CCl_4 as eluent: mp 168–169°, bright red needles (from CH_2Cl_2, Darco); uv max (CH_3OH) 216 mμ (ε 30,800), 242 (19,100), 250 (22,500), and 285 (146,000); nmr ($CDCl_3$) δ 8.85 (s, 1, C-11 proton), 8.11–7.33 (m, 11, aromatic), 2.90 (s, 3, C-1 CH_3), and 2.57 (s, 3, C-4 CH_3).

Anal. Calcd for $C_{24}H_{18}N_2$: C, 86.19; H, 5.42; N, 8.38. Found: C, 85.99; H, 5.29; N, 8.62.

1-Methyl-6-phenylbenzo[*b*]phenazine (39, 0.30 g, 54%) was obtained from **14** (0.60 g, 0.0018 mol) using 30% CH_2Cl_2–CCl_4 as eluent: mp 217–218°, red needles (from CH_2Cl_2, Darco); uv max (CH_3OH) 215 mμ (ε 20,800), 254 (24,000), and 284 (101,000); nmr ($CDCl_3$) δ 8.80 (s, 1, C-11 proton), 8.07–7.20 (m, 12, aromatic), and 2.86 (s, 3, CH_3).

Anal. Calcd for $C_{23}H_{16}N_2$: C, 86.22; H, 5.03; N, 8.74. Found: C, 86.08, H, 5.26; N, 8.66.

1-Methyl-11-phenylbenzo[*b*]phenazine (40) was obtained from a crude **14**–**15** mixture (1.0 g, 0.029 mol) using 30% CH_2Cl_2–CCl_4 as eluent. The first 600 ml of eluent gave 0.30 g (32%) of **39**. Further elution afforded ultimately 0.37 g (39%) of **40**: mp 217.5–218°, dark red cubes (from CH_2Cl_2, Darco); uv max (CH_3OH) 215 mμ (ε 22,400), 255 (34,300), and 285 (134,000); nmr ($CDCl_3$) δ 8.77 (s, 1, C-6 proton), 8.20–7.20 (m, 12, aromatic) and 2.60 (s, 3, CH_3).

Anal. Calcd for $C_{23}H_{16}N_2$: C, 86.22; H, 5.03; N, 8.74. Found: C, 86.23; H, 5.16; N, 8.75.

1-Methoxy-6-phenyl- (41, 57%) **and 1-methoxy-11-phenylbenzo[*b*]phenazine (42,** 43%) were obtained by cyclodehydration of 0.50 g (0.0014 mol) of **16**–**17** mixture. Elution with $CHCl_3$ ultimately gave 0.27 g of **41**: mp 248–249°, red needles (from CH_2Cl_2, Darco); uv max (CH_3OH) 218 mμ (ε 26,800), 248 (16,800), and 287 (147,000); nmr ($CDCl_3$) δ 9.10 (s, 1, C-11 proton), 7.80–7.20 (m, 12, aromatic), and 4.18 (s, 3, OCH_3).

Further elution with 30% Et_2O–CCl_4 ultimately afforded 0.20 g of **42**: mp 229–230°, red plates (from CH_2Cl_2, Darco); uv max (CH_3OH) 218 mμ (ε 24,100), 248 (15,400), and 287 (136,500); nmr ($CDCl_3$) δ 8.89 (s, 1, C-6 proton), 8.00–7.20 (m, 12, aromatic), and 3.93 (s, 3, OCH_3).

Anal. Calcd for $C_{23}H_{16}N_2O$: C, 82.12; H, 4.79; N, 8.33. Found for **41**: C, 82.28; H, 4.79; N, 8.45. Found for **42**: C, 82.02; H, 4.81; N, 8.37.

1,4,11-Trimethyl-6-phenylbenzo[*b*]phenazine (45, 0.40 g, 60%) was obtained from **22** (0.70 g, 0.0019 mol) using CCl_4 as eluent: mp 201–202°, red needles (from CH_2Cl_2, Darco); uv max (CH_3OH) 217 mμ (ε 28,700), 261 (26,050), and 291 (141,500); nmr ($CDCl_3$) δ 8.36–7.18 (m, 11, aromatic), 3.43 (s, 3, C-11 CH_3), 2.86 (s, 3, C-1 CH_3), and 2.50 (s, 3, C-4 CH_3).

Anal. Calcd for $C_{25}H_{20}N_2$: C, 86.18; H, 5.78; N, 8.03. Found: C, 86.28; H, 6.14; N, 7.99.

1-Hydroxy-6-phenylbenzo[*b*]phenazine (43).—A mixture of 0.40 g (0.0012 mol) of **41** in 30 ml of dry C_6H_6 and 0.40 g (0.003 mol) of $AlCl_3$ was refluxed 12 hr under anhydrous conditions. The reaction mixture was cooled and poured onto ice, and the whole mixture was extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and filtered, and the solvent removed *in vacuo*. The residue was placed on a 2.5 × 25 cm Woelm alumina column (neutral activity III) and successively eluted with CH_2Cl_2 (to wash out minor components) and 30% Et_2O–$CHCl_3$. From the latter was ultimately obtained 0.20 g (53%) of **43** as a red powder: mp 247–248° (from CH_2Cl_2, Darco); ir 2.96 μ (OH); uv max (CH_3OH) 220 mμ (ε 8400) and 289 (84,300); nmr ($CDCl_3$, 100 Mc) δ 8.91 (s, C-11 proton) and 8.29–7.05 (m, 13, OH and aromatic).

Anal. Calcd for $C_{22}H_{14}N_2O$: C, 81.97; H, 4.38; N, 8.69. Found: C, 82.10; H, 4.38; N, 8.76.

1-Hydroxy-11-phenylbenzo[*b*]phenazine (44) (9.39 g, 78%) was obtained by similar treatment of **42** (0.40 g, 0.0012 mol) using CCl_4 instead as the final eluent: mp 250–251°; ir 2.96 and 2.98 μ (OH); uv max (CH_3OH) 220 mμ (ε 16,800) and 289 (150,000);

nmr ($CDCl_3$, 100 Mc) δ 8.93 (s, 1, C-6 proton) and 8.20–7.00 (m, 13, OH and aromatic).

Anal. Calcd for $C_{22}H_{14}N_2O$: C, 81.97; H, 4.38; N, 8.69. Found: C, 81.99; H, 4.64; N, 8.50.

2,5-Dimethylquinoxaline.—A mixture of 2,3-dinitro- and 2,5-dinitro-*p*-xylene (5.0 g, 0.026 mol) was hydrogenated in EtOAc over 10% Pd/C at 3 atm. The mixture was filtered, and the crude oil (0.018 mol containing 68% of the desired 2,3-diamino isomer), obtained by evaporation of the solvent, was heated for 2 hr at 60° with 4.65 g (0.018 mol) of the $NaHSO_3$ adduct of glyoxal (10% excess of the adduct was added after 1 hr). The solution was made strongly alkaline with aqueous KOH and extracted with Et_2O. The combined ether extracts were dried (Na_2SO_4), filtered, and evaporated to dryness *in vacuo*. The residue was deposited on a 2.5 × 25 cm silica gel column and elution with 1:1 CH_2Cl_2–CCl_4 ultimately afforded **2,5-dimethylquinoxaline** (0.30 g, 11%) as white needles: mp 71–72° (from 30–60° petroleum ether, Darco); uv max 245 mμ (ε 39,000) and 318 (5400); nmr ($CDCl_3$) δ 8.78 (s, 2, C-2,3 protons), 7.41 (s, 2, C-6,7 protons), and 2.70 (s, 6, CH_3).

Anal. Calcd for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.70; H, 6.38; N, 17.92.

5,8-Dimethylquinoxaline 1-Oxide.—A mixture of 5,8-dimethylquinoxaline (1.0 g, 0.0063 mol) in 25 ml of $CHCl_3$ and 5 ml of 40% peracetic acid was refluxed for 16 hr. After cooling to room temperature, the solution was diluted with $CHCl_3$ and washed four times with H_2O. The $CHCl_3$ layer was dried (Na_2SO_4) and filtered, and the solvent was evaporated *in vacuo*. Deposition of the residue on a 2.5 × 25 cm silica gel column and elution with 1:1 CH_2Cl_2–CCl_4 ultimately gave 0.80 g of recovered starting material. Further elution with $CHCl_3$ yielded 0.15 g (12%) of **5,8-dimethylquinoxaline 1-oxide** as yellow needles: mp 109.5–110° (from 30–60° petroleum ether, Darco); uv max 252 mμ (ε 36,100), 292 (3850), 337 (4600), and 349 (5000); nmr ($CDCl_3$) δ 8.48–8.10 (AB pattern, 2, C-2,3 protons), 7.44–7.10 (AB pattern, 2, C-6,7 protons), 2.96 (s, 3, C-8 CH_3), and 2.60 (s, 3, C-5 CH_3).

Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 69.17; H, 5.94; N, 16.04.

Reduction of the *N*-**oxide** (0.10 g, 0.00052 mol) with 0.10 g (0.00058 mol) of sodium hydrosulfite in 20 ml of 80% EtOH gave **5,8-dimethylquinoxaline** (40%).

Registry No.—**4** *cis*, 26940-78-3; **4** *trans*, 26940-79-4; **5** *cis*, 26940-80-7; **5** *trans*, 26940-81-8; **6** *cis*, 26940-82-9; **6** *trans*, 26940-83-0; **7** *cis*, 26940-84-1; **7** *trans*, 26940-85-2; **8** *cis*, 26940-86-3; **8** *trans*, 26940-87-4; **9** *cis*, 26940-88-5; **9** *trans*, 26940-89-6; **10a** *cis*, 26940-90-9; **10a** *trans*, 26992-53-0; **10b** *cis*, 26940-91-0; **10b** *trans*, 26940-92-1; **13**, 26940-93-2; **14**, 26940-94-3; **15**, 26940-95-4; **16**, 26940-96-5; **17**, 26940-97-6; **18**, 26940-98-7; **19**, 26940-99-8; **20**, 26941-00-4; **21**, 26941-01-5; **22**, 26941-02-6; **24**, 26941-03-7; **26**, 26941-04-8; **27**, 26941-05-9; **28**, 26941-06-0; **31**, 26941-07-1; **32**, 26941-08-2; **33**, 26941-09-3; **34**, 26941-10-6; **35**, 26941-11-7; **38**, 26941-12-8; **39**, 26941-13-9; **40**, 26941-14-0; **41**, 26941-15-1; **42**, 26941-16-2; **43**, 26941-17-3; **44**, 26941-18-4; **45**, 26941-19-5; 2,5-dimethylquinoxaline, 26941-20-8; 5,8-dimethylquinoxaline, 26941-21-9.

Notes

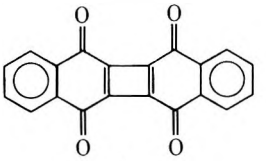
A Study of the Bromination of the Syn and Anti Photodimers of 1,4-Naphthoquinone. The Chemistry of the Brominated Derivatives

NICOLAAS P. DU PREEZ, DANIEL P. VENTER, PETRUS JANSE VAN VUUREN, GERT J. KRUGER, AND JOHANNES DEKKER*

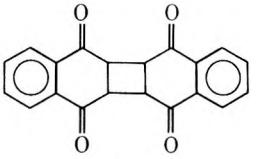
Department of Chemistry, Potchefstroom University for Christian Higher Education, Potchefstroom, South Africa

Received March 18, 1970

Various efforts to synthesize cyclobutadiene or derivatives thereof are cited in the literature.[1] These efforts were, however, unsuccessful, supporting calculations[2] which show zero aromatic nature for cyclobutadiene. In some cases[3,4] the presence of nonisolable cyclobutadiene derivatives has been claimed. The symmetrically substituted diphthaloylcyclobutadiene **1** should exhibit an enhanced stability compared to cyclobutadiene owing to the electronegative carbonyl groups adjacent to the four-membered ring. In order to attempt the synthesis of **1**, we first considered it necessary to investigate the bromination and chemistry of the syn (**2a**) and anti (**2b**) dimers[5,6] of 1,4-naphthoquinone.



1



2a, syn
b, anti

It has been shown that both **2a** and **2b** enolize in acidic media to establish an equilibrium between **2b** and **3**.[7] Both **3** and its fully enolized derivative **4**[8] exhibit typical olefinic reactions, *e.g.*, bromination[7] to **5** and **6**, respectively.

The bromination of **2** leads to various products, depending on the reaction conditions. If the reaction is carried out with 4 equiv of bromine in acetic acid

(1) M. P. Cava and M. J. Mitchell, "Cyclobutadiene and Related Compounds," Academic Press, New York, N. Y., 1967.

(2) M. J. S. Dewar and G. J. Gleicher, *J. Amer. Chem. Soc.*, **87**, 3255 (1965); L. Watts, J. D. Fitzpatrick, and R. Pettit, *ibid.*, **88**, 623 (1966); J. D. Roberts, A. Streitwieser, Jr., and C. M. Regan, *ibid.*, **74**, 4579 (1952).

(3) R. Criegee, W. Eberius, and H. Brune, *Chem. Ber.*, **101**, 94 (1968); G. Maier and U. Mende, *Tetrahedron Lett.*, **37**, 3155 (1969), and references therein; L. Watts, J. D. Fitzpatrick, and R. Pettit, *J. Amer. Chem. Soc.*, **87**, 3253 (1965); M. Neuenschwander and A. Niederhauser, *Chimia*, **22**, 491, (1968); G. Maier and U. Mende, *Angew. Chem.*, **81**, 932 (1969).

(4) R. Compper and G. Seybold, *ibid.*, **80**, 804 (1968).

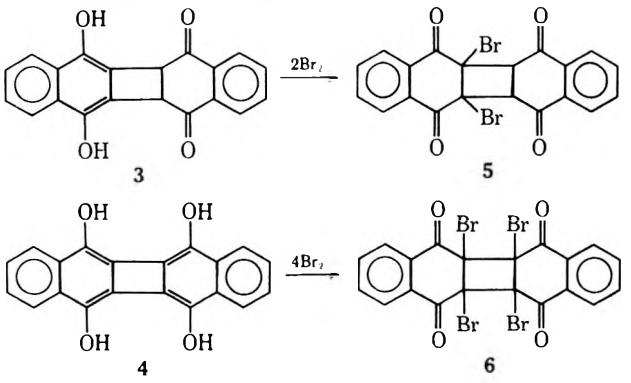
(5) A. Schönberg, M. Mustafa, M. Z. Barahat, N. Latif, R. Moubasher, and A. Mustafa, *J. Chem. Soc.*, 2126 (1948).

(6) J. Dekker, P. J. van Vuuren, and D. P. Venter, *J. Org. Chem.*, **33**, 464 (1968).

(7) D. P. Venter and J. Dekker, *ibid.*, **34**, 2224 (1969).

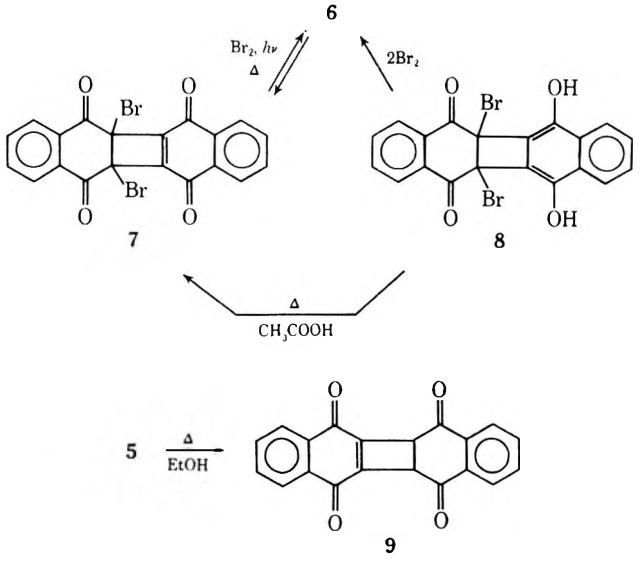
(8) J. M. Bruce, *J. Chem. Soc.*, 2782 (1962).

at 70°, the fairly insoluble **6** is obtained. The infrared spectrum of **6** closely resembles that of **2**,[6] showing a shift in carbonyl absorption to higher frequency (1692 cm^{-1}) with reference to that of **2a** (1678



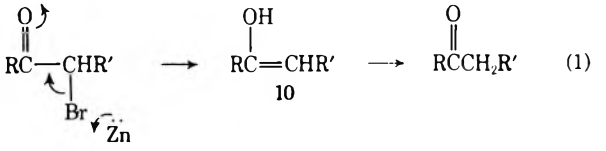
cm^{-1}). The mass spectrum and analysis are consistent with the structure. The structure and anti configuration of **6** recently have been proved[9] by means of X-ray crystallography.

The bromination of **2** with 4 equiv of bromine in boiling acetic acid produces a yellow crystalline dibromo derivative **7**, which exhibits α,β-unsaturated (1680 cm^{-1}) and α-brominated (1703 cm^{-1}) carbonyl absorption. It is logical to expect that the latter bromination should initially incorporate the formation of **6**, followed by a cis elimination of 1 mol of bromine. The labile character of two of the bromine atoms of **6** is demonstrated by its smooth conversion to **7** in boiling acetic acid. The reverse reaction, *i.e.*, the bromination of **7** to **6**, is accomplished by ultraviolet-induced bromination of a suspension of **7** in carbon tetrachloride. The phenomenon of cis elimination of 1 mol of bromine is also encountered in the case of **5**. A solution of **5** in boiling ethanol yields a yellow crystalline product, characterized as the quinone **9**. Treatment of **9** with 2 equiv of bromine in acetic acid leads to the formation of **7**, illustrating the correctness of structure **9**.



If the bromination of **2** is conducted in acetic acid at 90° with 2 equiv of bromine, an orange crystalline product **8**, which displays typical α-bromo ketonic (1685 cm^{-1}) and hydroxylic (3460 cm^{-1}) absorption in the infrared region, is obtained. Further bromination of **8** results in the formation of **6**. Further structural proof for **8** is obtained by thermal treatment (boiling acetic acid) of **8**, whereby **7** is produced.[10]

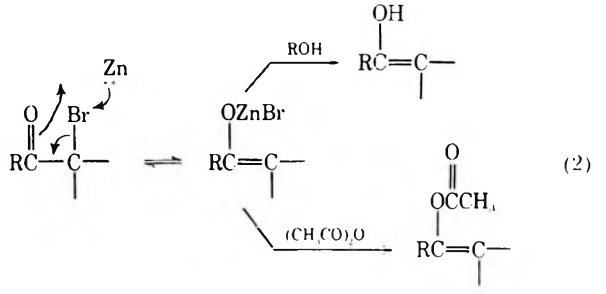
According to Corey,[11] the acidic debromination of α-bromo ketones with zinc proceeds according to eq 1.



(1)

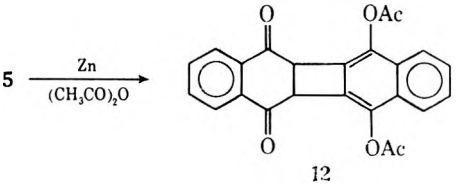
Zimmerman[12] showed that **10** does, in fact, exist as an intermediate.

Treatment of a suspension of **6** in acetic acid or ethanol with activated zinc powder at 20° accomplishes complete conversion to **4** within 20 min. Treatment of **6** with activated zinc powder in absolute acetic anhydride at 20° leads quantitatively to the formation of the tetraacetate[8] **11**. This reaction, which we prefer to call an acetylative dehalogenation, must proceed in much the same way as the acidic dehalogenation of α-bromo ketones, probably *via* the route of eq 2.



(2)

The proposed mechanism is favored by the fact that treatment of **4** with zinc powder in acetic anhydride at 20° for 2 hr produces **11** in less than 4% yield. Further supporting evidence for the proposed acetylative dehalogenation reaction is given by the fact that treatment of **5** with zinc powder in acetic anhydride at 20° yields the diacetate **12**[7] as sole product.



Treatment of **8** with zinc powder in ethanol or acetic acid leads quantitatively to **4**, while **11**[8] is obtained with zinc powder in acetic anhydride. The latter reaction indicates that the initially formed diacetate **13** suffers further acetylation owing to the presence of zinc acetate bromide. This statement is proved by the fact that, when treated with acetic

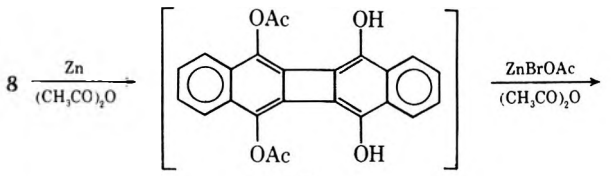
(9) G. J. Kruger and J. C. A. Boeyens, *J. Phys. Chem.*, **72**, 2120 (1968).

(10) A proposed mechanism for this dehydrogenation reaction will be published shortly.

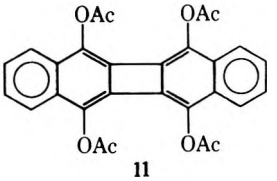
(11) E. J. Corey and R. A. Sneen, *J. Amer. Chem. Soc.*, **78**, 6269 (1956).

(12) H. E. Zimmerman and A. Mais, *ibid.*, **81**, 3644 (1959).

anhydride and zinc bromide at 20°, **4** is converted rapidly and quantitatively to **11**.

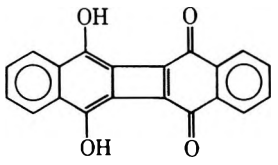


13



11

An attempt to obtain the "internal quinhydrone" **14** by treating **7** with zinc in acetic acid leads to the formation of **4**, showing that further reduction of **14** occurs. A noncrystalline, unidentified product is obtained when the reaction is carried out in ethanolic solution. The reaction of **7** with zinc powder in acetic anhydride at 20° yields **11**.



14

Dehalogenation of **6** with lithium amalgam should lead to the formation of **1**. A stirred suspension of **6** and lithium amalgam in sodium-dried ether yields a yellow solution, as can be expected for a bisquinonoid system, with an intense green fluorescence. The reaction is performed under a nitrogen atmosphere and in the absence of light. This compound is possibly **1**, which, however, is so light and air sensitive that its isolation or characterization is impossible.

Experimental Section

The following instruments were used for the recording of physical properties: a Perkin-Elmer Model 221 spectrophotometer, a MS 9 mass spectrometer, and a Gallenkamp (Design No. 889339) melting point apparatus. Melting points are uncorrected. Because of the low solubilities of the various compounds, no nmr spectra could be obtained. Microanalyses were done by the Council for Scientific and Industrial Research of South Africa.

5a,5b,11a,11b-Tetrabromo-5,6,11,12-tetraketo-5,5a,5b,6,11,-11b,12-octahydrodibenzo[*b*,*h*]biphenylene (6).[7]—Bromine (0.24 g) was added to a stirred solution of **2**[6] (0.1 g) in acetic acid (50 ml) at 90°. After 2 min the temperature was lowered to 70°; the reaction mixture was kept at this temperature for 1 hr and then cooled. Colorless needles of **6** (0.18 g, 91%) separated: mp 255–258° dec (lit.[7] mp 255–258°); ir (KBr) 1692 (C=O), 1591 (Ar), 1254 (C=O), 1005 cm^{-1} (cyclobutane ring); mass spectrum (70 eV) *m/e* (rel intensity) 628 (<5), 549 (34), 470 (38), 391 (93), 312 (52), 284 (22), 256 (15), 228 (34), 200 (100).

Anal. Calcd for $C_{20}H_8O_4Br_4$: C, 38.01; H, 1.28; Br, 50.59. Found: C, 38.00; H, 1.28; Br, 50.94.

1,2-Phthaloyl-2a,8a-dibromo-2a,3,8,8a-tetrahydro-3,8-diketonaphtho[*b*]cyclobutadiene (7). 1. From the Anti Dimer 2b.[6]—Bromine (0.21 g) was added to a boiling solution of **2b** (0.1 g) in acetic acid (40 ml). The reaction mixture was refluxed for 30 min, concentrated to 10 ml, and cooled. Yellow needles of **7** (0.14 g, 95%) separated: mp 276–278° dec; ir (KBr) 1703 (α-bromo C=O), 1680 (α,β-unsaturated C=O), 1630 (C=C), 1590 (Ar), 1246 (C=O), 985 cm^{-1} (cyclobutene ring); mass spectrum (70 eV) *m/e* (rel intensity) 470 (21), 393 (100), 391 (98), 312 (40), 284 (13), 256 (7), 228 (28), 200 (74).

Anal. Calcd for $C_{20}H_8O_4Br_2$: C, 50.88; H, 1.71; Br, 33.85. Found: C, 50.71; H, 1.68; Br, 33.99.

2. From the Tetrabromide 6.[7]—A suspension of **6** (0.05 g) in acetic acid (50 ml) was refluxed for 30 min. The clear, yellow solution was concentrated to 10 ml and cooled. Yellow needles of **7** (0.03 g, 80%) separated.

5b,11a-Dibromo-5,12-dihydroxy-5b,6,11,11a-tetrahydro-6,11-diketodibenzo[*b*,*h*]biphenylene (8).—Bromine (0.1 g) was added to a stirred solution of **2**[6] (0.1 g) in acetic acid (15 ml) at 90°. After 5 min the solution was cooled. Light yellow needles of **8** (0.11 g, 74%) separated: mp 191–193° dec; ir (KBr) 3460 (OH), 1685 (C=O), 1632 (C=C), 1605 (Ar), 1590 (Ar), 1260 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 472 (<5), 393 (32), 314 (65), 313 (100), 286 (66), 258 (35), 229 (24), 200 (62).

Anal. Calcd for $C_{20}H_{10}O_4Br_2$: C, 50.67; H, 2.13; Br, 33.71. Found: C, 50.62; H, 2.11; Br, 33.96.

Bromination of 7.—Bromine (0.03 g) was added to a suspension of **7** (0.01 g) in carbon tetrachloride (5 ml). Ultraviolet irradiation of the reaction mixture for 30 min led to the formation of a clear solution, which was concentrated to 1 ml. Compound **6** (0.012 g, 90%) separated.[13]

Bromination of 8.—Bromine (0.08 g) was added to a stirred solution of **8** (0.1 g) in dichloromethane (100 ml). After 40 min the solution was concentrated to 10 ml. Colorless crystals of **6** (0.11 g, 83%) separated.

Thermal Treatment of 8.—A solution of **8** (0.1 g) in acetic acid (40 ml) was refluxed for 5 min. The solution was concentrated to 4 ml and cooled. Golden yellow needles of **7** (0.09 g, 90%) separated.

1,2-Phthaloyl-2a,3,8,8a-tetrahydro-3,8-diketonaphtho[*b*]cyclobutadiene (9). 1. From the Diol 3.[7]—A solution of **3** (0.25 g) in benzene (100 ml) and acetone (30 ml) was treated with activated, powdered manganese dioxide (3 g) and anhydrous sodium sulfate (3 g), and the reaction mixture was shaken for 4 hr and filtered. The yellow solution was concentrated to 10 ml. Yellow needles of **9** (0.17 g, 66%) separated. Another 0.075 g was recovered from the mother liquor by precipitation with cyclohexane. Recrystallization from benzene yielded yellow needles of the quinone **9**: mp 233–237° dec; ir (KBr) 1691 (C=O), 1670 (α,β-unsaturated C=O), 1633 (C=C), 1590 (Ar), 1289 (C=O), 1230 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 314 (100), 286 (32), 258 (68), 230 (43), 202 (92).

Anal. Calcd for $C_{20}H_{10}O_4$: C, 76.43; H, 3.18. Found: C, 76.38; H, 3.20.

2. From the Dibromide 5.[7]—A solution of **5** (0.1 g) in ethanol (20 ml) was refluxed for 15 min and then cooled to 0°. Yellow needles of **9** (0.063 g, 95%) separated.[13]

Bromination of 9.—Bromine (0.1 g) was added to a stirred solution of **9** (0.1 g) in acetic acid (40 ml). The reaction mixture was refluxed for 30 min and concentrated to 6 ml. Yellow needles of **7** (0.12 g, 84%) separated.[13]

Acetylative Debromination of the Brominated Derivatives. 1. At 140°.—A suspension of **5**,[7] **6**,[7] **7**, or **8** (0.1 g) and activated zinc powder (0.5 g) in acetic anhydride (15 ml) was refluxed for 30 min. The reaction mixture was filtered and cooled. Colorless crystals of **11**[8] (0.08, 0.07, 0.095, and 0.09 g, respectively) were obtained, mp 358–360° dec (lit.[8] 358–360°).[13]

2. At 20°.—A suspension of **6**,[7] **7**, or **8** (0.1 g) and activated zinc powder (0.5 g) in acetic anhydride (5 ml) was stirred vigorously for 30 min. The insoluble crystalline product (**11**)[13] was separated from the zinc, filtered, and washed with acetic acid and water successively.

A suspension of **5**[7] (0.5 g) and activated zinc powder (3 g) in acetic anhydride (20 ml) was stirred vigorously for 15 min. The clear solution was filtered and decomposed with ethanol and water. The precipitated product was recrystallized from benzene, yielding **12** (0.25 g, 59%) as colorless needles: mp 192–194° dec; ir (KBr) 1768 (ester C=O), 1688 (C=O), 1643 (C=C), 1352 (ester C=O), 1279 (C=O), 1194 and 1177 cm^{-1} (ester C=O); mass spectrum (70 eV) *m/e* (rel intensity) 400 (24), 358 (74), 316 (100).

Anal. Calcd for $C_{24}H_{16}O_6$: C, 71.99; H, 4.03. Found: C, 71.94; H, 3.97.

Acetylation of the Tetraol 4.[8] **1. With Zinc Powder and Acetic Anhydride.**—A suspension of **4** (0.18 g) and activated

(13) The product was identified by ir spectroscopy and melting point.

zinc powder (0.3 g) in acetic anhydride (15 ml) was stirred vigorously for 3 hr at 20°. The insoluble product[13] (4, 0.17 g) was separated from the zinc, filtered, and washed with acetic acid and then water. The filtrate was concentrated to 5 ml. Colorless needles of 11 (0.01 g, <4%) separated.[13]

2. **With Zinc Bromide and Acetic Anhydride.**—A suspension of 4[8] (0.1 g) and zinc bromide (0.5 g) in acetic anhydride (8 ml) was stirred vigorously for 20 min at 20°. The insoluble colorless needles of 11[13] (0.15 g, 95%) were filtered and washed with acetic acid and water successively.

Acidic Debromination of the Brominated Derivatives.—A suspension of 6,[7] 7, or 8 (0.2 g) and activated zinc powder (0.5 g) in acetic acid[14] (15 ml) was stirred vigorously for 20 min. The suspended 4 was separated from the zinc. The insoluble 4[13] (0.09, 0.11, and 0.1 g, respectively) was filtered and washed with diluted hydrochloric acid and water successively.

Registry No.—2a, 14734-20-4; 2b, 14734-19-1; 7, 27150-37-4; 8, 27150-38-5; 9, 27189-17-9; 12, 19817-51-7.

Acknowledgment.—The authors are indebted to the Council for Scientific and Industrial Research of South Africa for financial support and for postgraduate grants to N. P. du P. and D. P. V. Grants by the Industrial Development Corporation of South Africa, Ltd., to N. P. du P and by "Afrikaanse Pers Beperk (1962)" to D. P. V. are gratefully acknowledged.

(14) If ethanol was used as solvent, 6 and 8 yielded 4. In the case of 7, however, an unidentified, noncrystalline product was obtained.

Sulfur-Containing Polypeptides. XIV. Removal of the *tert*-Butyloxycarbonyl Group with Boron Trifluoride Etherate[1,2]

RICHARD G. HISKEY,* LOWRIE M. BEACHAM, III, VICTOR G. MATL, J. NORTH SMITH, E. BRADY WILLIAMS, JR., A. M. THOMAS, AND ERIK T. WOLTERS

Venable Chemical Laboratory, The University of North Carolina, Chapel Hill, North Carolina 27514

Received July 13, 1970

In recent years the *tert*-butyloxycarbonyl (*t*-BOC) nitrogen protective group[3,4] has become widely used in peptide synthesis. The utility of the *t*-BOC group has been primarily due to the ease of introduction by the controlled pH technique,[5] the properties of *t*-BOC peptide derivatives, and the relatively mild conditions required for removal of the group. Although hydrogen chloride in various solvents[3,4] and neat trifluoroacetic acid[6] have been classically employed for cleavage of the *t*-BOC group, the availability of a reagent that would permit clean, rapid removal without the necessity of a strongly acidic solvent would be advantageous in many circumstances.[7]

These criteria can be met in many situations by use of boron trifluoride diethyl etherate in either glacial acetic acid or acetic acid–chloroform mixtures. While attempts to conduct the cleavage in chloroform alone have proved unsatisfactory, the addition of as little as 10% acetic acid gave good results. An important requirement is the exclusion of moisture from reagent and solvent.

In general, the *t*-BOC peptide is treated with a threefold excess of freshly distilled boron trifluoride diethyl etherate (0.4 ml/mmol). The reaction mixture is maintained at room temperature for 15–30 min and neutralized with either aqueous sodium acetate, 5% ammonium hydroxide, or potassium bicarbonate. The reaction is conveniently followed by tlc and generally goes to completion in 5 min although at 0° the reaction requires about 1 hr.

The *N*-carbobenzoxy group is not affected by these conditions; methyl, ethyl, benzyl, and trimethylbenzyl esters are likewise not affected, permitting possible use of this reagent with solid-phase resins. The stability of the *S*-trityl and *S*-benzhydryl thioethers of cysteine as well as the sulfur–sulfur bond of unsymmetrical cystine derivatives to these conditions has also been of considerable utility. Several protective groups are cleaved at rates comparable to cleavage of the *t*-BOC group; thus selective removal of the *t*-BOC group with boron trifluoride in the presence of benzhydryl or *tert*-butyl esters, *tert*-butyl ethers, of the *N*-triphenylmethyl group is uncertain and depends on the nature of the particular substrate.

Although this reagent has been superior for *t*-BOC removal with water-insoluble peptide derivatives, use with small water-soluble peptides must be approached with care due to the possible formation of boric acid salts. In such cases trifluoroacetic acid usually is the reagent of choice.

Experimental Section[8]

***N*-*tert*-Butyloxycarbonyl-*S*-diphenylmethyl-L-cysteine Dicyclohexylammonium Salt (I).**—A suspension of *S*-diphenylmethyl-L-cysteine[9] (57.4 g, 0.20 mol) in 400 ml of dioxane–water (1:1) was adjusted to pH 10.2 with 4.0 *N* NaOH. *tert*-Butyloxycarbonylazide (42.9 ml, 0.3 mol) was added and the reaction was stirred 9 hr at 25°, maintaining the pH at 10.2. The resulting clear yellow solution was extracted with ether and then acidified to pH 3 with 1 *N* H_2SO_4. The oily product was extracted into 500 ml of ether, washed with water and brine, dried over $MgSO_4$, and precipitated by addition of 40 g of dicyclohexylamine. The product was collected and dried over P_2O_5 to yield 101.3 g (90%): mp 158–159°; $[\alpha]^{22}D$ +6.38° (c 0.925, $CHCl_3$); homogeneous system D.

Anal. Calcd for $C_{33}H_{48}N_2O_4S$: C, 69.68; H, 8.51; N, 4.93; S, 5.64. Found: C, 69.64; H, 8.62; N, 4.82; S, 5.31.

***N*-*tert*-Butyloxycarbonyl-*S*-diphenylmethyl-L-cysteine *N*-Hydroxysuccinimide Ester (II).**—The salt, I (187 g, 0.33 mol), was neutralized with 2 *N* sulfuric acid. The resulting oil was dissolved in 300 ml of dimethoxyethane (DME) along with *N*-hydroxysuccinimide (37.5 g, 0.33 mol). The solution was cooled to −10° and treated with dicyclohexylcarbodiimide (DCC) (68.1

(1) The preceding paper of this series: R. G. Hiskey, G. W. Davis, M. E. Safdy, T. Inui, R. A. Upham, and W. C. Jones, Jr., *J. Org. Chem.*, **35**, 4148 (1970).

(2) Supported by Grants A-3416 and GM-07966 from the Institute of Arthritis and Metabolic Diseases and the Institute of General Medical Science, National Institutes of Health, U. S. Public Health Science.

(3) F. C. McKay and N. F. Anderson, *J. Amer. Chem. Soc.*, **79**, 4686 (1957).

(4) G. W. Anderson and A. C. McGregor, *ibid.*, **79**, 6180 (1957).

(5) E. Schnabel, *Justus Liebigs Ann. Chem.*, **702**, 188 (1967).

(6) H. Happeler and R. Schwyzer, *Helv. Chim. Acta*, **44**, 1136 (1961).

(7) J. Meienhofer, *J. Amer. Chem. Soc.*, **92**, 3771 (1970).

(8) Melting points are uncorrected. Elemental analyses were performed by Micro Tech Laboratories, Skokie, Ill. Optical rotations were performed on a Perkin-Elmer Model 141 polarimeter. Thin layer chromatograms were on 3-in. plates of silica gel GF. Solvent systems used were: chloroform–methanol (9:1), system A; chloroform–methanol–17% ammonia (3:3:1), system B; chloroform–methanol–34% ammonia (5.5:3.5:1), system C; chloroform–acetic acid (9:1), system D. Controlled pH reactions were carried out using a Radiometer titrimeter and magnetic valve. Solvents were dried over $CaSO_4$. Boron trifluoride etherate was Eastman Technical grade distilled from CaH_2.

(9) R. G. Hiskey and J. B. Adams, Jr., *J. Org. Chem.*, **30**, 1340 (1965).

g, 0.33 mol). The reaction was stirred 3 hr at −10° and 48 hr at 27°. The reaction mixture was diluted with 200 ml of ethyl acetate and filtered to remove dicyclohexylurea (DCU). The residue was washed with 100 ml of ethyl acetate and the combined filtrates were evaporated to a foam which was dissolved in ether; this solution was washed with saturated $NaHCO_3$, water, and brine, dried over $MgSO_4$, and evaporated to a foam. The foam was dissolved in ethyl acetate and treated with hexane to give an oil which solidified on trituration under hexane; the crude solid (112.3 g) was used in the next step without further purification.

Benzyl *N*-*tert*-Butyloxycarbonyl-*S*-diphenylmethyl-L-cysteinylglycinate (III).—II (97.0 g, 0.20 mol) was added to a solution of benzyl glycinate *p*-toluenesulfonate[10] (81.0 g, 0.24 mol) and *N*-methylmorpholine (33 ml, 0.3 mol) in 500 ml of ethyl acetate. The solution was stirred at 26° for 15 hr and then washed with 1 *N* sulfuric acid (3 times), water, saturated $NaHCO_3$ (2 times), water, and brine, dried over $MgSO_4$, and evaporated to an oil which was chromatographed on silica gel, eluting with chloroform. The product was isolated from the column as oil (102 g), pure by tlc (system A), and was used without further characterization.

Benzyl *S*-Diphenylmethyl-L-cysteinylglycinate *p*-Toluenesulfonate Salt (IV).—The ester, III (102 g), was dissolved in 360 ml of chloroform–glacial acetic acid (5:1) at 25° and treated with 80 ml of boron trifluoride etherate. After 20 min, the reaction mixture was treated with 75 ml of NH_4OH (34%) in 300 ml of water. Solid $KHCO_3$ was added to bring the pH to 10. The layers were separated and the organic layer was dried over $MgSO_4$ and evaporated to an oil. This oil was dissolved in 1000 ml of ether and treated with an ethereal solution of *p*-toluenesulfonic acid. On cooling, IV precipitated as 83.1 g (68%) of needles: mp 181–183°; $[\alpha]^{28}D$ +25.6° (*c* 1, MeOH); homogeneous, system A.

Anal. Calcd for $C_{32}H_{34}N_2O_6S_2$: C, 63.34; H, 5.65; N, 4.62; S, 10.57. Found: C, 63.28; H, 5.69; N, 4.60; S, 10.29.

Benzyl *N*-*tert*-Butyloxycarbonylglycyl-*S*-diphenylmethyl-L-cysteinylglycinate (V).—IV (6.07 g, 10 mmol) and *N*-methylmorpholine (1.10 ml, 10 mmol) were dissolved in 25 ml of chloroform and treated with *N*-*tert*-butyloxycarbonylglycine *N*-hydroxysuccinimide ester.[11] The reaction was stirred at 26° for 4 hr. The solution was evaporated to a foam which was dissolved in 60 ml of ethyl acetate; this solution was washed with 1 *N* H_2SO_4 (3 times), water, saturated $NaHCO_3$ (3 times), water, and brine, dried over $MgSO_4$, and evaporated to a foam. Recrystallization from ethyl acetate–hexane gave V as long needles: 5.31 g (90%); mp 123–125°; $[\alpha]^{24}D$ −12.18° (*c* 1.02, $CHCl_3$); homogeneous, system A.

Anal. Calcd for $C_{32}H_{37}N_3O_6S$: C, 64.95; H, 6.30; N, 7.10; S, 5.42. Found: C, 64.67; H, 6.30; N, 7.03; S, 5.41.

Benzyl Glycyl-*S*-diphenylmethyl-L-cysteinylglycinate *p*-Toluenesulfonate Salt (VI).—A solution of V (11.83 g, 20 mmol) in 40 ml of chloroform–acetic acid (3:1) was treated with 8.0 ml of boron trifluoride etherate for 30 min at 26°. A solution of 11.8 ml of NH_4OH in 100 ml of water was added, along with 25 ml of chloroform. The pH was adjusted to 10 with solid $KHCO_3$. The chloroform layer was separated, washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo* to a foam which was dissolved in 300 ml of ether–ethyl acetate (2:1) and treated with *p*-toluenesulfonic acid in ether. The product precipitated on cooling: 8.20 g (61%); mp 79–80°; homogeneous, system A.

Anal. Calcd for $C_{34}H_{37}N_3O_7S_2 \cdot H_2O$: C, 59.89; H, 5.77; N, 6.16; S, 9.41. Found: C, 60.04; H, 5.52; N, 6.45; S, 9.43.

***N*-*tert*-Butyloxycarbonyl-*S*-diphenylmethyl-L-cysteinylglycine Dicyclohexylammonium Salt (VII).**—A solution of II (4.84 g, 10.0 mmol) in 25 ml of DME was treated with a solution of glycine (0.83 g, 11.0 mmol) and $KHCO_3$ (2.20 g, 22.0 mmol) in 25 ml of water. The solution was stirred 2 hr at 28°. The pH was adjusted to 3 with 2 *N* H_2SO_4 giving a gummy precipitate which was extracted into ether. The ether extract was washed with water (3 times) and brine, dried over $MgSO_4$, and treated with dicyclohexylamine (2.0 g). After cooling, the crystalline product was collected and dried over P_2O_5: 5.7 g (82%); mp 153–154°; $[\alpha]^{23}D$ −23.55° (c 1.04, DMF); homogeneous, system A, system D.

Anal. Calcd for $C_{35}H_{51}N_3O_5S$: C, 67.18; H, 8.21; N, 6.71; S, 5.11. Found: C, 66.98; H, 8.20; N, 6.83; S, 4.98.

***S*-Diphenylmethyl-L-cysteinylglycine (VIII).**—A solution of VII (3.13 g, 5 mmol) in glacial acetic acid (20 ml) was treated with boron trifluoride etherate (2.0 ml) for 30 min at 25°. The reaction mixture was then poured onto a solution of sodium acetate (10 g) in 50 ml of ice water. The flocculent precipitate was collected and washed with water (5 times) and ether (5 times) and then dried over P_2O_5 *in vacuo*: 1.68 g (97%); mp 182–185° dec; $[\alpha]^{22}D$ −2.63° (*c* 1.0, hexamethylphosphoramide); homogeneous, system B.

Anal. Calcd for $C_{18}H_{20}N_2O_3S$: C, 62.77; H, 5.85; N, 8.13; S, 9.31. Found: C, 62.53; H, 5.97; N, 8.21; S, 9.21.

***N*-*tert*-Butyloxycarbonylglycyl-*S*-diphenylmethyl-L-cysteinylglycine (IX).**—A slurry of VIII (865 mg, 2.5 mmol) in 10 ml of chloroform was treated with *N*-methylmorpholine (1.0 ml) and then with *N*-*tert*-butyloxycarbonylglycine *N*-hydroxysuccinimide ester (680 mg, 2.5 mmol). The mixture was stirred 7 hr, slowly going to a clear solution. The solvent was removed *in vacuo* and the residue was partitioned between 50 ml of ethyl acetate and 50 ml of 2 *N* H_2SO_4. The organic layer was washed with water (2 times) and brine and then dried over $MgSO_4$. The remaining solution was heated to boiling and diluted with an equal volume of hexane. On cooling, IX appeared as 1.04 g (83%) of needles: mp 174–176°; $[\alpha]^{30}D$ −13.1° [*c* 1.01, $CHCl_3$–DMF (2:1)]; homogeneous, system D.

Anal. Calcd for $C_{25}H_{31}N_3O_6S$: C, 59.86; H, 6.23; N, 8.38; S, 6.40. Found: C, 59.77; H, 6.14; N, 8.29; S, 6.40.

Glycyl-*S*-diphenylmethyl-L-cysteinylglycine (X).—A solution of IX (502 mg, 1.0 mmol) in 10 ml of acetic acid was treated with boron trifluoride etherate (0.4 ml) for 30 min at 26°. The reaction was then poured onto a solution of sodium acetate (5 g) in 50 ml of water. The fine white precipitate was collected, washed with water (5 times) and ether (5 times), and dried over P_2O_5: yield, 330 mg (83%); mp 206–207°; $[\alpha]^{24}D$ −13.04° (c 1.00, hexamethylphosphoramide); homogeneous, system C.

Anal. Calcd for $C_{20}H_{23}N_3O_4S \cdot {}^1/_2H_2O$: C, 58.52; H, 5.89; N, 10.21; S, 7.81. Found: C, 58.38; H, 5.75; N, 10.18; S, 7.72.

***N*-*tert*-Butyloxycarbonyl-*S*-triphenylmethyl-L-cysteine (XI).**—A suspension of *S*-triphenylmethyl-L-cysteine[9] (18.3 g, 50 mmol) in 200 ml of dioxane–water (1:1) was adjusted to pH 10.2 with 4 *N* NaOH. *tert*-Butyloxycarbonylazide (10.8 g, 75 mmol) was added and the pH was maintained at 10.2 for 5 hr. The clear, yellow solution was extracted with ether (2 times) and then treated with 2 *N* H_2SO_4 to pH 3. The oily precipitate was extracted into ether. The ether solution was washed with water (2 times) and brine, dried over $MgSO_4$, and evaporated to a foam, 19.32 g (83.2%). For characterization, a 463-mg sample was dissolved in ether and treated with 0.2 ml of dicyclohexylamine to yield 640 mg (99%) of the salt: mp 210–211° dec; $[\alpha]^{20}D$ +23.8° (*c* 1.0, methanol); homogeneous, system D.

Anal. Calcd for $C_{39}H_{52}N_2O_4S$: C, 72.63; H, 8.13; N, 4.34; S, 4.97. Found: C, 71.96; H, 8.10; N, 4.19; S, 4.97.

***N*-*tert*-Butoxycarbonyl-*S*-triphenylmethyl-L-cysteinylglycine Dicyclohexylammonium Salt (XII).**—A solution of XI (18.6 g, 40.0 mmol) and *N*-hydroxysuccinimide (5.06 g, 44 mol) in 40 ml of DME was cooled to −10° and treated with DCC (9.3 g, 44 mol). The reaction was stirred at −10° for 1 hr and at 25° for 12 hr. The DCU was removed by filtration and the remaining solution was evaporated *in vacuo* to a foam which was dissolved in 200 ml of ether; this solution was washed with saturated $NaHCO_3$ (2 times), water, and brine, dried over $MgSO_4$, and evaporated to a foam which was dried over P_2O_5 *in vacuo*.

The foam was dissolved in 80 ml of DME and treated with a solution of glycine (3.30 g, 44 mmol) and $KHCO_3$ (4.41 g, 44 mmol) in 80 ml of water. After 4 hr, the reaction mixture was acidified to pH 3 with 2 *N* H_2SO_4, and the precipitated product was extracted into ether, washed with water (2 times) and brine, dried over $MgSO_4$, and treated with dicyclohexylamine (8.0 ml). Cooling produced XII which was 25.4 g (90.7%) of microcrystalline solid: mp 130.5–133°; $[\alpha]^{21}D$ +14.56° (*c* 1.00, $CHCl_3$); homogeneous, system D.

Anal. Calcd for $C_{41}H_{55}N_3O_5S$: C, 70.15; H, 7.90; N, 5.99; S, 4.57. Found: C, 70.18; H, 7.88; N, 5.95; S, 4.48.

***S*-Triphenylmethyl-L-cysteinylglycine (XIII).**—A solution of XII (7.02 g, 10 mmol) in 50 ml of acetic acid was treated with boron trifluoride etherate (4.0 ml) for 30 min and then poured onto a solution of sodium acetate (18 g) in 100 ml of ice water. The gelatinous precipitate was collected, washed with water (6

(10) H. Miller and H. Waelch, *J. Amer. Chem. Soc.*, **74**, 1092 (1952).

(11) G. W. Anderson, J. E. Zimmerman, and F. M. Callahan, *ibid.*, **86**, 1839 (1964).

times) and ether (5 times), and dried over P_2O_5 *in vacuo* to yield 4.05 (96%) of solid: mp 114–116°; $[\alpha]^{25}D$ −6.03 (*c* 1.028, hexamethylphosphoramide); homogeneous, system B.

Anal. Calcd for $C_{24}H_{24}N_2O_3S \cdot {}^1/_2H_2O$: C, 67.10; H, 5.85; N, 6.51; S, 7.45. Found: C, 67.23; H, 5.86; N, 6.29; S, 7.87.

N-tert-**Butyloxycarbonylglycyl-*S*-triphenylmethyl-L-cysteinylglycine (XIV).**—A suspension of XIII (3.15 g, 7.5 mmol) and *N-tert*-butyloxycarbonylglycine *N*-hydroxysuccinimide ester (2.24 g, 8.2 mmol) in 20 ml of chloroform was treated with 1.65 ml of *N*-methylmorpholine. The suspension was stirred 18 hr at 27°, with the solid slowly dissolving. The reaction mixture was evaporated to an oil which was taken up in 50 ml of ethyl acetate and equilibrated with 50 ml of 2 *N* H_2SO_4. The organic layer was washed with water (2 times) and brine, dried over $MgSO_4$, and evaporated to a foam which was recrystallized from chloroform–hexane. The product crystallized as small needles: 2.21 g (51%); mp 190–191°; $[\alpha]^{25}D$ +2.89° (c 1.00, $CHCl_3$), homogeneous, system D.

Anal. Calcd for $C_{31}H_{35}N_3O_6S$: C, 64.45; H, 6.11; N, 7.27; S, 5.55. Found: C, 64.71; H, 6.21; N, 7.24; S, 5.32.

Glycyl-*S*-triphenylmethyl-L-cysteinylglycine (XV).—A solution of XIV (1.154 g, 2.0 mmol) in 20 ml of acetic acid was treated with boron trifluoride etherate (0.80 ml) for 30 min at 26°. The reaction was then poured into a solution of sodium acetate (10 g) in ice water (100 ml). The product appeared as a gum which was collected by decantation and triturated under ice water to give a white powder which was washed with water (5 times) and ether (5 times) and dried over P_2O_5 *in vacuo* to yield 684 mg (71%) of solid: mp 154–155°; homogeneous, system B.

Anal. Calcd for $C_{26}H_{27}N_3O_4S \cdot H_2O$: C, 63.27; H, 5.93; N, 8.51; S, 6.50. Found: C, 63.05; H, 5.80; N, 8.16; S, 6.42.

N-tert-**Butyloxycarbonyl-*S*-triphenylmethyl-L-cysteinyl-L-asparagine Trimethylbenzyl Ester (XVI).**—A suspension of the DCHA salt of XI (6.43 g, 10 mmol) and L-asparagine trimethylbenzyl ester hydrochloride[12] in 70 ml of DMAC was stirred 45 min at 20°, cooled to −10°, and treated with *N*-hydroxysuccinimide (1.15, 10 mmol) and DCC (2.06 g, 10 mmol). The reaction was stirred 2 hr at 0° and 16 hr at 27°. The DCU was removed by filtration and the filtrate was poured into brine and extracted with ethyl acetate (3 times). The extracts were combined and washed with water, 2 *N* H_2SO_4, water, saturated $NaHCO_3$, and brine, and then evaporated to a foam which was recrystallized from ether–petroleum ether. The product contained some XI which was precipitated from ether as the DCHA salt. The supernatant liquid was poured into hexane to give pure XVI: 4.4 g (61%); mp 161°; $[\alpha]^{31}D$ +19.5° (*c* 1.4, methanol); homogeneous, system A.

Anal. Calcd for $C_{41}H_{47}N_3O_6S$: C, 69.07; H, 6.59; N, 5.84; S, 4.40. Found: C, 69.37; H, 6.67; N, 5.92; S, 4.51.

***S*-Triphenylmethyl-L-cysteinyl-L-asparagine Trimethylbenzyl Ester (XVII).**—A solution of XVI (3.55 g, 5.0 mmol) in 15 ml of acetic acid was treated with boron trifluoride etherate (2.0 ml) for 60 min at 20°. The reaction was then poured into saturated $NaHCO_3$ and ethyl acetate. The aqueous layer was washed with ethyl acetate, and the combined extracts were washed with saturated $NaHCO_3$, water, and brine, dried over $MgSO_4$, and evaporated *in vacuo* to an oil. The oil was taken up in ether–methanol (5:1) and treated with anhydrous oxalic acid (425 mg) in ether. The precipitated oxalate salt was recrystallized from methanol–ether to yield 2.72 g (70%) of product: mp 119–121°; $[\alpha]^{27}D$ +48.9° (*c* 1.65, methanol); homogeneous, system C.

Anal. Calcd for $C_{36}H_{39}N_3O_4S \cdot C_2H_2O_4$: C, 64.68; H, 5.97; N, 6.06; S, 4.78. Found: C, 65.22; H, 5.91; N, 6.00; S, 4.58.

N-tert-**Butyloxycarbonyl-*S*-triphenylmethyl-L-cysteinyl-*S*-diphenylmethyl-L-cysteinylglycyl-L-phenylalanylglycine *tert*-Butyl Ester (XVIII).**—A solution of *S*-diphenylmethyl-L-cysteinylglycyl-L-phenylalanylglycine *tert*-butyl ester[13] (1150 mg, 0.95 mmol) and XI (884 mg, 1.95 mmol) in 7 ml of DMF–methylene chloride (2.5:1) was cooled to −10° and treated with *N*-ethyl-*N'*-(3-diethylaminopropyl)carbodiimide (WSC) (372 mg, 1.95 mmol). The solution was stirred at −10° for 1 hr and at 20° for 24 hr. Methylene chloride (9 ml) was added to effect stirring. The resulting mixture was evaporated to a slurry which was washed into 40 ml of cold 1 *N* H_2SO_4 with 20 ml of methanol, and the suspension was filtered. The solid was washed with methanol–ether and dried over P_2O_5 to yield 1.69 g (82.5%) of product: mp 220–221°; $[\alpha]^{25}D$ −22.3° (*c* 1.0, dimethylformamide); homogeneous, system A.

Anal. Calcd for $C_{60}H_{67}N_5O_8S_2$: C, 68.61; H, 6.43; N, 6.67; S, 6.10. Found: C, 68.65; H, 6.49; N, 6.63; S, 6.03.

Studies on Cleavage of XVIII with Boron Trifluoride Etherate. A. Cleavage at 20°.—A solution of 10.5 mg of XVIII in 1 ml of chloroform–acetic acid (3:1) was treated with 0.1 ml of boron trifluoride etherate at 20°. Thin layer chromatography was used to follow the progress of the reaction. These conditions led to rapid cleavage of both *tert*-butyloxycarbonyl and *tert*-butyl ester. After 20 min only the completely deblocked peptide was identifiable on the chromatogram. At intermediate times, some amine ester was present but there appeared to be significant *tert*-butyl cleavage from the start.

B. Cleavage at 0°.—Conditions were identical with A, except the temperature was 0°. Cleavage was considerably slower, about 90 min being required for complete cleavage to the peptide. The transient free amine–ester had a considerably longer existence, but removal of both amine and ester protective groups occurred at comparable rates.

Investigation of the Action of Boron Trifluoride Etherate on *N*-Carbobenzoxyglycine (XIX).[14]—A solution of XIX (149 mg, 1.0 mmol) in acetic acid (1 ml) was treated with 0.4 ml of boron trifluoride etherate. The reaction was followed for 4 hr by thin layer chromatography. No evidence could be seen of consumption of starting material or of generation of any product; no ninhydrin positive material could be located. The reaction mixture was poured onto water and extracted with chloroform. The extract was washed with water, dried over $MgSO_4$, and evaporated. Recrystallization gave 98% recovery of starting material.

Registry No.—I, 26988-51-2; IV, 26988-52-3; V, 26988-54-5; VI, 26988-53-4; VII, 26988-55-6; VIII, 26988-56-7; IX, 26988-57-8; X, 26988-58-9; XI, 26988-59-0; XII, 26988-60-3; XIII, 26988-61-4; XIV, 26988-62-5; XV, 26988-63-6; XVI, 26985-35-3; XVII, 26985-36-4; XVIII, 27039-89-0.

(12) F. H. C. Stewart, *Aust. J. Chem.*, **20**, 365 (1967).

(13) R. G. Hiskey, J. T. Staples, and R. L. Smith, *J. Org. Chem.*, **32**, 2772 (1967).

(14) H. Bergmann and L. Zervas, *Ber.*, **65**, 1192 (1932).

Fill yourself in on reagents...

Every one of the reagents here is new. Recently synthesized in our laboratories, one or more of them could be the reagent you've been looking for.

For protection of the alcoholic hydroxyl group in nucleotide synthesis

2-Chloroethyl Orthoformate (EASTMAN 11251)

The alcoholic hydroxyl groups of nucleosides such as thymidine, adenosine, inosine, guanosine, ribofuranosyl, theophilline, and uridine are protected by formation of the di-2-chloroethyl orthoformate derivatives. The reaction is carried out at 100° with an excess of 2-chloroethyl orthoformate. The protecting group is stable to alkali, but easily removed by 80% acetic acid. [*Tetrahedron Letters*, No. 51, 4443 (1969)].

For the catalytic cleavage of 1,2-diols

Cobalt Acetate (EASTMAN 11183)

Cobalt acetate catalyzes the oxidative cleavage of 1,2-diols. The reaction is carried out in an aprotic, polar solvent, with aldehyde yields of 60-81%. Oxidation to the corresponding carboxylic acids is possible. [*Tetrahedron Letters*, 5689 (1968)].

For complexometric titration

- o-Cresolphthalein Complexon (EASTMAN 11206)
- m-Cresolsulfonephthalein Complexon (EASTMAN 11277)
- Fluorescein Complexon (EASTMAN 11280)
- Phenolsulfonephthalein Complexon (EASTMAN 11275)
- Thymolphthalein Complexon (EASTMAN 11279)

These five metallochromic indicators exhibit color changes with metals through changes in electronic configuration due to chelation, rather than through deformation of the cation's electronic structure, to adsorption effects, or redox changes.

For protein and peptide synthesis

- 4-Methoxybenzyl 2,4,5,-Trichlorophenyl Carbonate (EASTMAN 11213) N-blocking reagent for amino acids
- [3-(Dimethylamino)propyl]ethyl Carbodiimide Hydrochloride (EASTMAN 10819) Water-soluble coupling reagent for peptide synthesis
- p-Iodobenzenesulfonyl Chloride (EASTMAN 10955) Sulfhydryl reagent for proteins, and reagent for amino acid analysis
- Diphenylphosphor (isothiocyanatidate) (EASTMAN 11220) Reagent for peptide terminal-group determination through formation of thiohydantoins
- 6-p-Toluidino-2-naphthalenesulfonyl Chloride (EASTMAN 11002) Fluorescent probe for protein conformation studies

For hydride abstraction, dehydrogenation, and for synthesis of heterocycles and olefins

Tritylium Tetrafluoroborate (EASTMAN 11217)

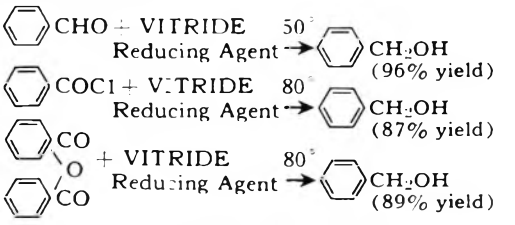
Among the many applications of this versatile reagent, tropylium salts are prepared from cycloheptatriene and tritylium tetrafluoroborate in acetonitrile or liquid SO_2 at −20°. [*J.A.C.S.*, 79, 4557 (1957)]. Tritylium tetrafluoroborate is a reagent for the dehydrogenation of 9,10-dihydroanthracene to anthracene and for the conversion of perinaphthanones to perinaphthenones [*J. Chem. Soc.*, 2773 (1959)].

VITRIDE™ Reducing Agent [Sodium Bis(2-methoxyethoxy)aluminum Hydride (70% in Benzene)] REACTION OF THE MONTH

Reduction of carbonyl and carboxyl groups

The use of VITRIDE Reducing Agent for carbonyl and carboxyl group reduction results in excellent product yields. This is due in part to good solubility of the intermediate alkoxides . . . even in cases where $LiAlH_4$ fails. A wide choice of solvents is possible because of the solubility of the reagent.

For example:



VITRIDE is a trademark of National Patent Development Corp. Manufactured by Realco Chemical Co. Available as EASTMAN 13112.

All of these new chemicals are available from the Eastman Organic Chemicals dealer nearest you. For a copy of the EASTMAN Organic Chemicals Catalog List 45, listing more than 6,000 reagents, and to receive periodic supplements to it automatically, simply complete and return the coupon.

B&A	HOWE & FRENCH	SARGENT-
CURTIN	NORTH-STRONG	WELCH
FISHER	PREISER	WILL/VW&R

West of the Rockies, your dealer can obtain quick delivery of Eastman Organic Chemicals and Laboratory Supplies from our newly established stock in San Ramon, California.

Dept. 412L
Eastman Organic Chemicals
Eastman Kodak Company, Rochester, N.Y. 14650

☐ Send JJ-1, "EASTMAN Organic Chemicals" catalog

Name _____

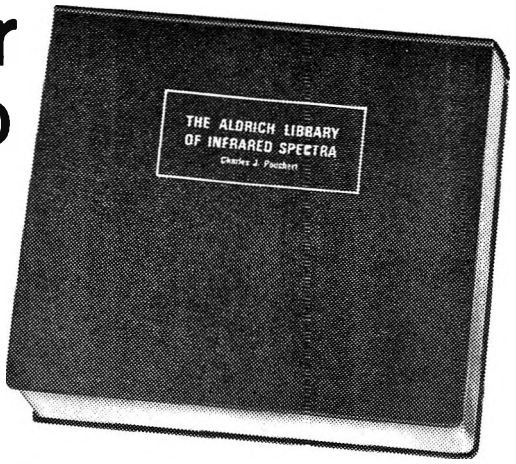
Address _____

City _____

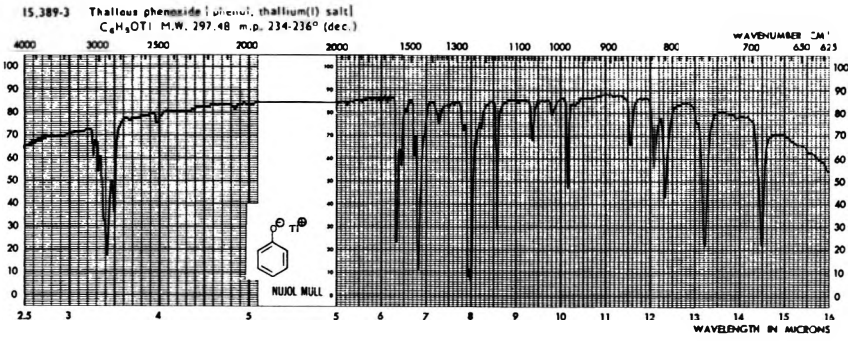
State _____ Zip _____ 2-86

Kodak

8,000 IR Spectra in one convenient volume for only $44.50



The new **Aldrich Library of Infrared Spectra** is a conveniently arranged reference containing more than 8,000 spectra chosen for purity of chemical and curve quality. The spectra were selected from more than 90,000 spectra in Aldrich files. The curves are arranged by functional groups, in order of increasing structural complexity, and are separately indexed by empirical formula. Each functional group section includes a summation of characteristic group absorption bands. The chemicals included in this volume were prepared as nujol mulls, melts, or as films neat between NaCl plates. Ninety-five percent of the spectra were run on a grating infrared spectrophotometer; the other 5% on a prism instrument. This new **Aldrich Library of Infrared Spectra** is a most useful volume for students and advanced investigators.



Address orders to **DEPARTMENT J**

Aldrich Chemical Company, Inc.

CRAFTSMEN IN CHEMISTRY

940 WEST SAINT PAUL AVENUE · MILWAUKEE, WISCONSIN 53233